

Important drug interactions in opioid-related deaths

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Declaration - No conflicts of interest

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Polydrug use by heroin users

Heroin addicts frequently take other drugs including

- **Alcohol**
- **Benzodiazepines**
- **Cocaine (speedballing)**
- **Pregabalin/gabapentin (gabapentinoids)**

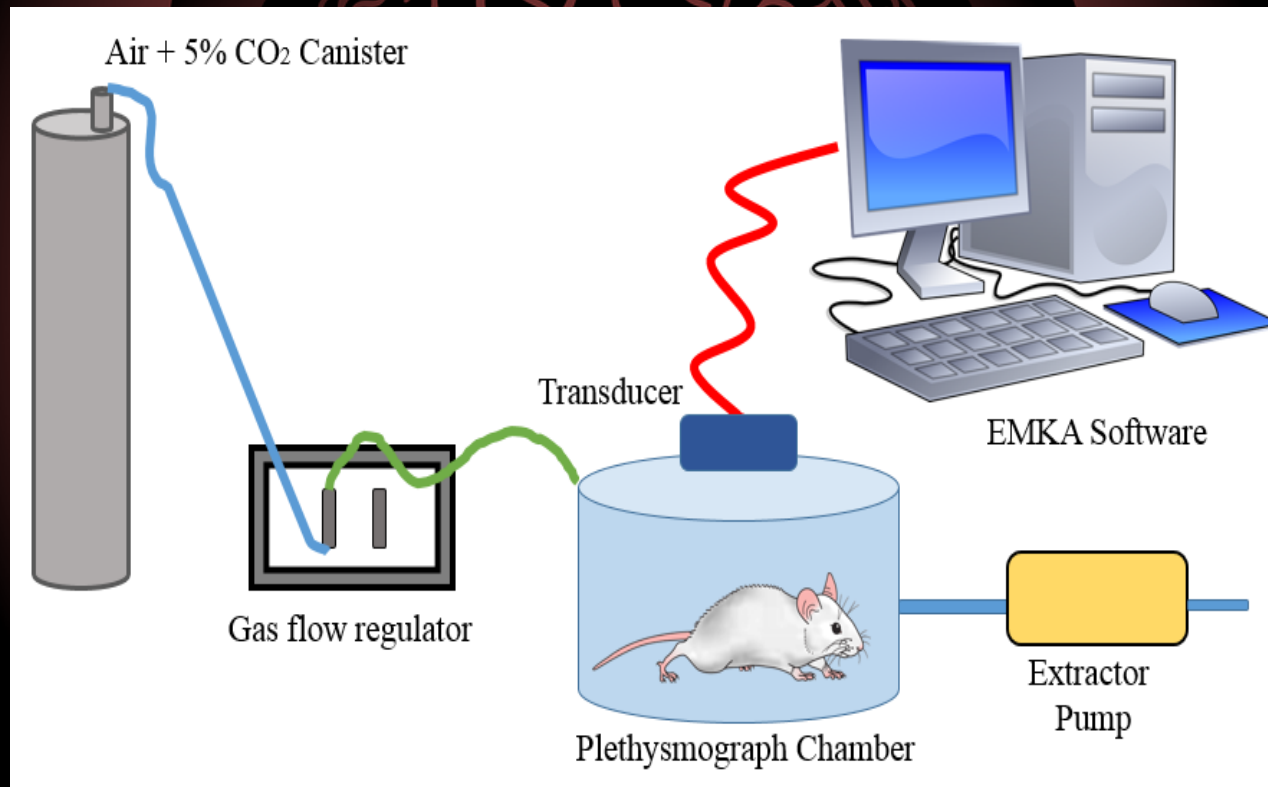
Do these drugs contribute to opioid overdose deaths and if so how?

Potential ways to enhance overdose

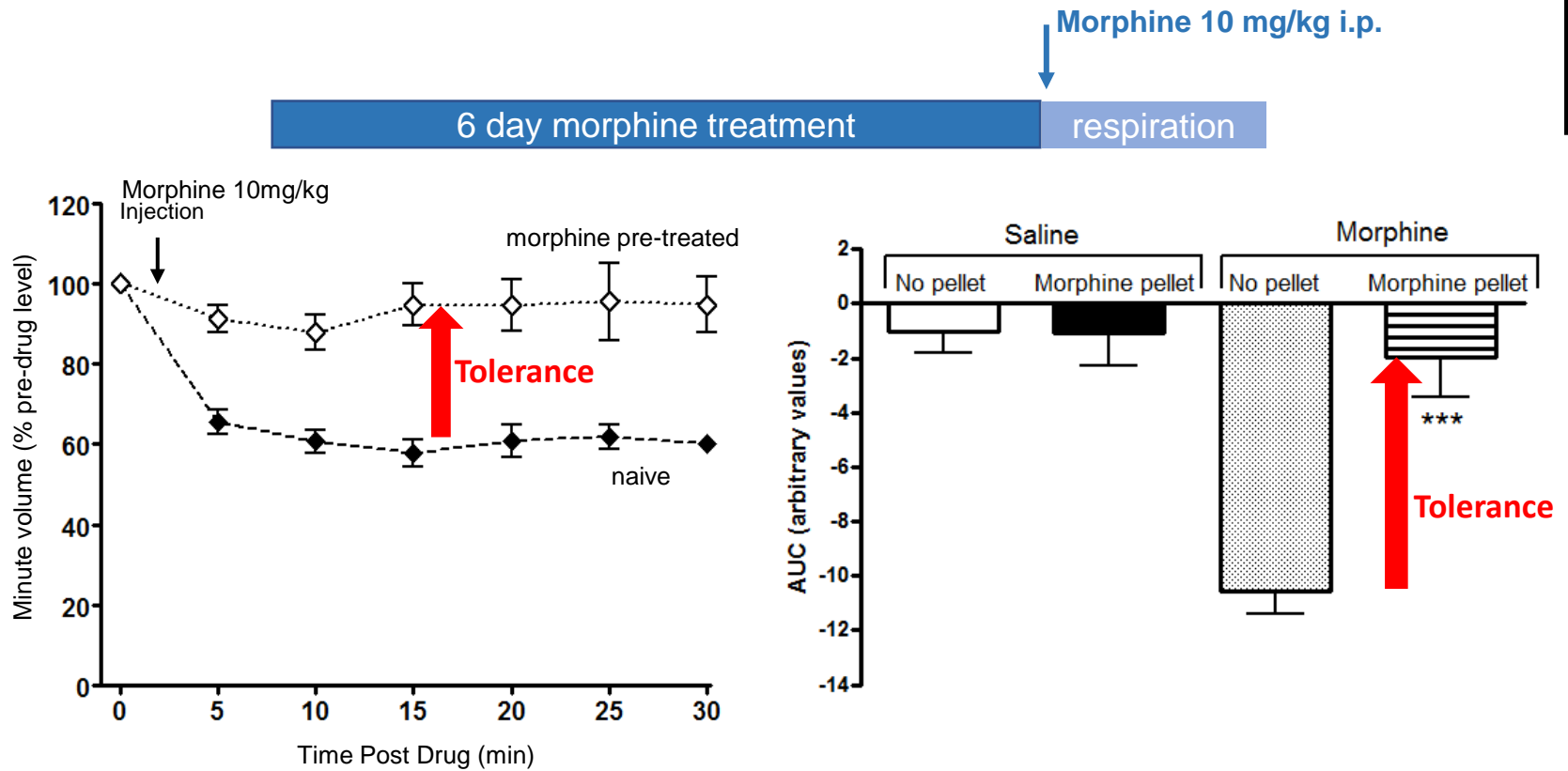
- Additive depressant effects?
- Synergistic effects?
- Reducing opioid tolerance?

Opioid overdose deaths result from respiratory depression

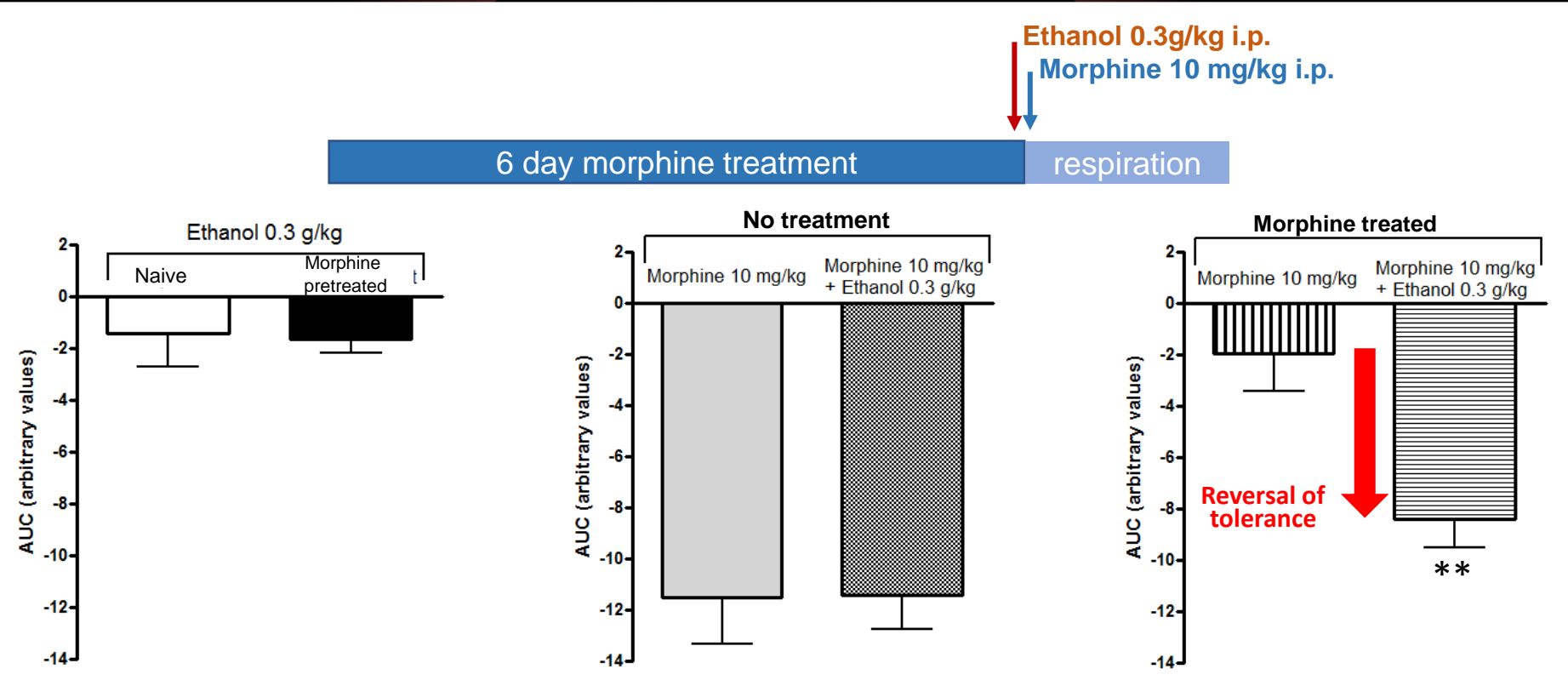
Monitoring mouse respiration



Tolerance to morphine depression of respiration



Tolerance to morphine respiratory depression: reversal by ethanol



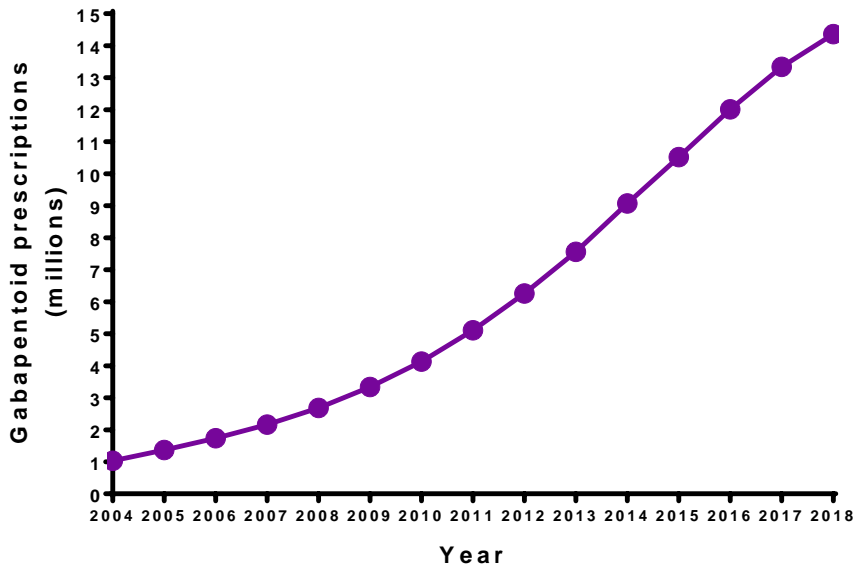
Low dose ethanol has no effect alone

Ethanol does not potentiate or summate with morphine in naïve animals

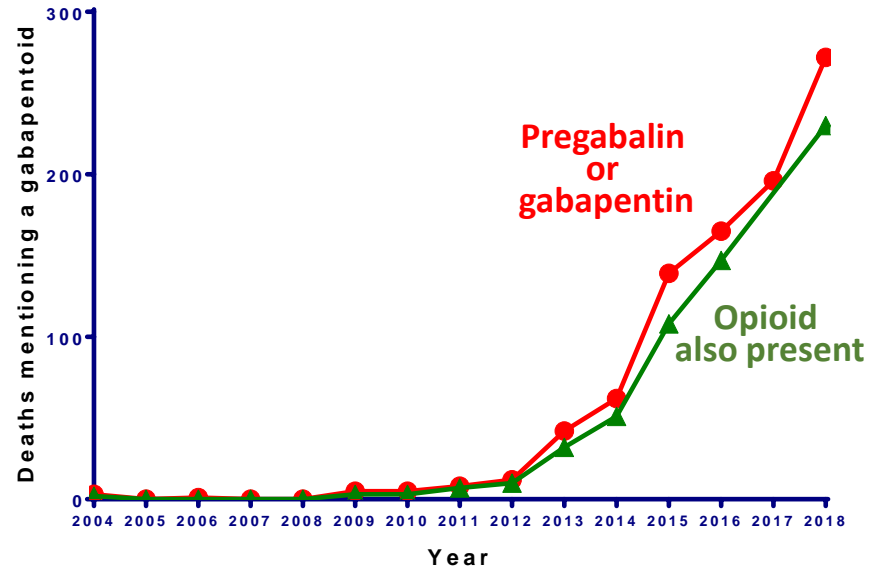
Low dose ethanol reverses tolerance

Gabapentinoid deaths

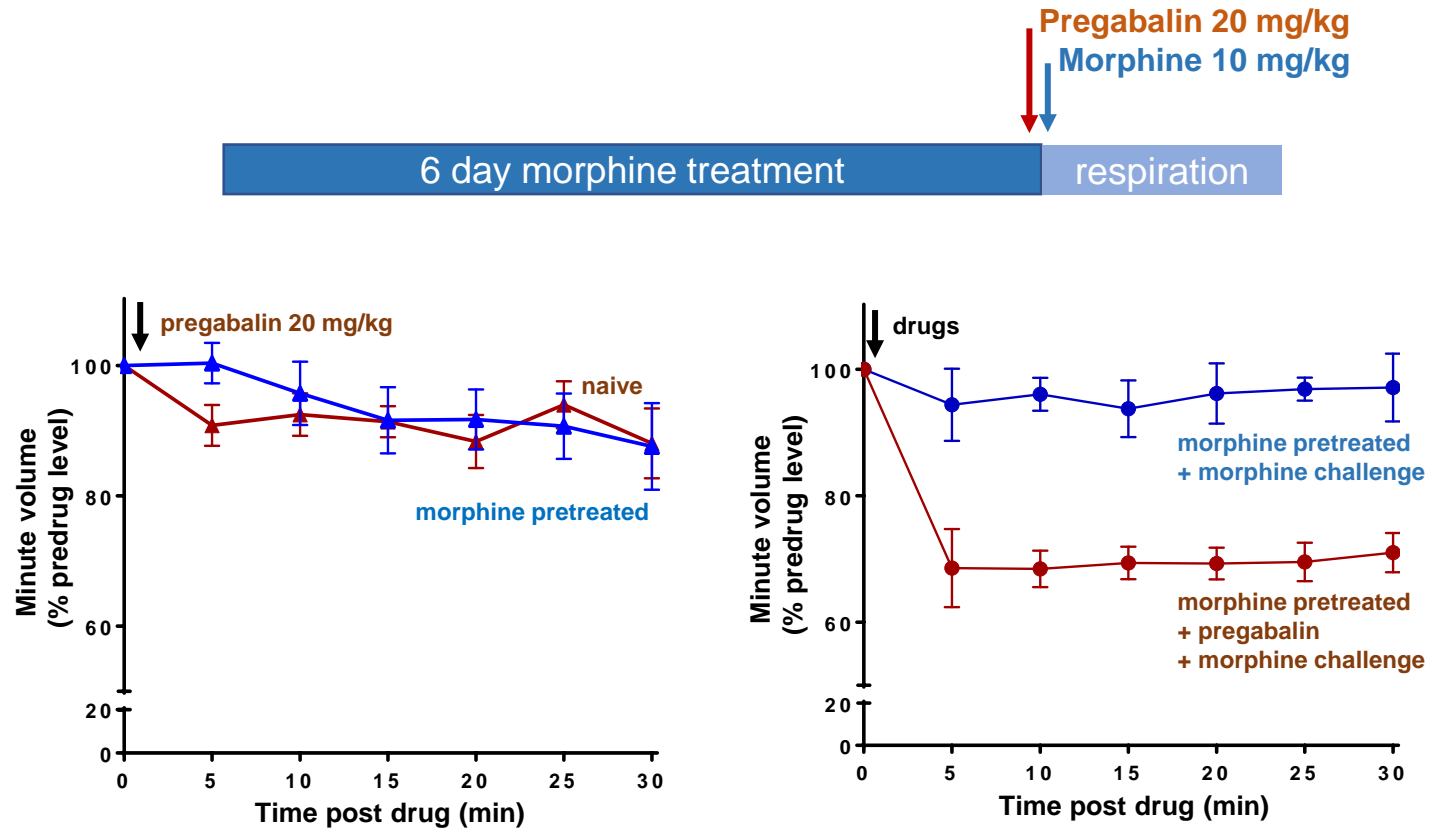
Primary care prescriptions (England)



Drug overdose deaths involving gabapentinoids (England and Wales)



Pregabalin reverses morphine tolerance



Acute ethanol and pregabalin

reverse tolerance induced by

- morphine
- oxycodone

do NOT reverse tolerance induced by

- methadone

do NOT reverse protection induced by prolonged treatment with

- buprenorphine

Chronic ethanol

prevents the development of morphine tolerance

μ opioid receptor activation

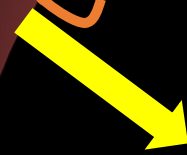
Methadone



μ -opioid receptors

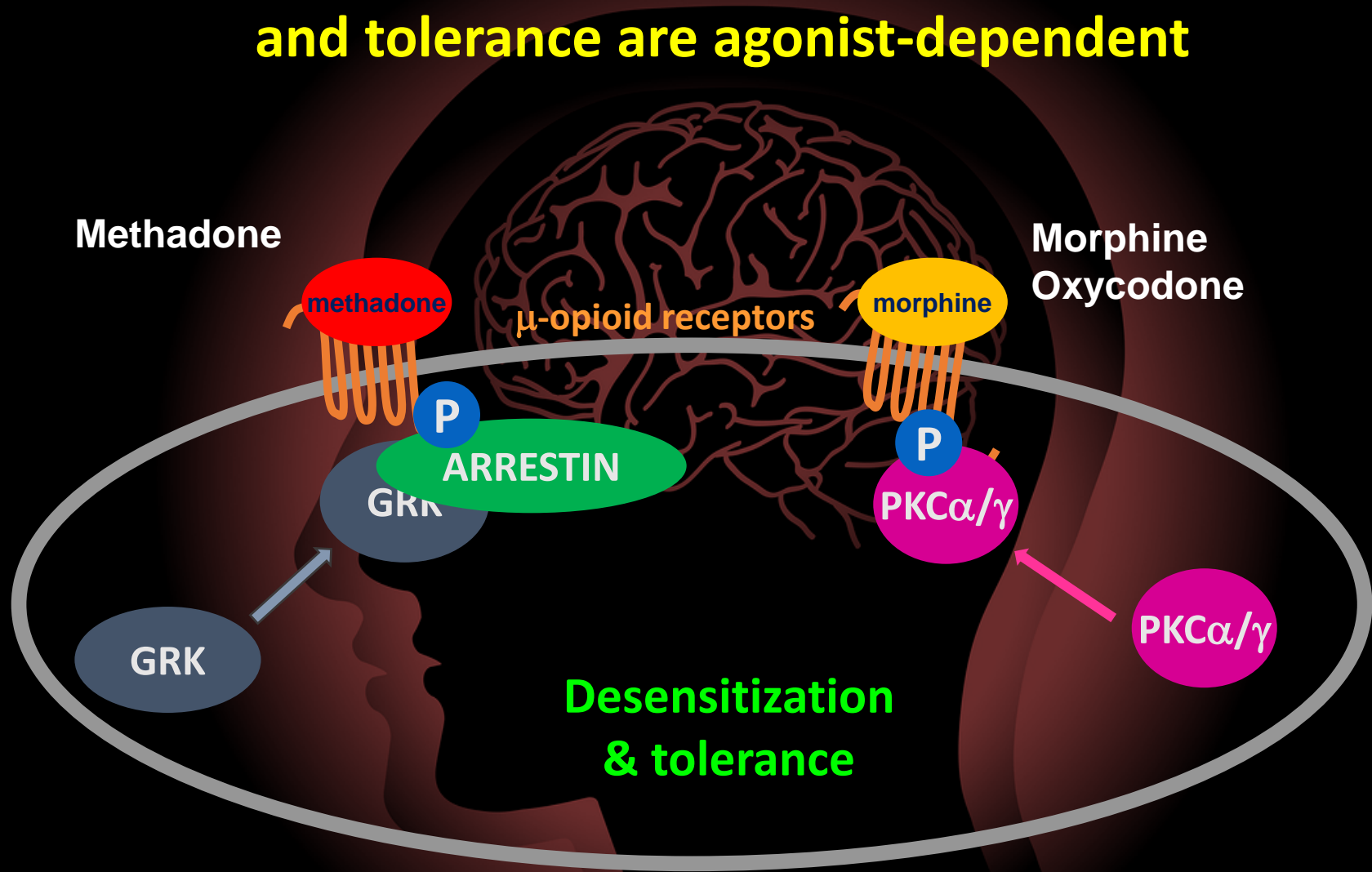


Morphine
Oxycodone

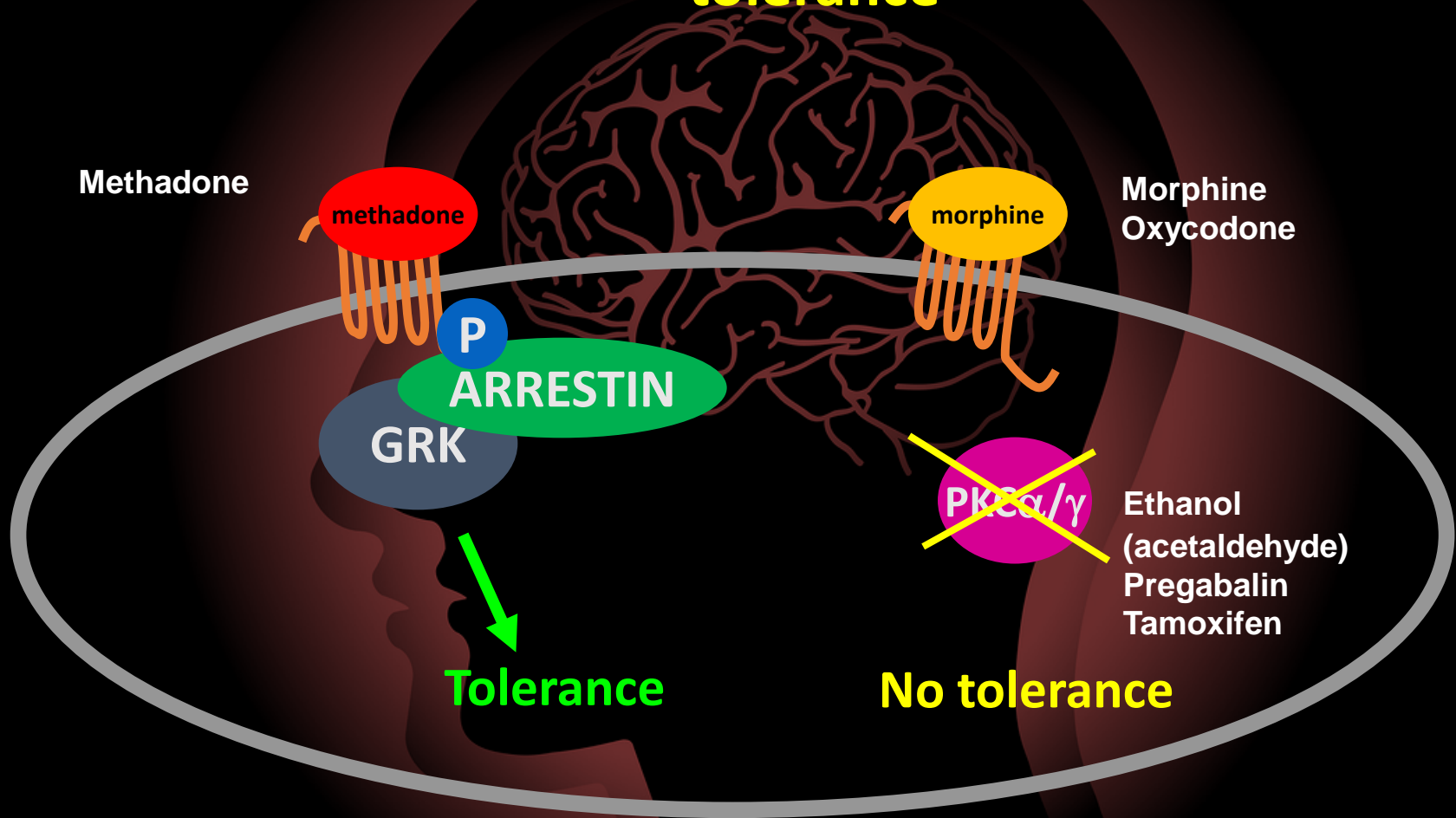


Signalling

Mechanism of μ -opioid receptor desensitization and tolerance are agonist-dependent



Inhibition of PKC reduces morphine/oxycodone tolerance



Take home message

Alcohol and pregabalin reduce tolerance to morphine/oxycodone depression of respiration and thus increase the likelihood of overdose

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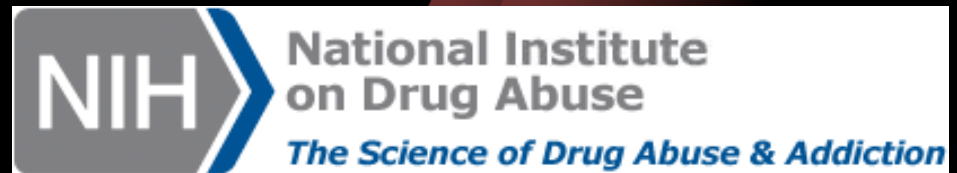
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Ethanol does not reverse the effect of chronic methadone or buprenorphine

