

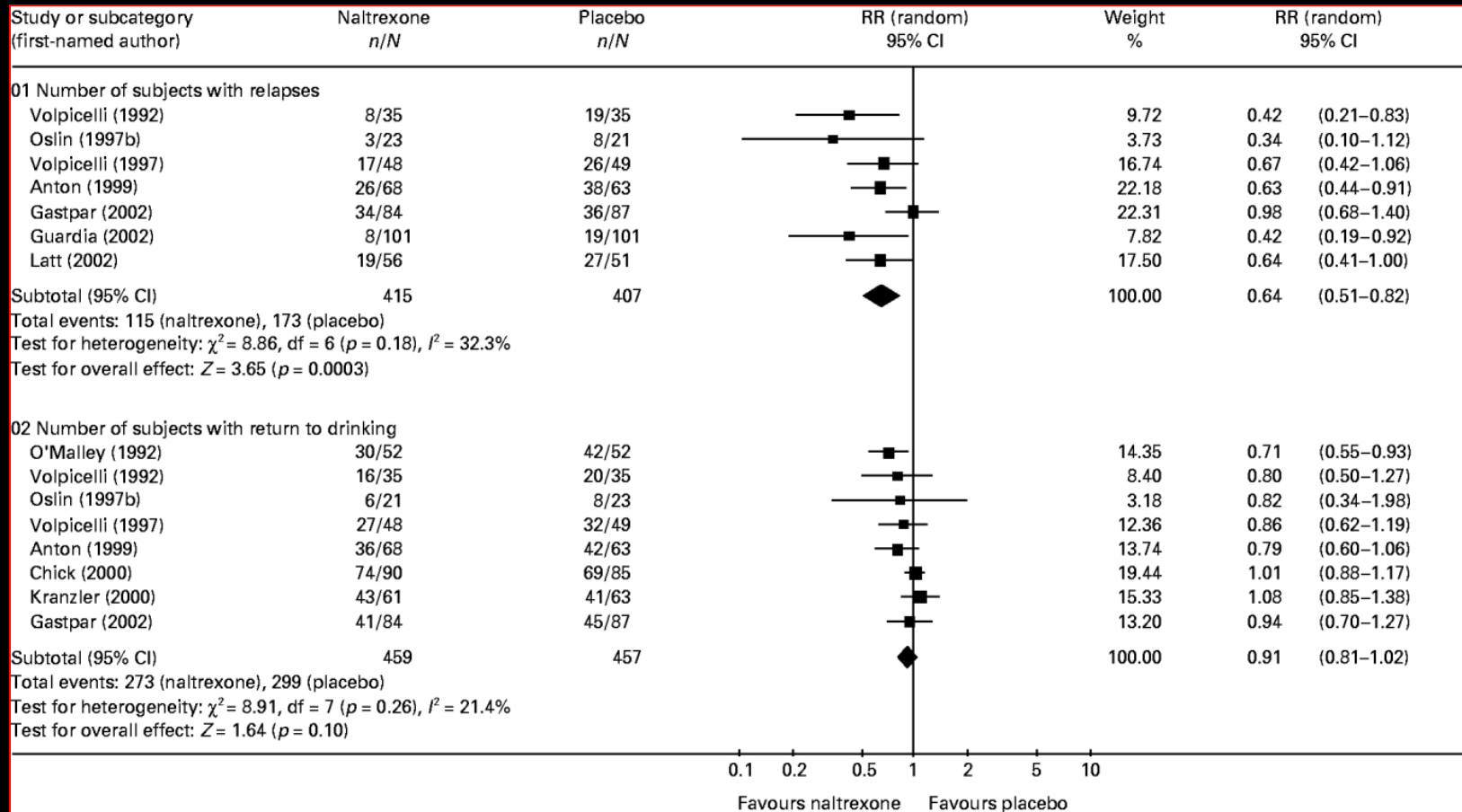
Opioids and alcoholism: Can we design a better Naltrexone?

CSAM
October, 2009

Treatment of alcohol abuse

- CBT & support groups
- Treatment of co-morbidities (anxiety, depression)
- Pharmacotherapy
 - Naltrexone (oral ReVia and depot Vivitrol)
 - Acamprosate (Campral)
 - Disulfiram (Antabuse)

Randomized placebo controlled clinical studies of naltrexone



Srisurapanont & Jarusuraisin, Int J Neuropsychopharm (2005), 8, 267–280.

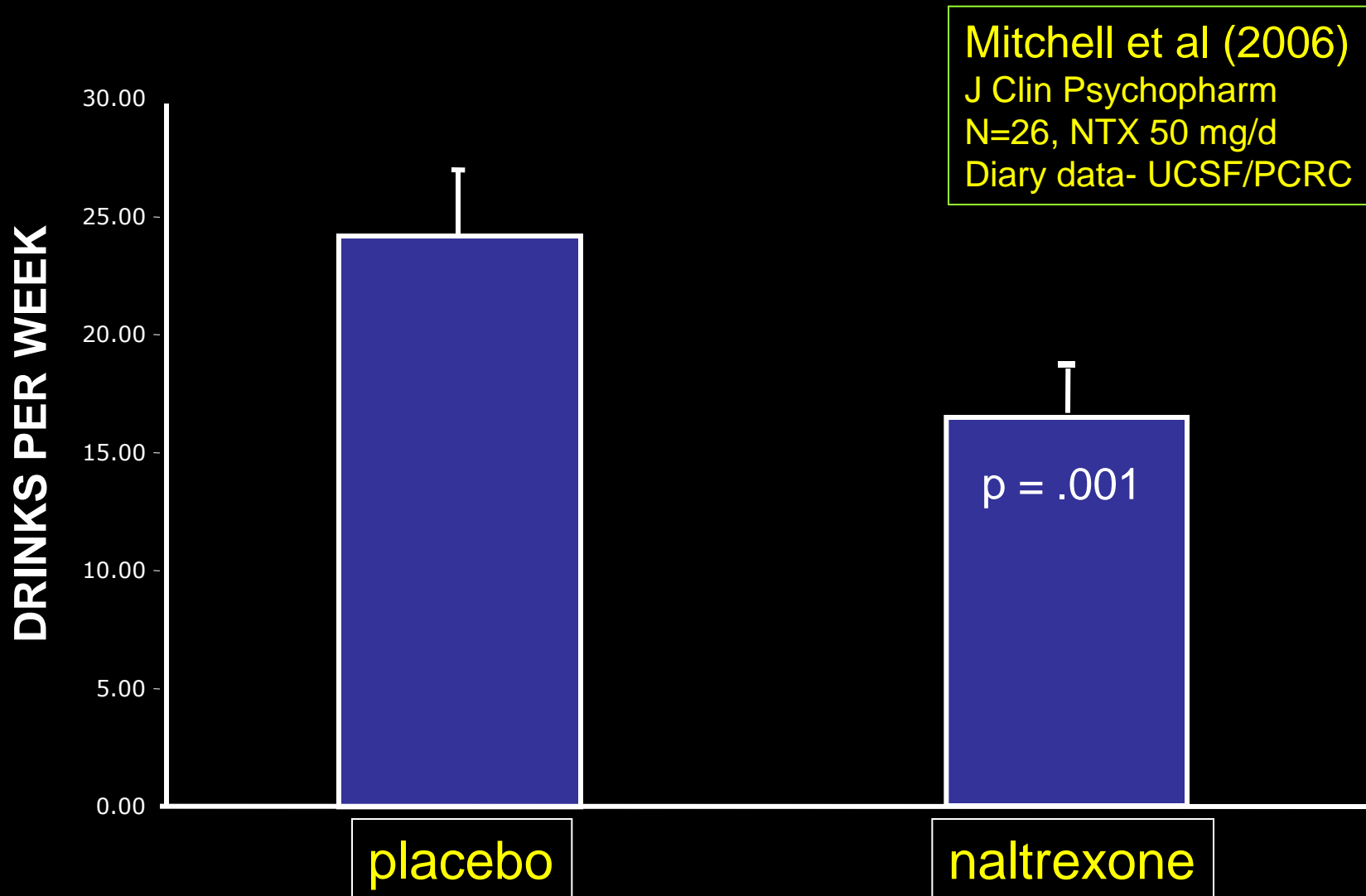
Sustained improvement in abstinent alcoholics is marginal

Table 4. Participants With ≥ 1 Heavy Drinking Day During Treatment*

	No. (%)		P Value
	Control	Intervention	
16 weeks treatment	Main Effects		
	Placebo (n = 618)	Acamprosate (n = 608)	
Acamprosate	433 (70.1)	423 (69.6)	.23
	Placebo (n = 612)	Naltrexone (n = 614)	
Naltrexone	437 (71.4)	419 (68.2)	.02
	No CBI (n = 607)	CBI (n = 619)	
CBI	423 (69.7)	433 (70.0)	.16

Anton, R. F. et al. (2006)
JAMA; 295: 2003-2017.

Naltrexone very 'effective' in active drinkers



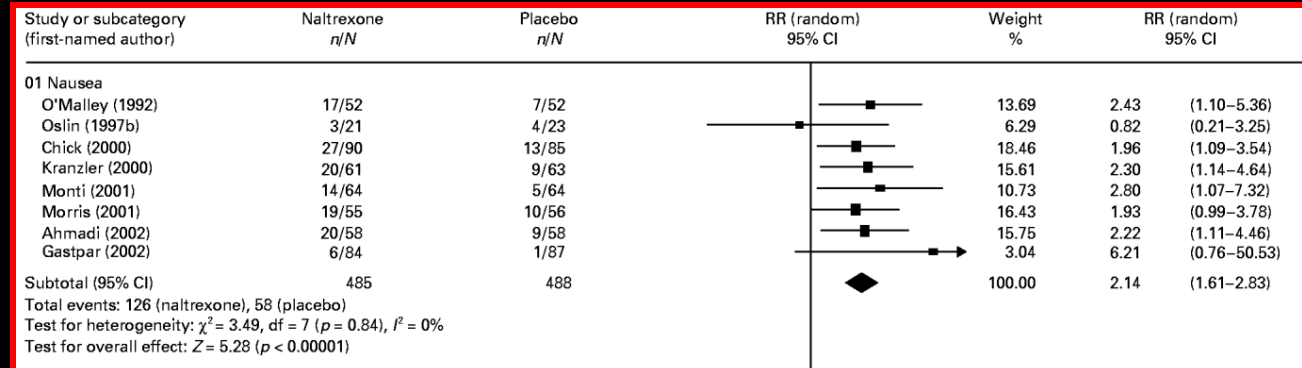
Naltrexone

- Significantly reduces relapse rates at one month. (Relapse = return to abuse or dependence)
- Return to drinking not affected
- Naltrexone better at reducing amount consumed than maintaining abstinence.
- Big problem is patient dropout

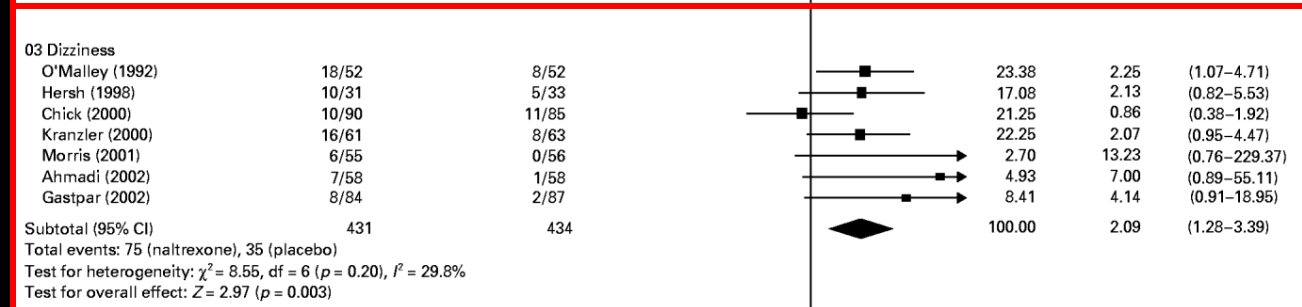
Naltrexone Side Effects

(May explain 36% dropout rate in clinical studies)

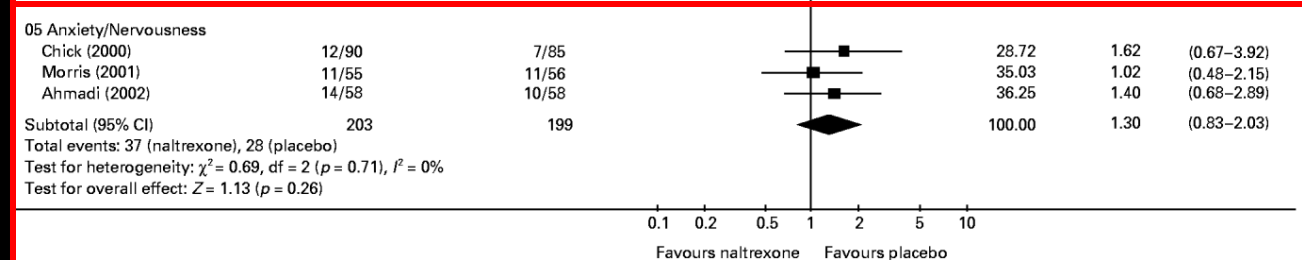
Nausea



Dizziness



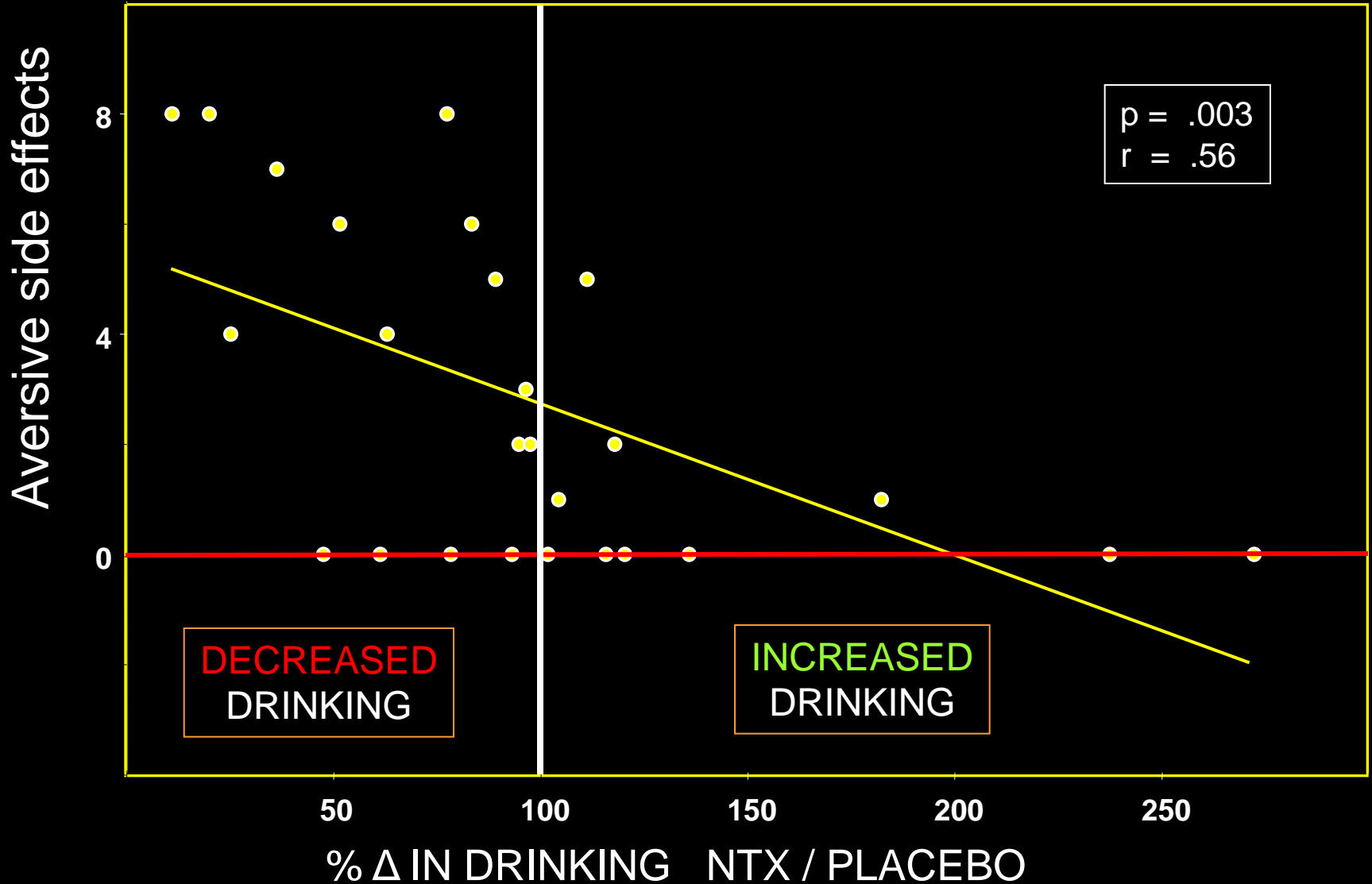
Anxiety



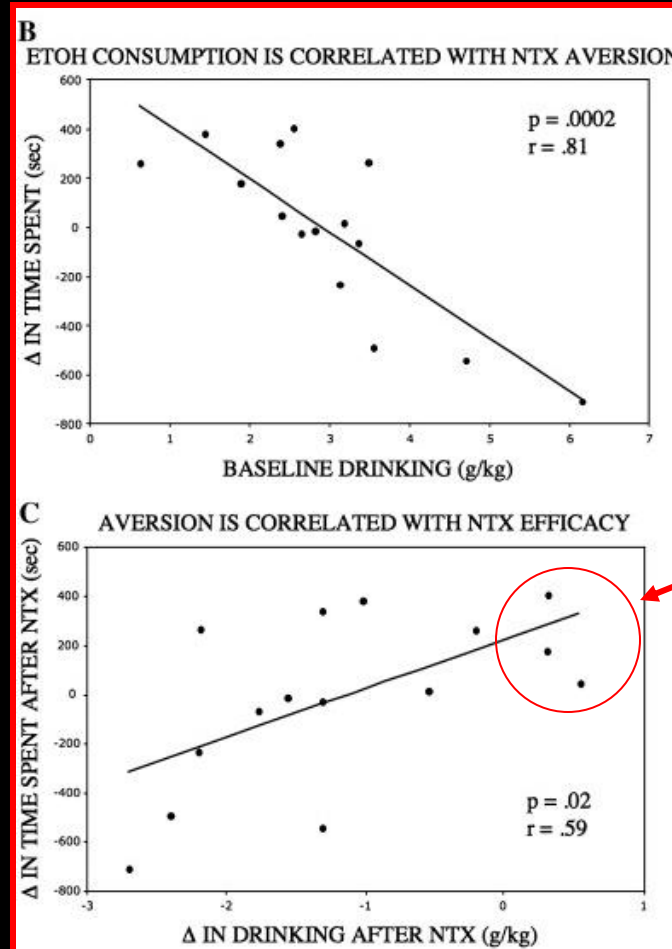
Naltrexone is effective but limited

- Proof of principle: endogenous opioids promote ethanol consumption

NTX effect is bidirectional in actively drinking human alcoholics



Naltrexone also has bidirectional effects in chronically drinking rats



Some rats like
NTX and it makes
them drink more

Mitchell et al
Neurobiology of
Disease, 2008.

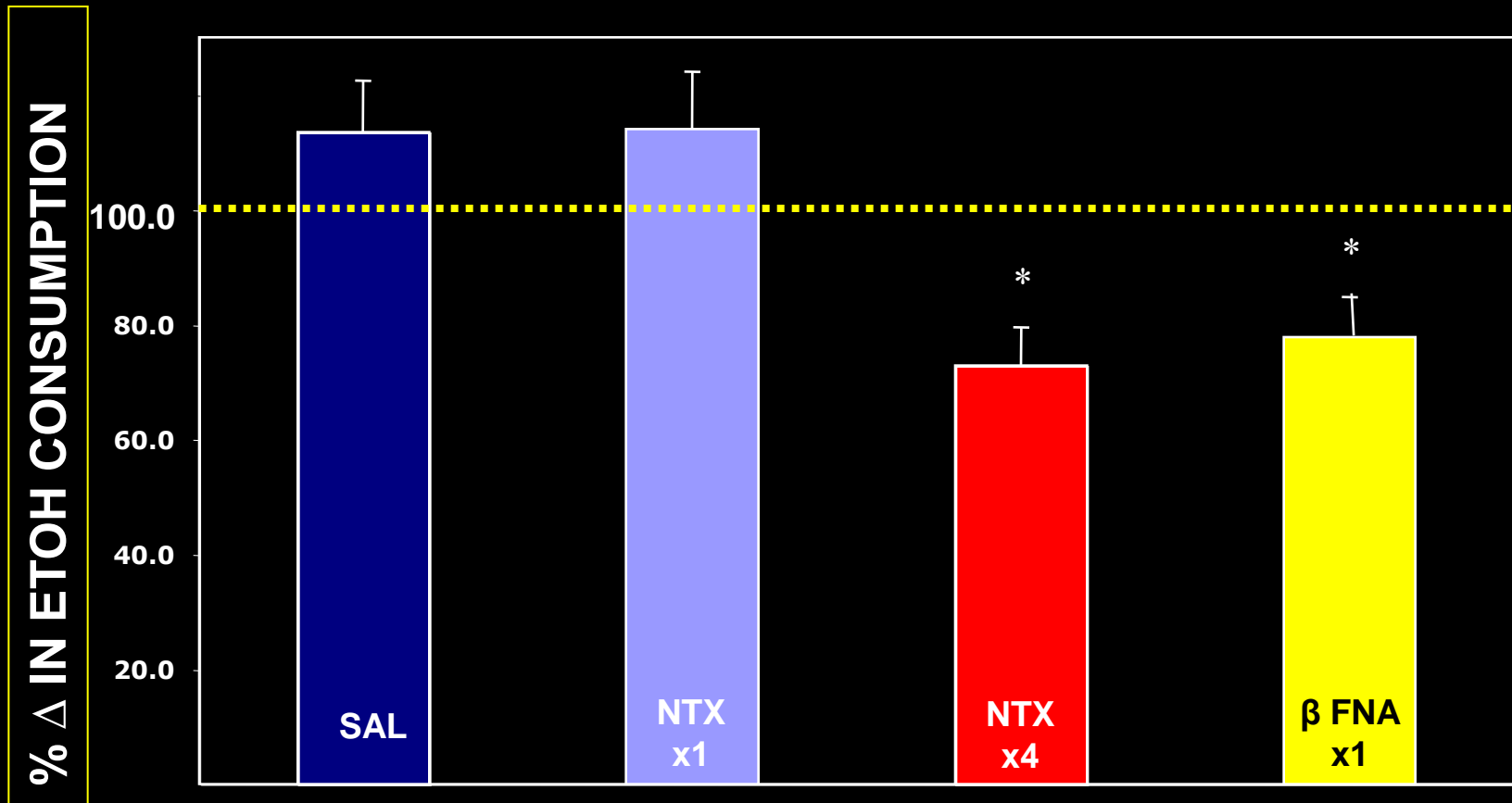
Naltrexone

- Why does it work better when individuals are actively drinking?
- How can it reduce drinking in some rats and increase it in others?

Naltrexone blocks three different opioid receptors

- Opioid Receptor Family
 - **Mu** (MOR, reward; antagonist reduces drinking)
 - **Kappa** (KOR, antagonist-- mixed)
 - **Delta** (DOR, antagonists-- mixed)
- Naltrexone is a non-selective antagonist
- Would a more selective opioid antagonist
 - Be more effective?
 - Have fewer aversive side effects (and reduce drop out rate)?

MOR selective antagonist β -FNA = NTX



RATS

J. Mitchell
Unpublished

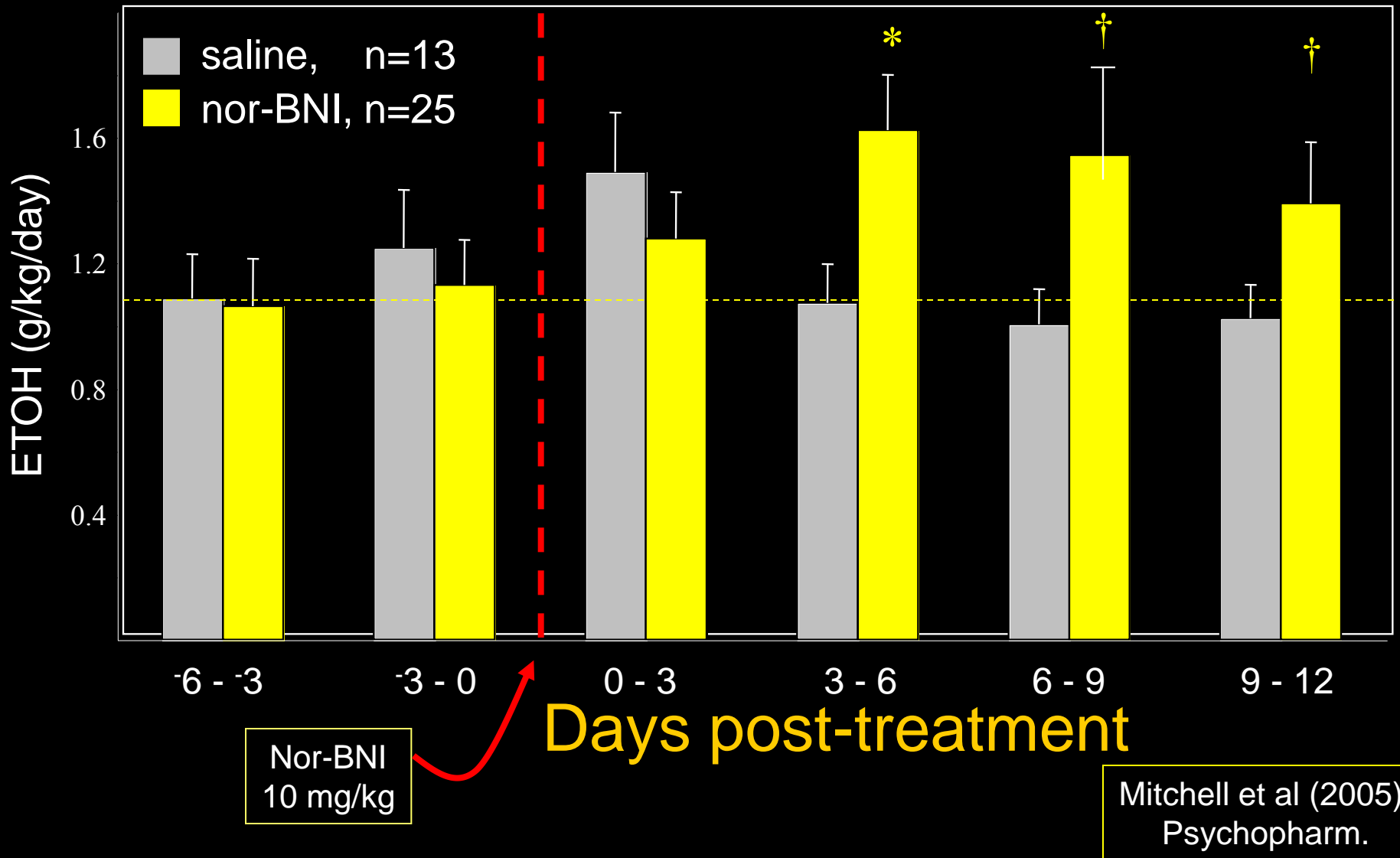
■ = Saline, n = 10, p > .05

■ = NTX, 1 mg/kg n = 14, p > .05

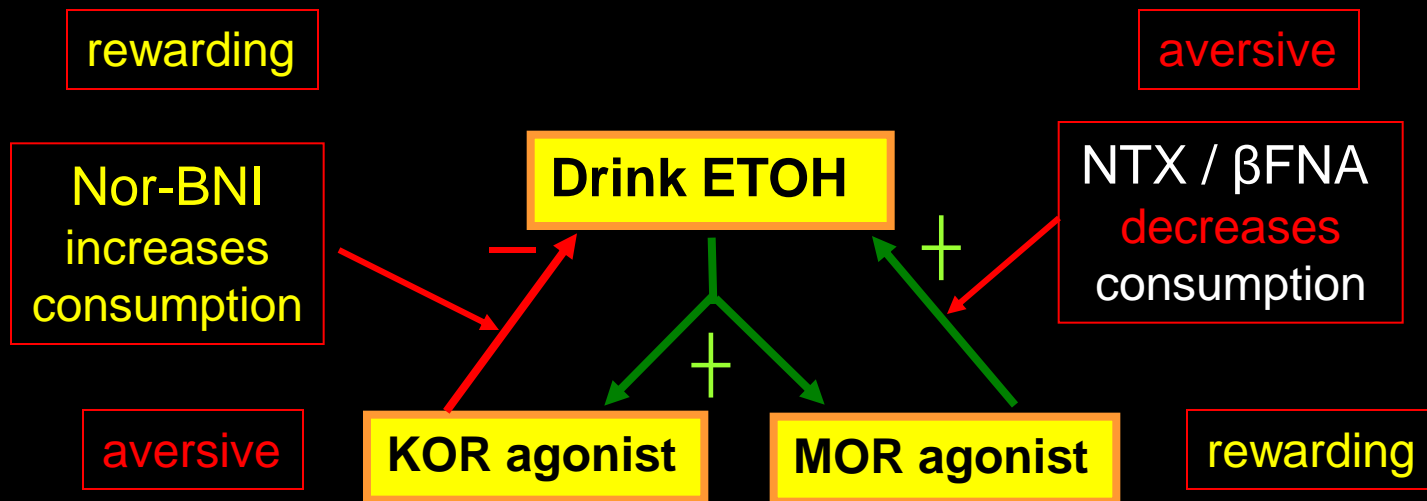
■ = NTX, 1 mg/kg n = 14, p = .002

■ = β -FNA, 1 mg/kg n = 14, p = .003

KOR selective antagonist *increases* ETOH consumption in rats



Hypothesis: MOR promotes, KOR inhibits ethanol intake



Hypothesis: active drinking leads to release of endogenous opioids that promote (MOR) and/or inhibit (KOR) ethanol consumption

Opioid Antagonists

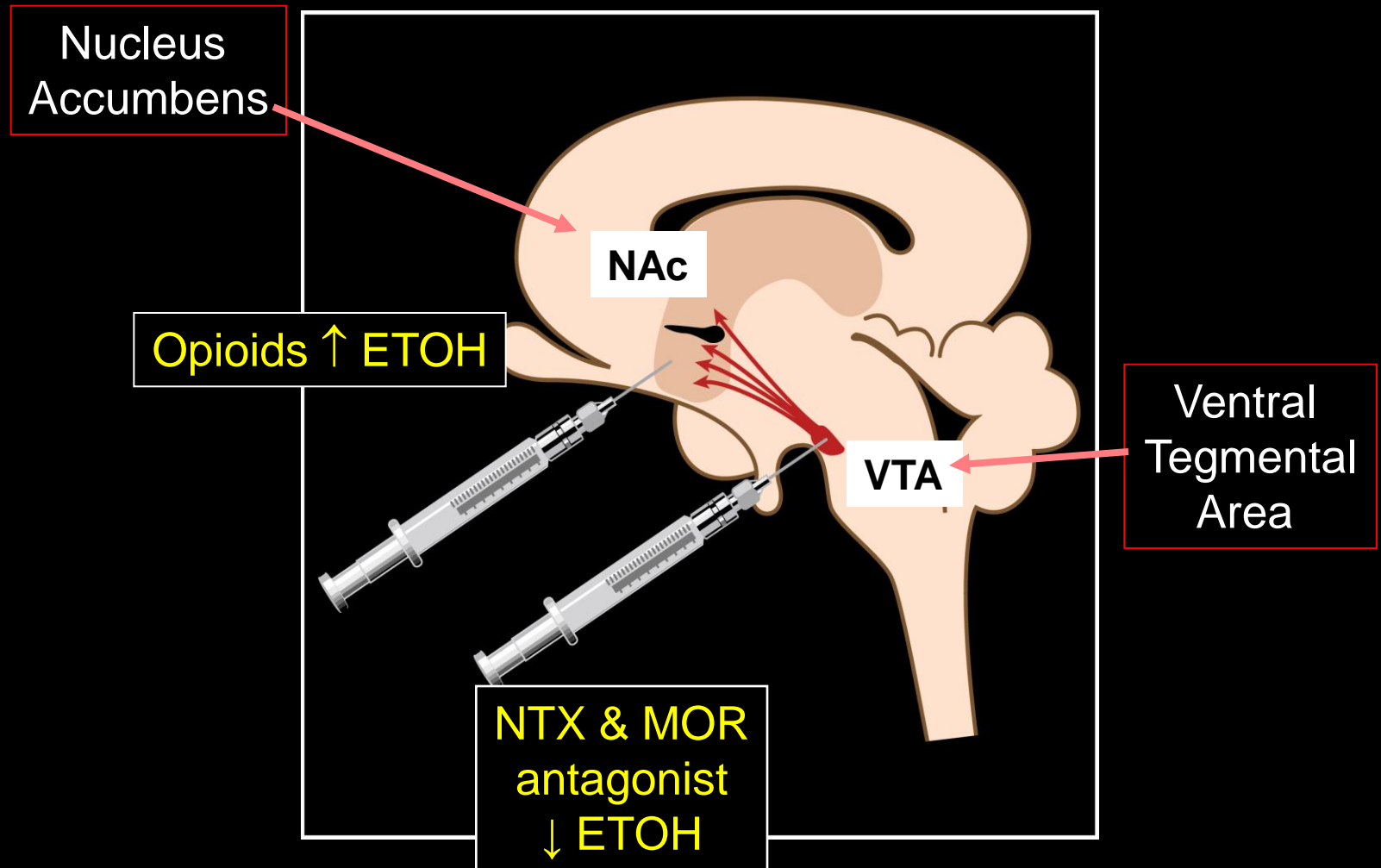
- Drinking releases endogenous opioids, required for the action of antagonists
- MOR selective antagonist should be better than Naltrexone (will not increase drinking by blocking KOR).
- KOR antagonists can increase drinking
- What about the delta opioid receptor (DOR) ?

What do mechanistic studies
tell us about DOR?

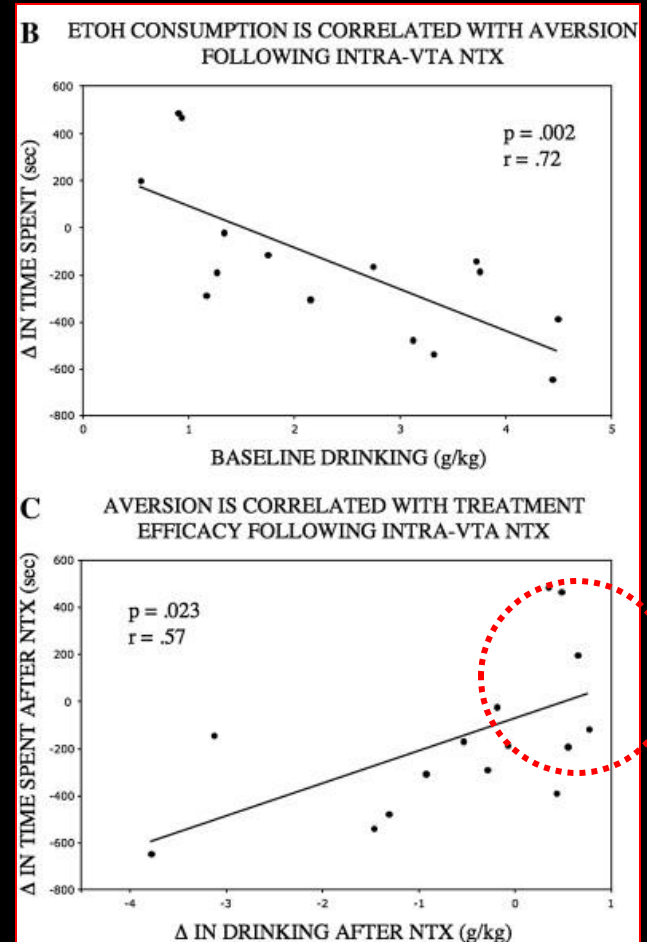
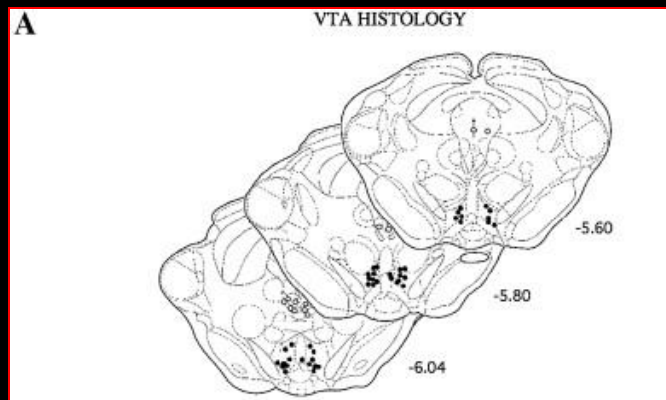
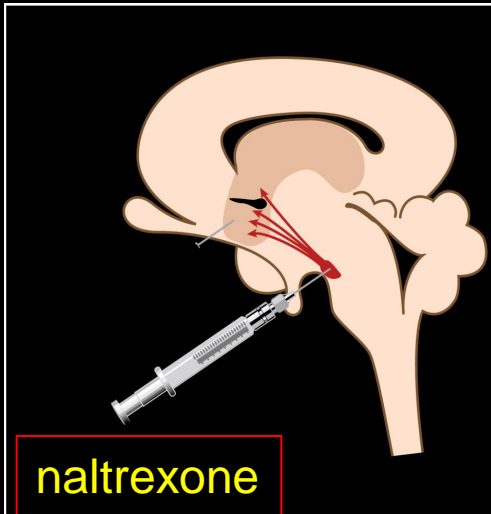
Where in the brain and how does naltrexone work?

- Find relevant circuit
- Determine synaptic mechanism (or mechanisms) of opioid/ethanol interaction

Mesolimbic circuit: target for opioid control of ethanol intake



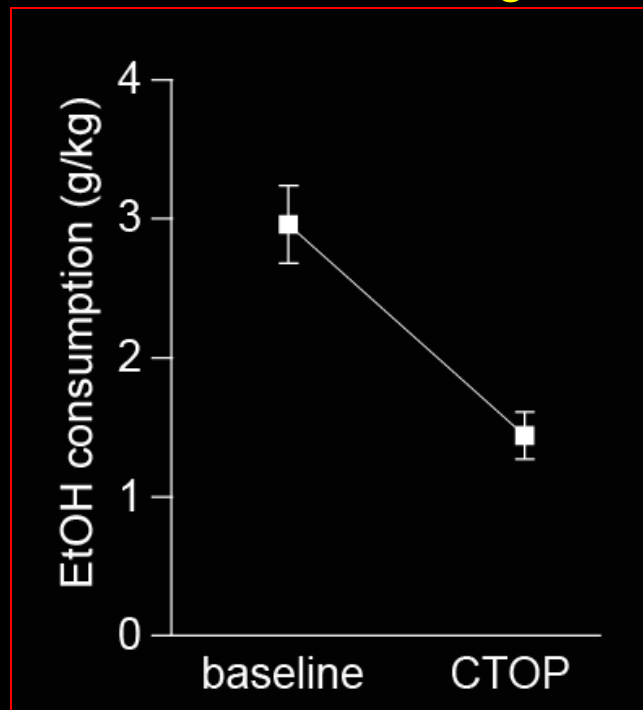
Naltrexone works in VTA to control ethanol consumption



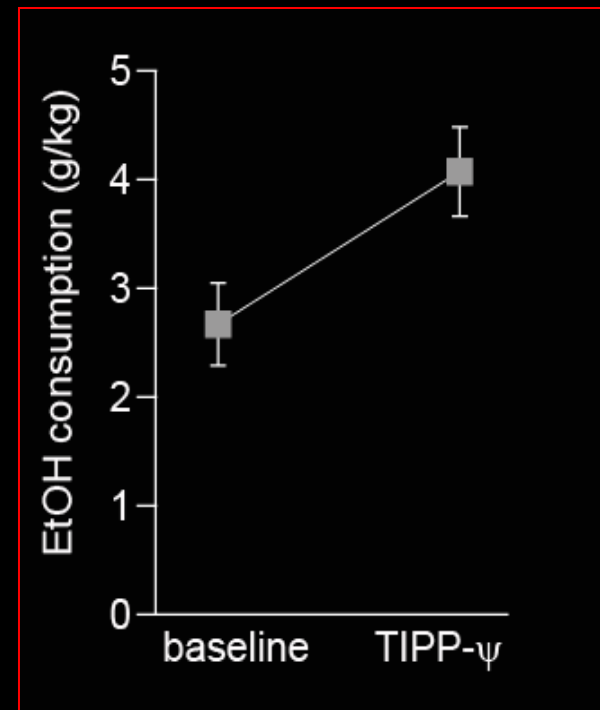
What do MOR and DOR selective antagonists in the VTA do?

In VTA MOR antagonists reduce and DOR antagonists increase drinking

MOR selective antagonist

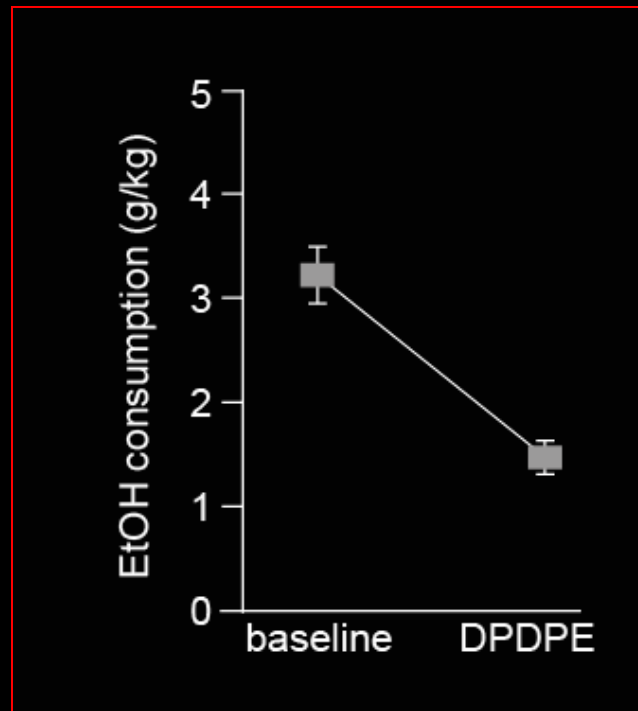


DOR selective antagonist



Margolis et al, J. Neurosci 2008

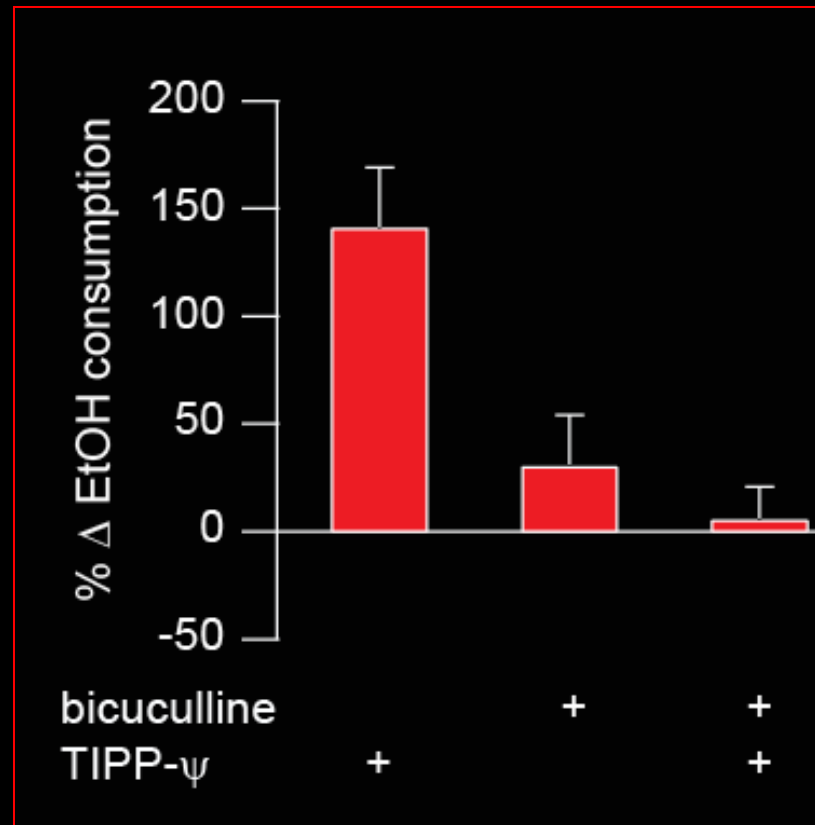
DOR selective agonist in VTA decreases drinking



Margolis et al, J. Neurosci 2008

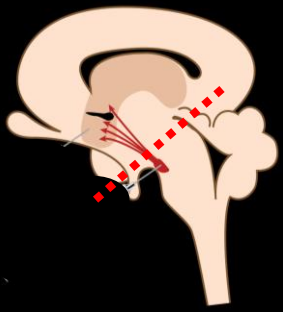
How does DOR act in the VTA to inhibit ethanol consumption?

When GABA-A signaling is blocked, TIPP Ψ does not increase ethanol consumption



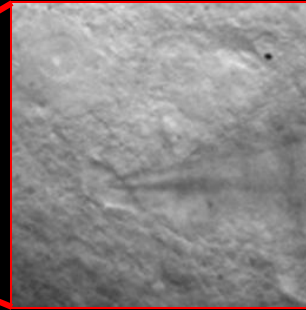
Therefore DOR works on GABA
release in VTA

VTA in vitro recording of GABA_A IPSCs

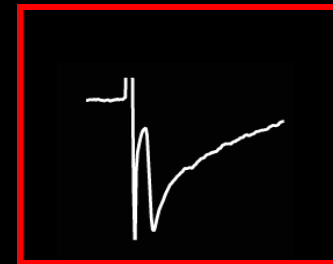


GABA-A IPSCs isolated with:

- DNQX (10 μ M)
- strychnine (1 μ M)
- sulpiride (10 μ M)

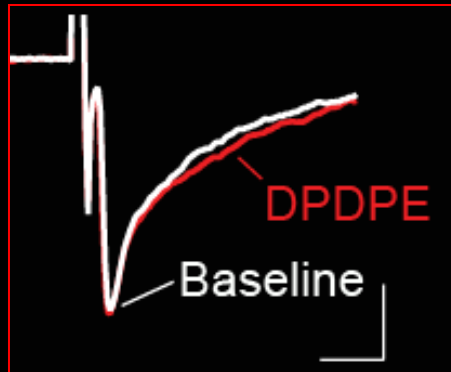


Evoked
GABA IPSC

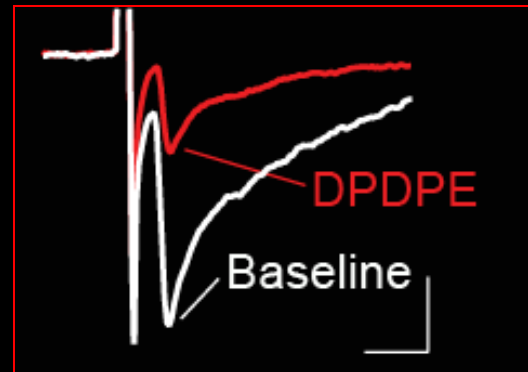


DOR agonist in VTA inhibits GABA release

Non drinking rats



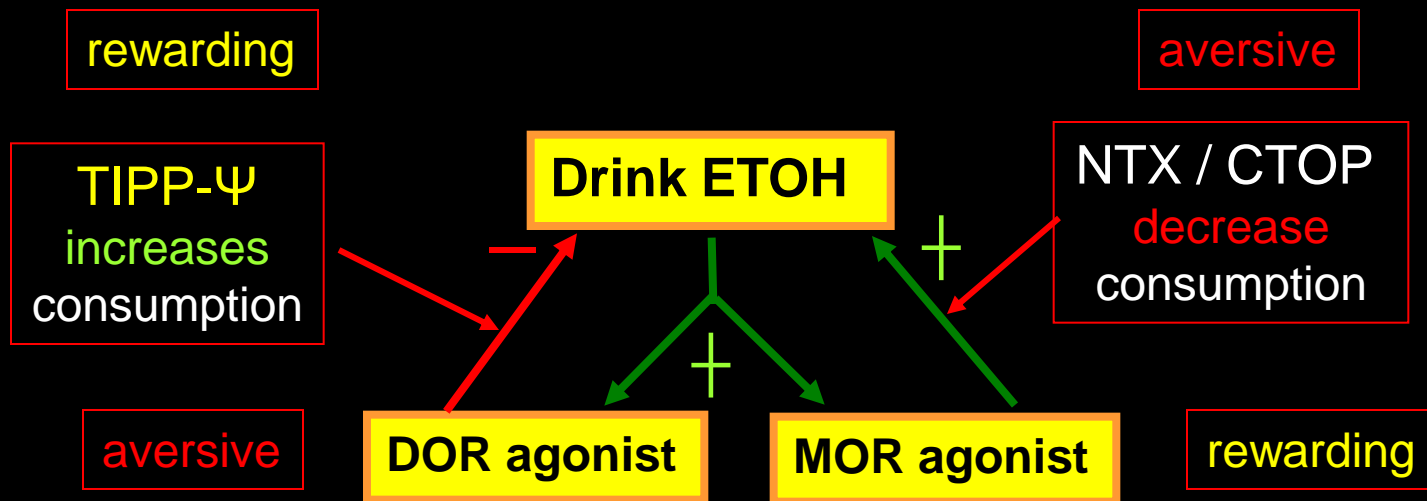
Active drinkers



DOR active on VTA
GABA terminals
only after rats have
Been drinking



Summary: MOR promotes, DOR inhibits ethanol intake



Hypothesis: active drinking leads to release of endogenous opioids that promote (MOR) and/or inhibit (DOR) ethanol consumption

Level of ethanol consumption
represents balance of MOR
enhancement and DOR
protection

Therapeutic implications:

Current use; future possibilities

- Naltrexone is most effective during active consumption.
- Naltrexone may **increase** consumption in some heavy drinkers through blockade of KOR & DOR protective effects.
- A selective MOR antagonist would not increase consumption.
- A DOR **protective** effect emerges with steady drinking (in some rodents).
- A DOR agonist should add to the effectiveness of a MOR antagonist.

Summary

- Limitations of naltrexone revealed
 - Aversion correlates with treatment efficacy
 - Selective MOR antagonism = NTX (rats)
 - KOR antagonism increases drinking (rats) but KOR agonists cause dysphoria
 - DOR antagonism increases drinking (rats)
 - DOR agonist reduces drinking

Implications for drug and clinical treatment protocols

- Antagonists work best when subject is actively drinking because endogenous opioids are released (may not prevent relapse)
- Ethanol consumption leads to activation of DOR and protects some subjects from heavy drinking
- MOR antagonist/DOR agonist may be optimal opioid ligand combination to reduce drinking
- Agonists may be more effective in maintaining abstinence (not tested yet)

Thanks

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