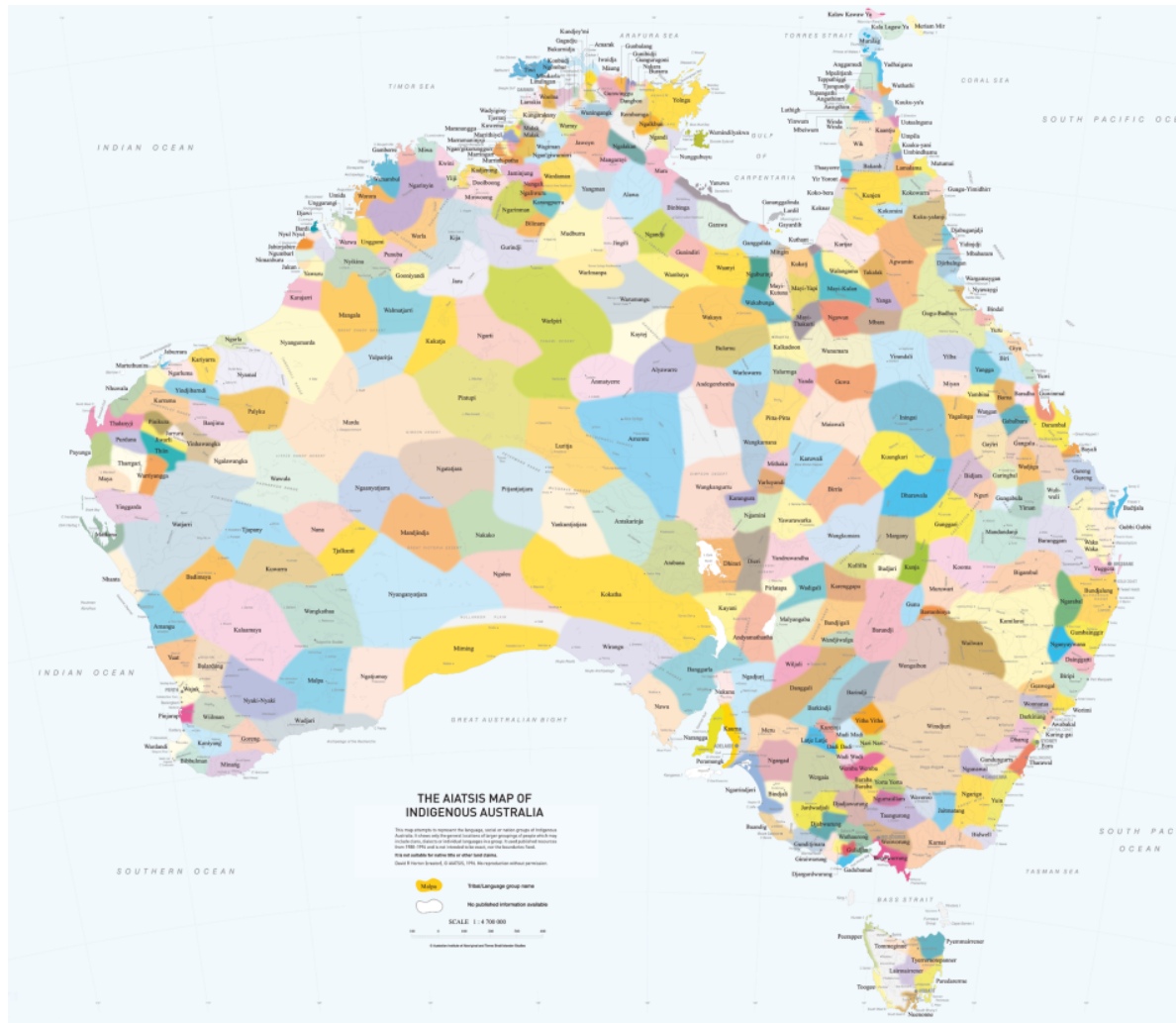


Welcome to today's Insight / APSAD webinar.

We'll be starting a little after 10am (QLD time).

- Use the chat icon for all questions and comments – *select All panelists and attendees.*
- If you are experiencing other problems or require further technical assistance call Zoom on **1800 768 027.**
- A pdf version of today's presentation will be available soon in the chat window.
- A recording of this webinar will be available on our YouTube channel in the coming weeks.





We acknowledge the Traditional Owners of the land on which this event takes place and pay respect to Elders past and present.

This map attempts to represent the language, social or nation groups of Aboriginal Australia. It shows only the general locations of larger groupings of people which may include clans, dialects or individual languages in a group. It used published resources from 1988-1994 and is not intended to be exact, nor the boundaries fixed. It is not suitable for native title or other land claims. David R Horton (creator), © AIATSIS, 1996. No reproduction without permission. To purchase a print version visit: www.aiatsis.ashop.com.au/



Metro North Hospital and Health Service *Putting people first*

Insight / APSAD webinar 17th March 2021

Gabapentinoids

Assoc Prof Mark Daglish
Director of Addiction Psychiatry, RBWH

Conflicts of Interest

I have received speaker's fees and travel from Indivior, Lundbeck, Janssen, Servier, Lilly

I am / have been on advisory boards for Indivior, Mundipharma and Lundbeck

I have been a site investigator for trials sponsored by Pfizer and Organon (now MSD)

Outline



Introduction to Gabapentinoids and Pharmacology



Current uses of gabapentinoids

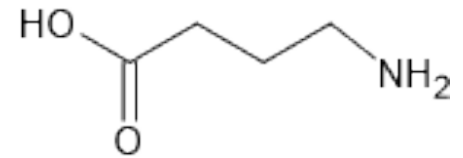


Harms

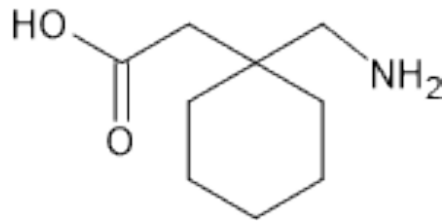


Possible benefits & future uses

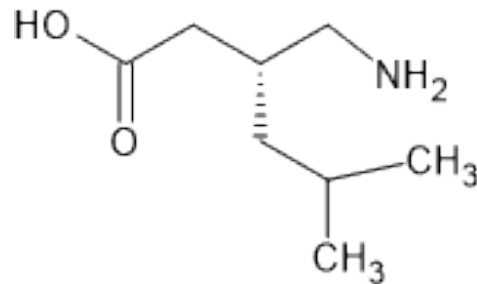
Gabapentinoids



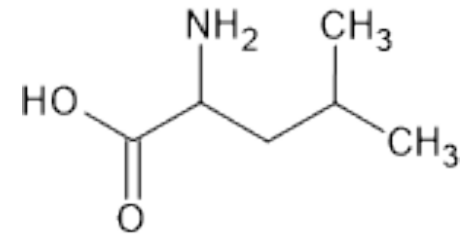
GABA



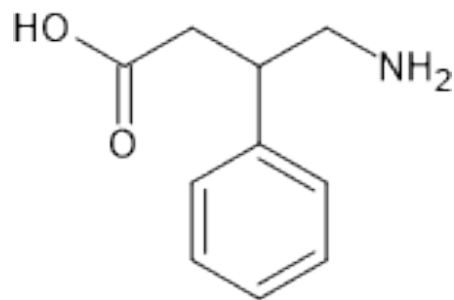
Gabapentin



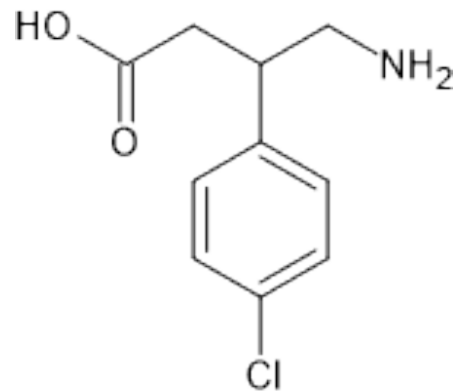
Pregabalin



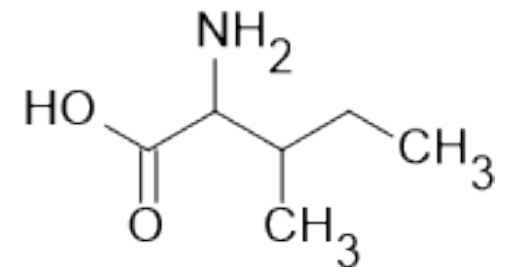
Leucine



Phenibut



Baclofen



Isoleucine

Gabapentinoids

Pregabalin, gabapentin, phenibut, (baclofen)

Short half-life meds (5-7 hours)

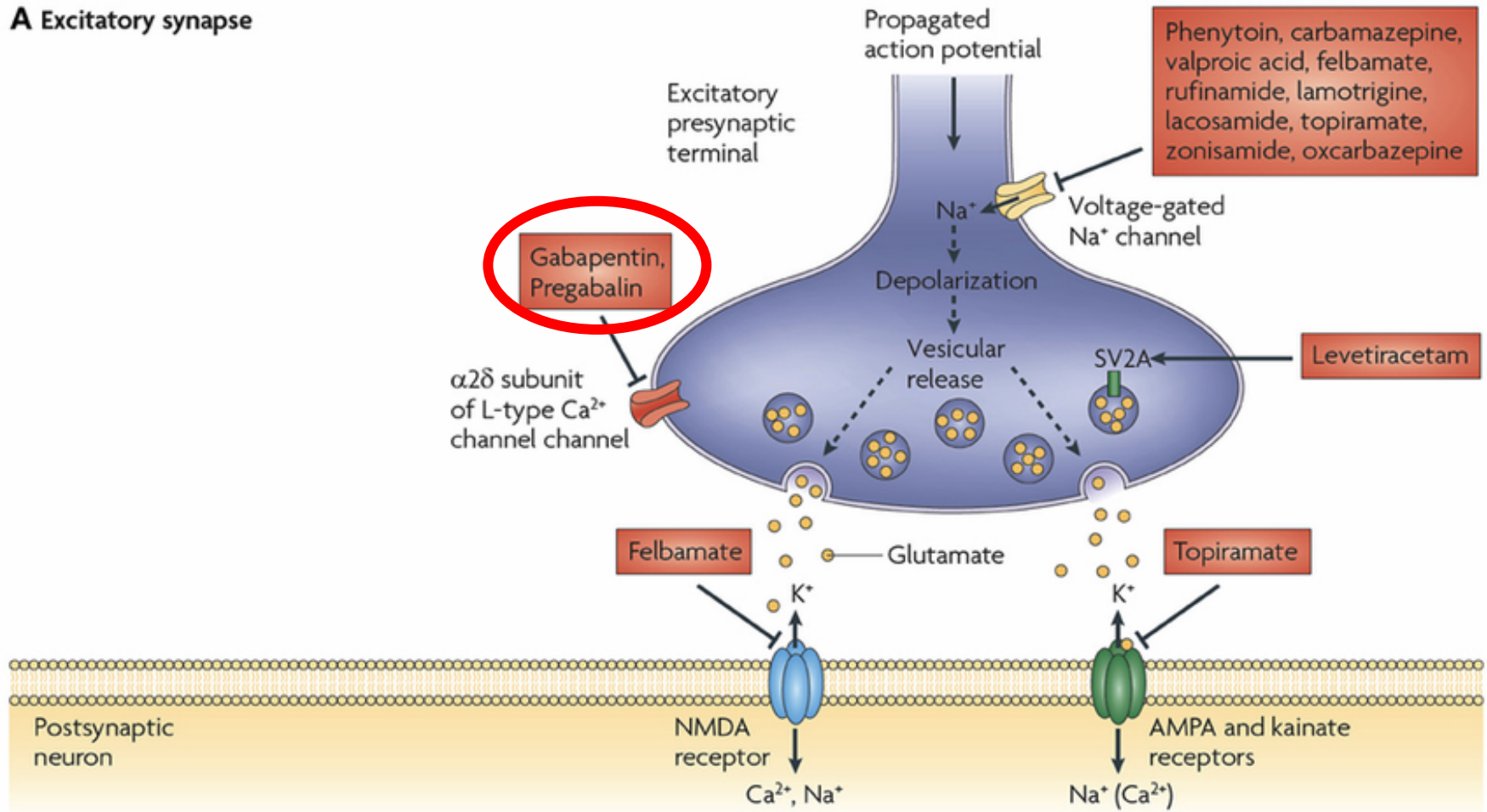
Plasma peak ~ 1-3 hours, CSF peak ~ 6-8 hours

Oral bioavailability limited for gabapentin due to saturable active transport mechanism for gut absorption

Morphine increased bioavailability of gabapentin (by slowing gut transit time)

Gabapentinoid Pharmacology

A Excitatory synapse



Gabapentinoids

Pregabalin

PBS indications:

- Authority (streamlined)
 - Neuropathic pain

TGA approved for:

- Neuropathic pain (refractory to other drugs)
- Epilepsy – adjunct in partial seizures

Gabapentin

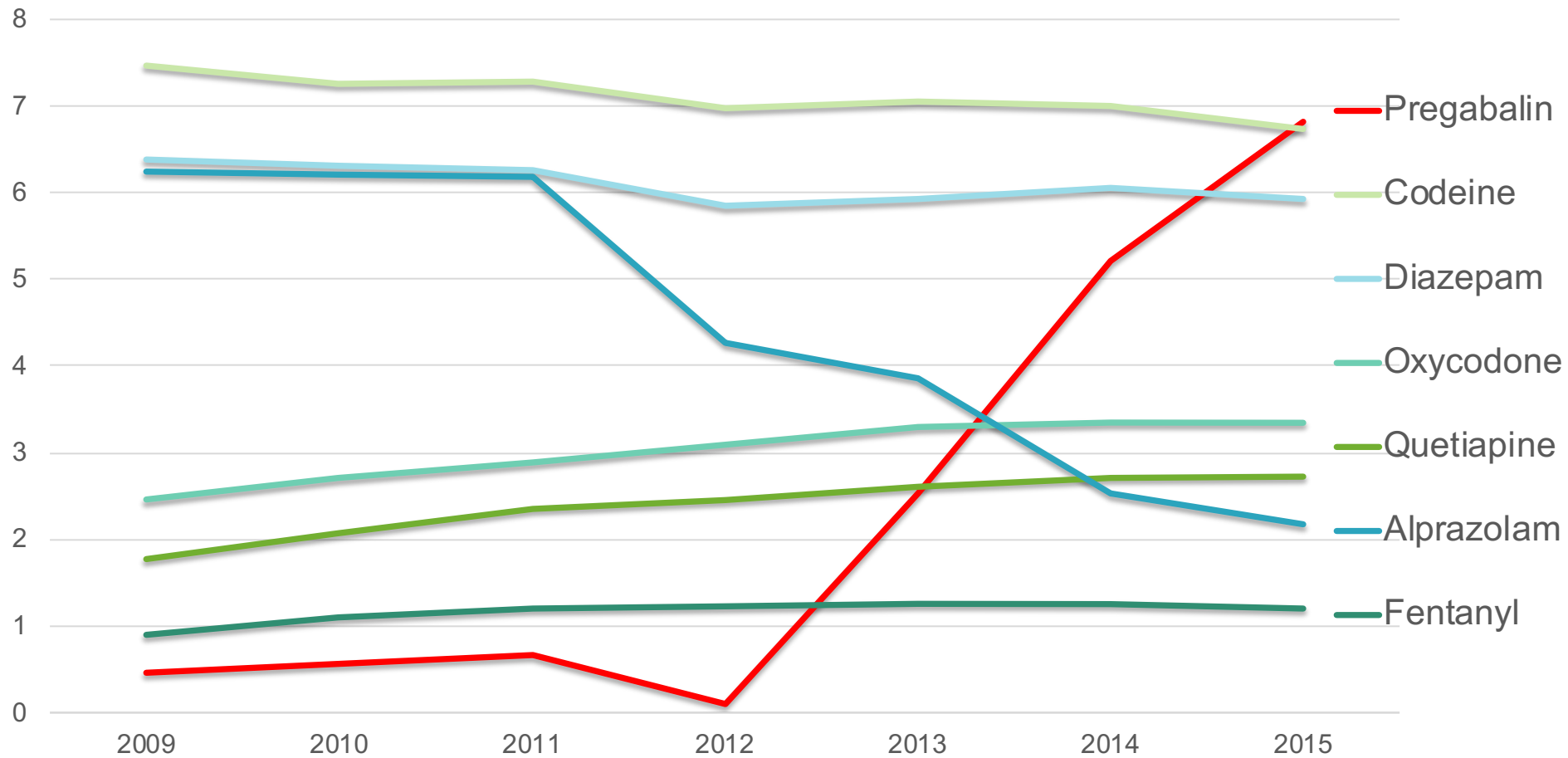
PBS indications:

- Authority (streamlined)
 - Partial epileptic seizures
- Authority (Repat)
 - Refractory neuropathic pain

TGA approved for:

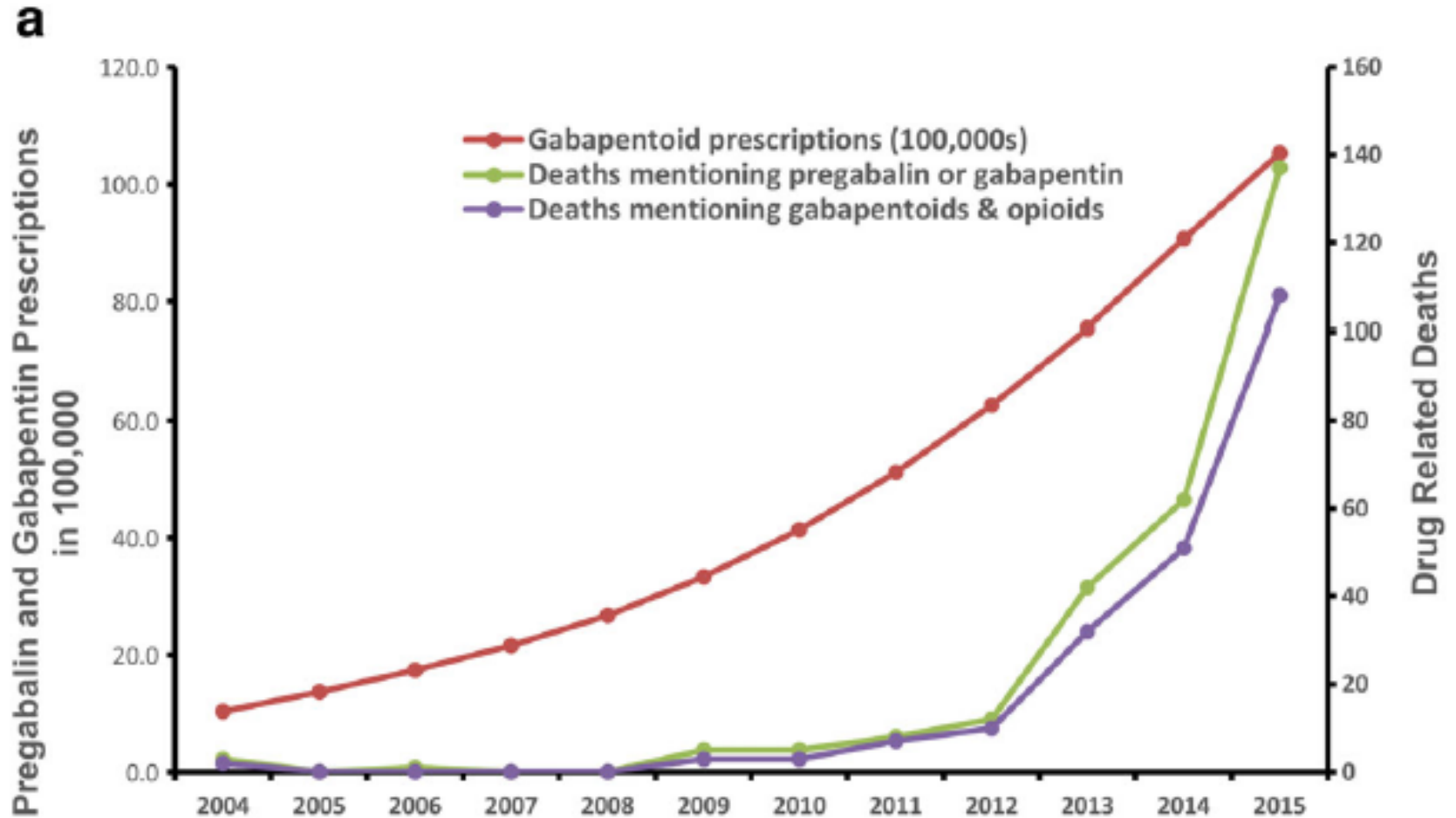
- Partial seizures
- Neuropathic pain

Prescription trends (2009-15)



ASM 2015 data

Pregabalin & opioids (in humans)



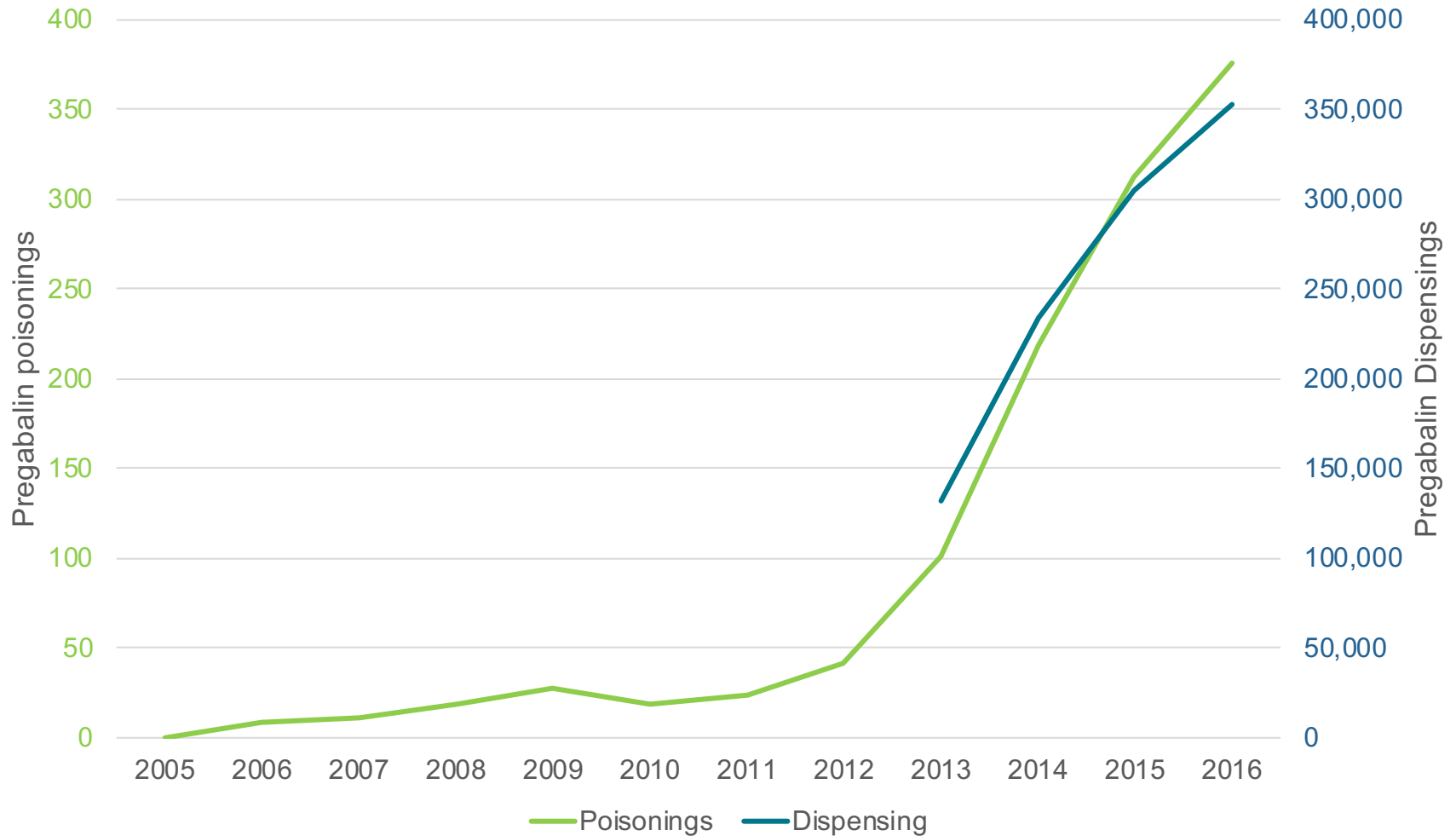
UK Deaths - results

- 24% annual rise in gabapentinoid prescriptions from 2004 to 2015
- Deaths increased
 - Mean <1 / year in 2004
 - 137 deaths in 2015 involving gabapentinoids
 - 79% gabapentinoid + opioid
- Correlation between prescriptions & deaths
 - 5% increase for every extra 100,000 prescriptions
 - RR[deaths] 1.64 / 1 million prescriptions

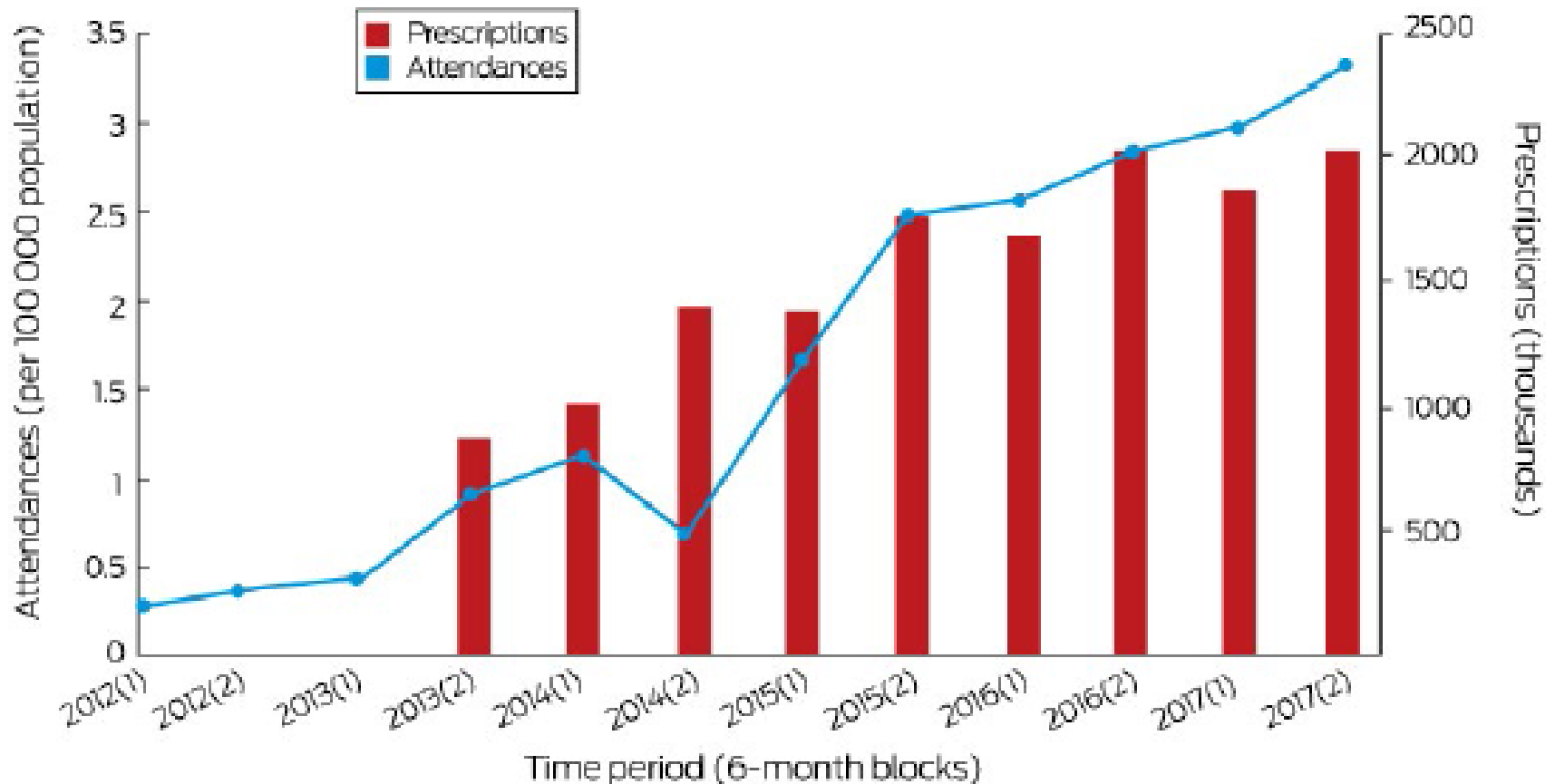
Interview Results

- Pregabalin “enhances” heroin
- Pregabalin might help reduce heroin use
 - “You don’t really want to use heroin, you want more pregabs, I don’t know why”
 - Reduces desire to use other things – “would be brilliant for detox”
 - “it just chills you out”
- Causes blackouts
 - Can’t remember what happened
- Overdoses
 - Enhances heroin
 - Slow onset so people take more or on top

Pregabalin PBS Dispensing and Poisonings

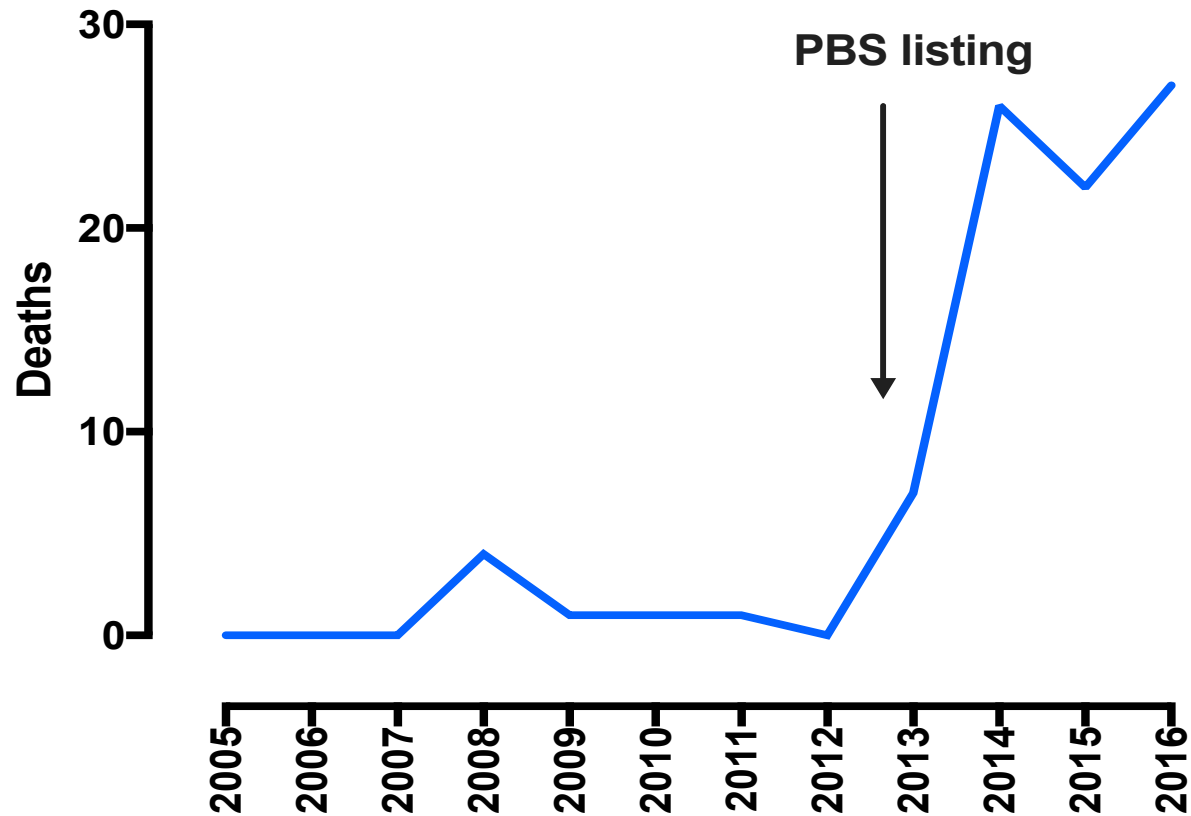


Pregabalin (Vic) ambulance attendances

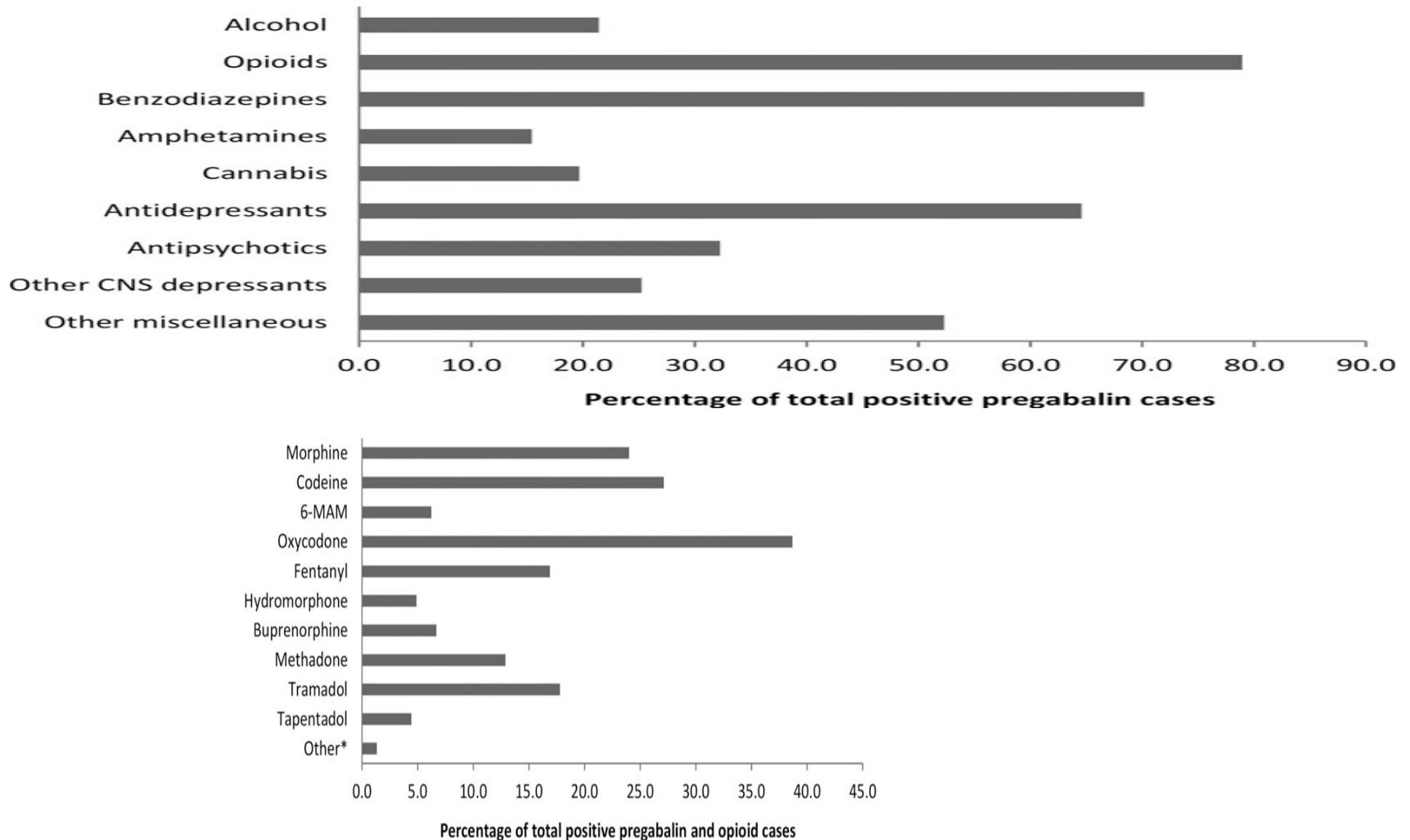


- 39% associated with suicide attempts
- Commonly (68%) ingested with other sedatives
 - 37% benzodiazepines, 27% alcohol

Rising pregabalin deaths



Co-ingested substances in coronial cases involving pregabalin (Qld 2015-17)



Thompson et al 2020 J Anal Tox 44(1). Only 5% of cases tested for pregabalin, 86% +ve

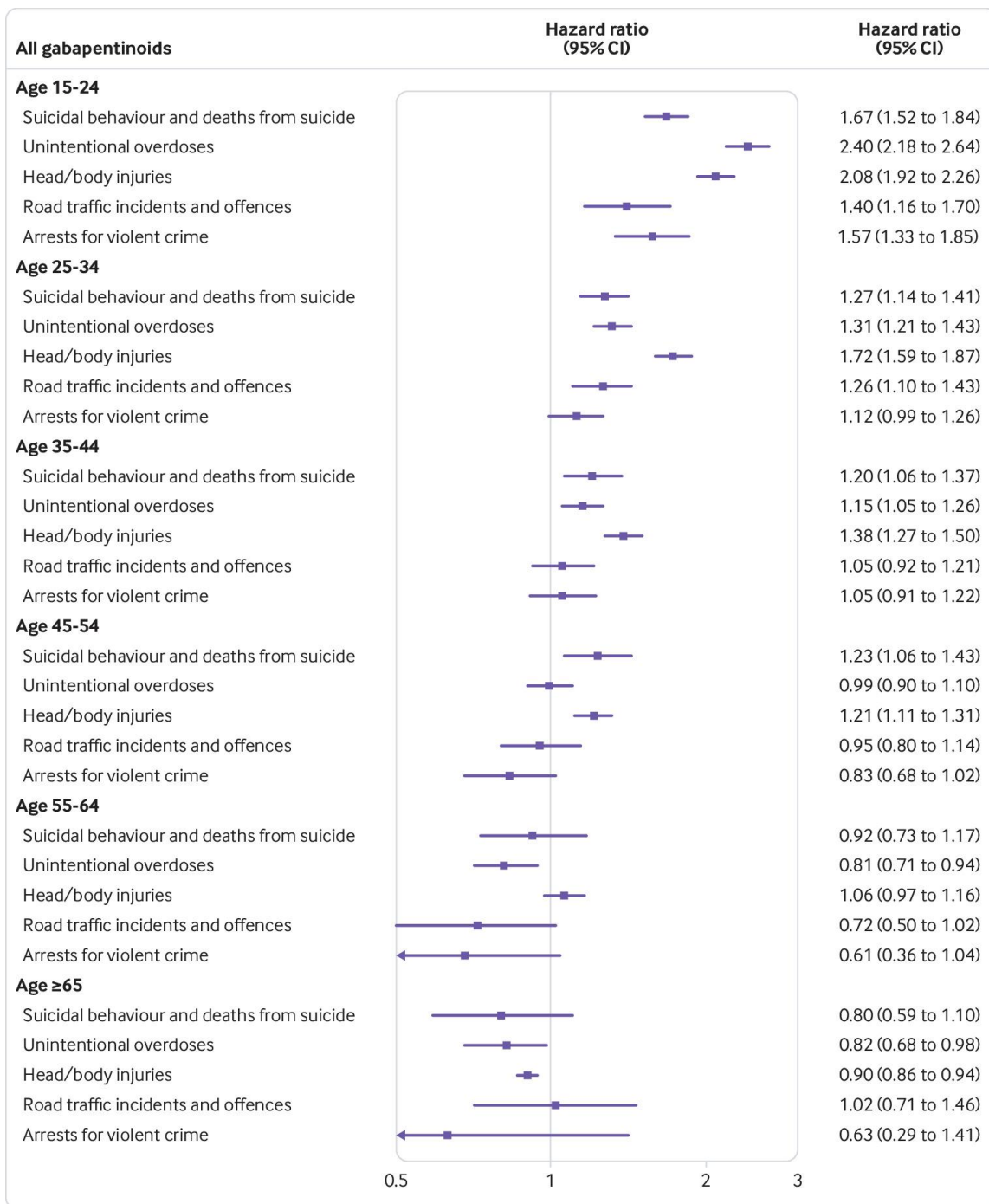
Gabapentinoids Population Risks

- Swedish population study
- Association not causation
- Within individual
- $n \approx 200,000$
- 2006-13
- At least 2 consecutive dispensed prescriptions for gabapentinoids
 - Molero et al 2019
- Increased risk of:
 - Suicidal behaviour
 - (5%, HR=1.26)
 - Unintentional overdose
 - (9%, HR=1.24)
 - Injuries
 - (37%, HR=1.22)
 - Road accidents
 - (6%, HR=1.13)
 - Violent offence arrests
 - (4%, HR=1.04 ns)

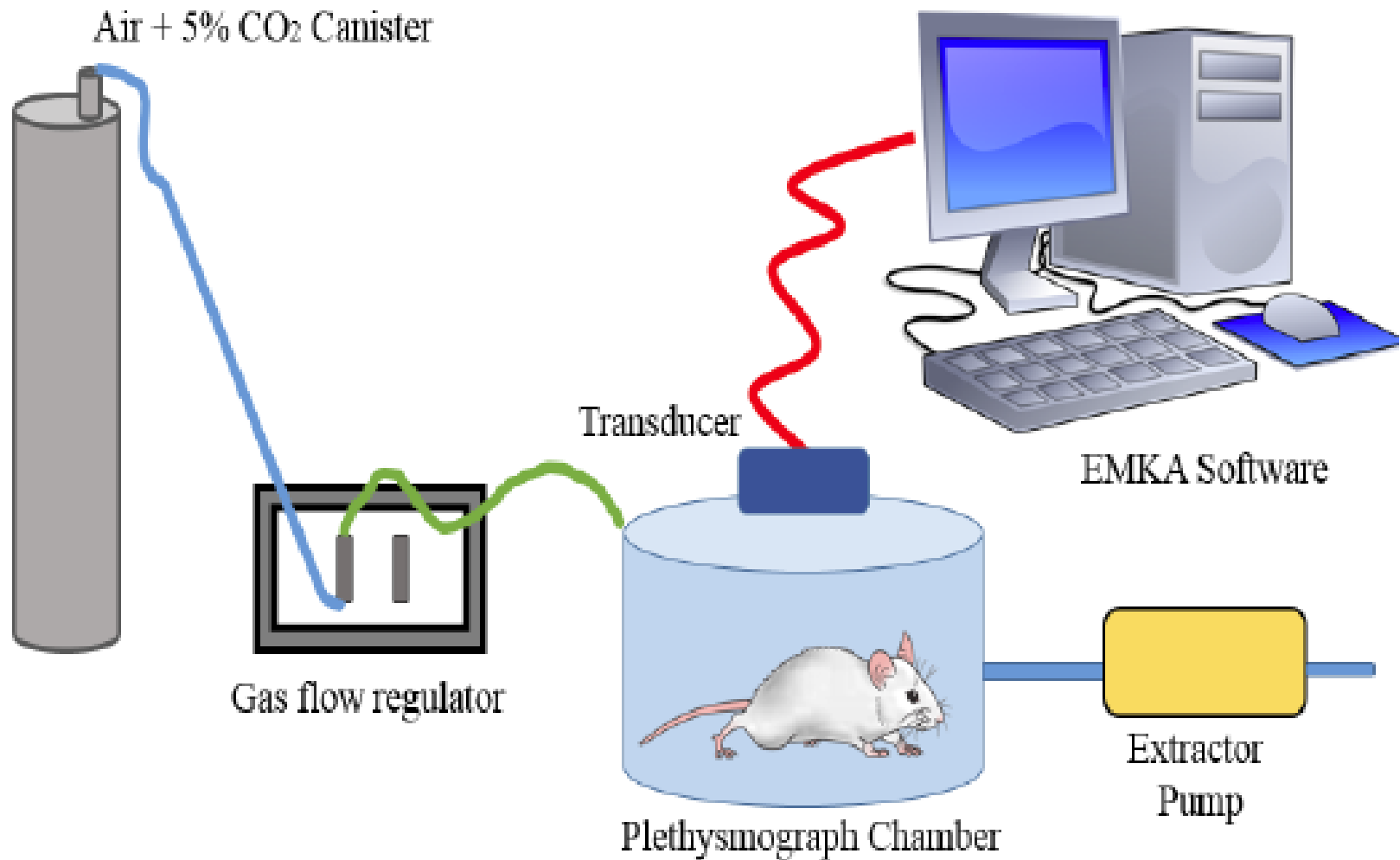
Who's most at risk with gabapentinoids?

- Younger, esp 15-24
- Pregabalin > gabapentin
- People not also prescribed another anticonvulsant
- People with other substance use disorders

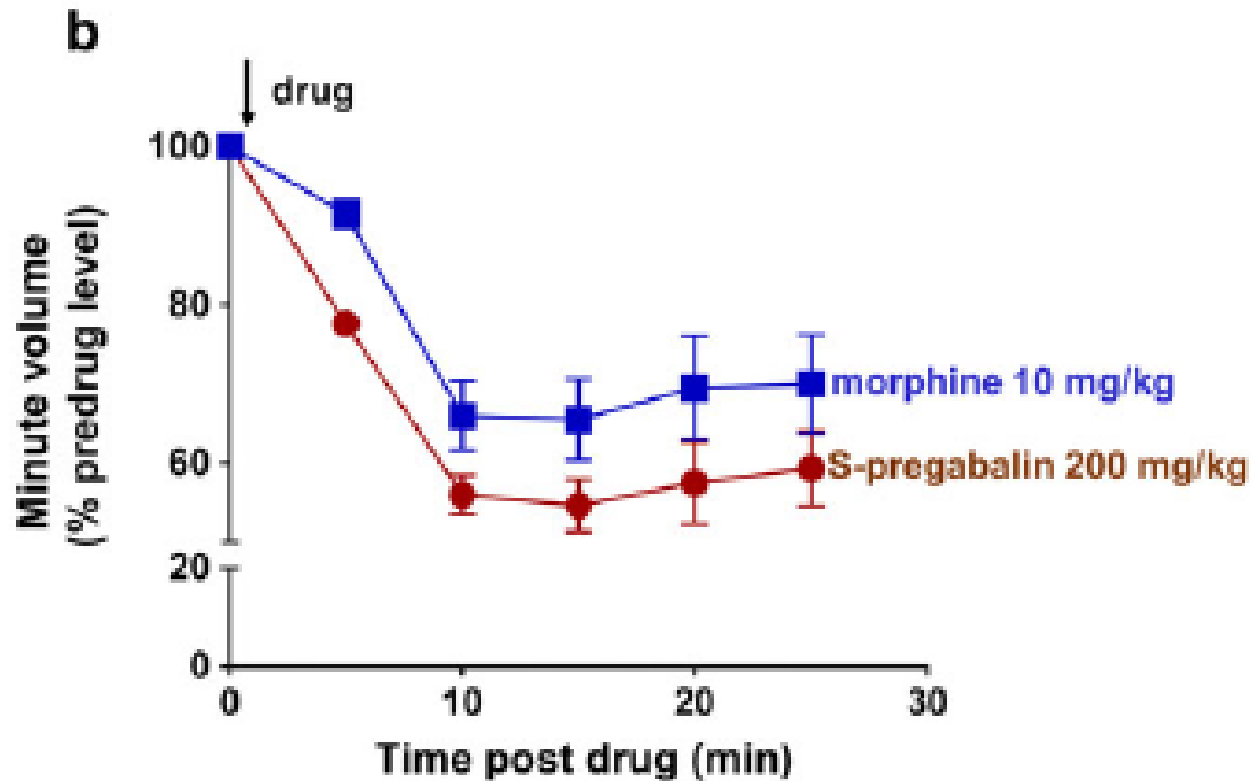
– Molero et al 2019



Mouse studies

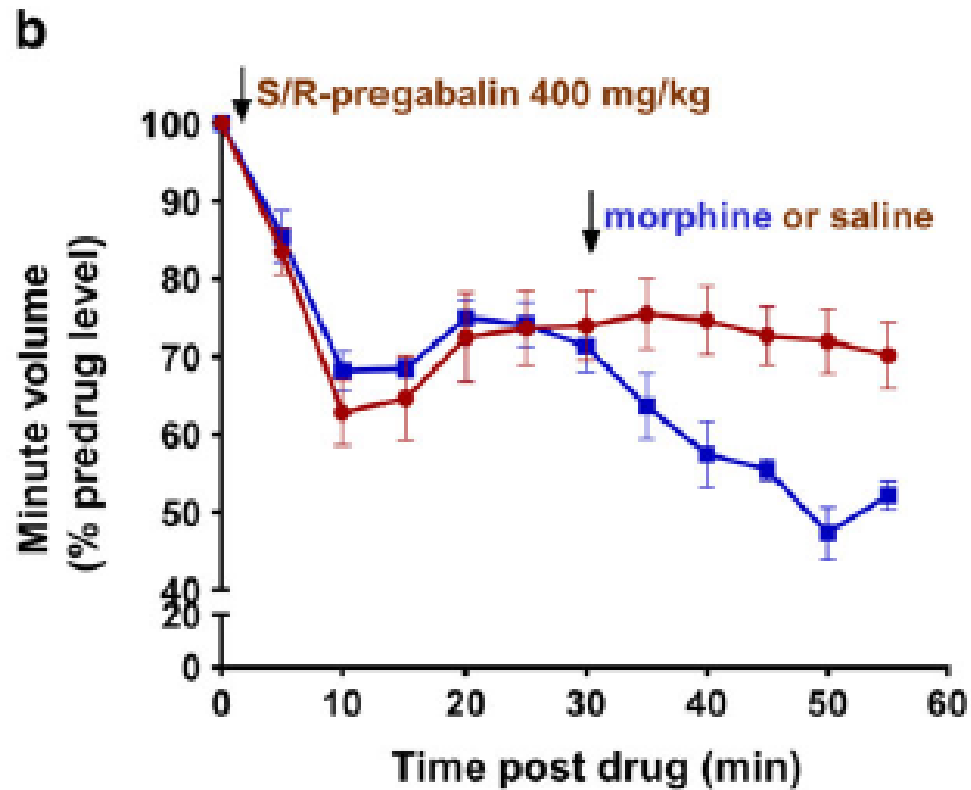


Single Drug Studies



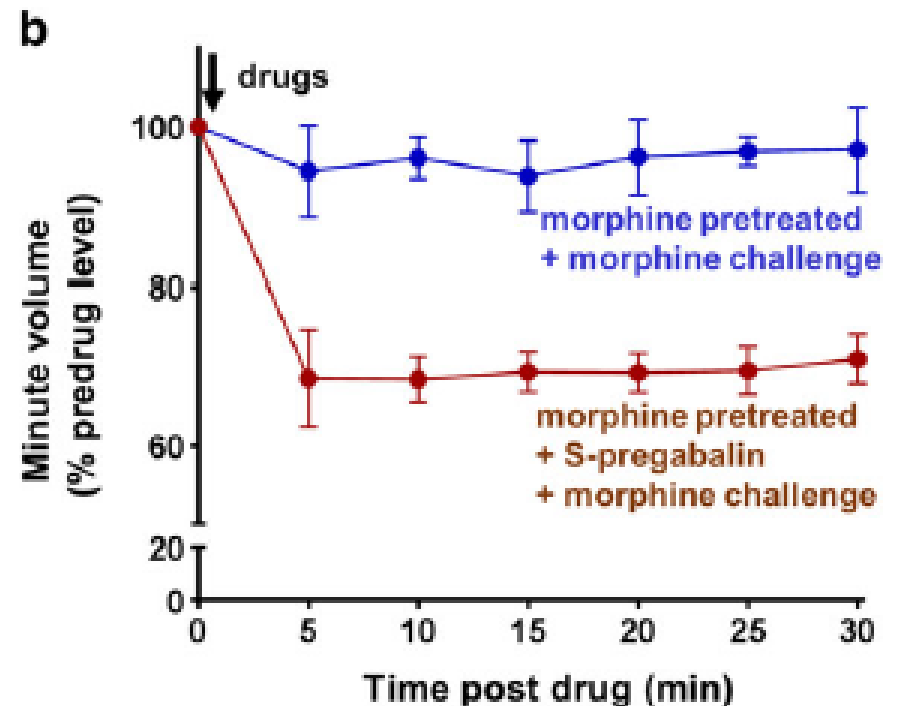
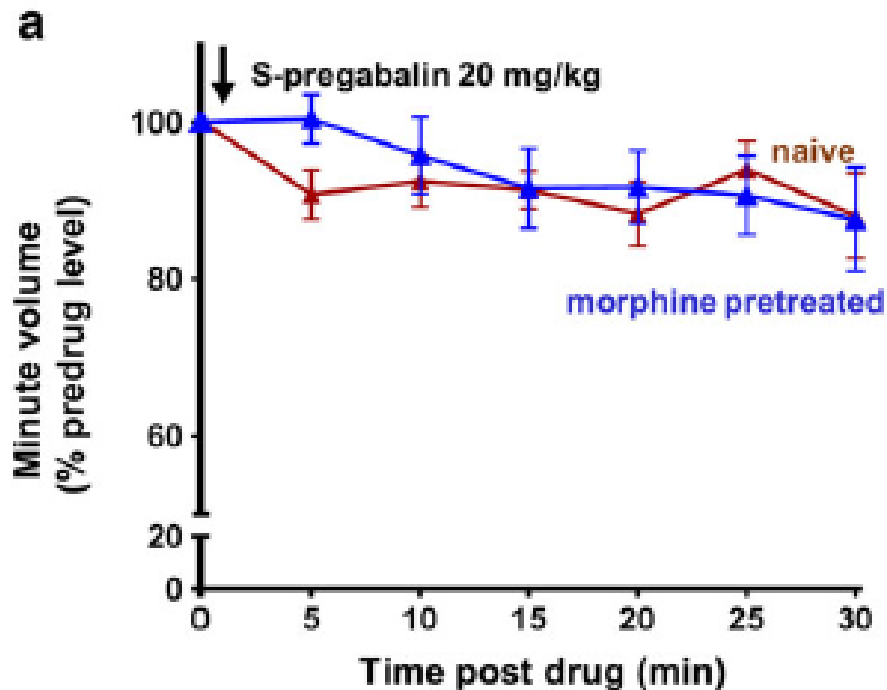
Naloxone blocked effects of morphine but not pregabalin

Combination

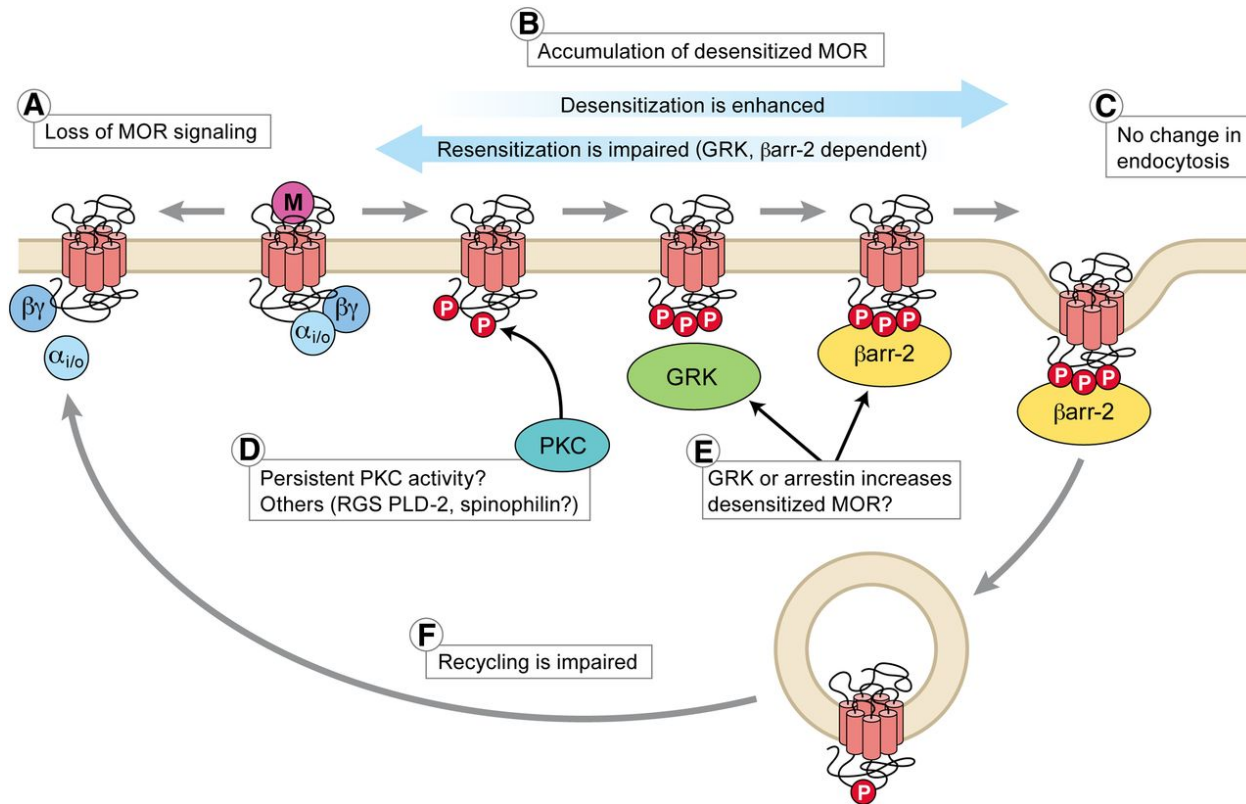


Additive (not synergistic) effect

Tolerance



Agonist Specific Mechanisms of Opioid Tolerance



- GRK / β -arrestin mediated
 - Methadone
 - Fentanyl
 - ?Buprenorphine

- PKC mediated
 - Morphine
 - Heroin
 - 6-MAM
 - Oxycodone

What to watch out for



Drugs that block PKC effects

Alcohol
Pregabalin
Tamoxifen



This is not the same as receptor blockade by a partial agonist (buprenorphine)

Interview Results

- Pregabalin might help reduce heroin use
 - “You don’t really want to use heroin, you want more pregabs; I don’t know why”
 - Reduces desire to use other things
 - “would be brilliant for detox”
 - “it just chills you out”

Pregabalin as an opioid withdrawal treatment (rodents)

- Pre-treatment with pregabalin
 - attenuated development of morphine tolerance in rats (Hasanein and Shakeri 2014)
 - reduced self-administration of morphine in mice (Vashchinkina et al 2018)
- Post-treatment with pregabalin
 - increased low-dose morphine conditioned place preference in mice (Vashchinkina et al 2018)
- Attenuated naloxone-precipitated withdrawal symptoms in rats & mice (Hasanein and Shakeri 2014, Vashchinkina et al 2018)

Pregabalin as an opioid withdrawal treatment (humans)

- Case reports for opioid withdrawal in humans
- Human trial (n=34) pregabalin vs clonidine RCT (Vashchinkina et al 2018)
 - 6 day trial, symptom triggered & combined with doxylamine + prn symptomatics
 - < 600mg/day pregabalin or < 600µg/day clonidine symptom triggered
 - 79% completed pregabalin treatment vs 47% completed clonidine

Pregabalin as a benzo withdrawal treatment

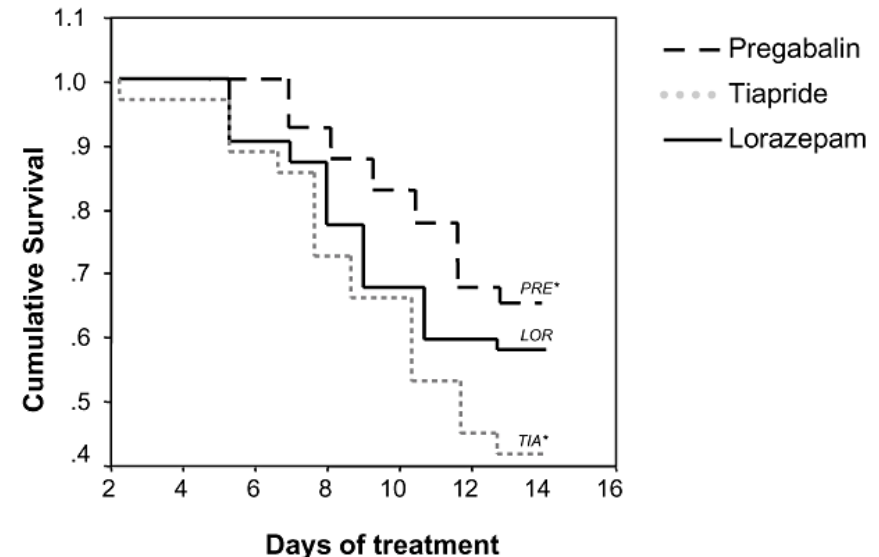
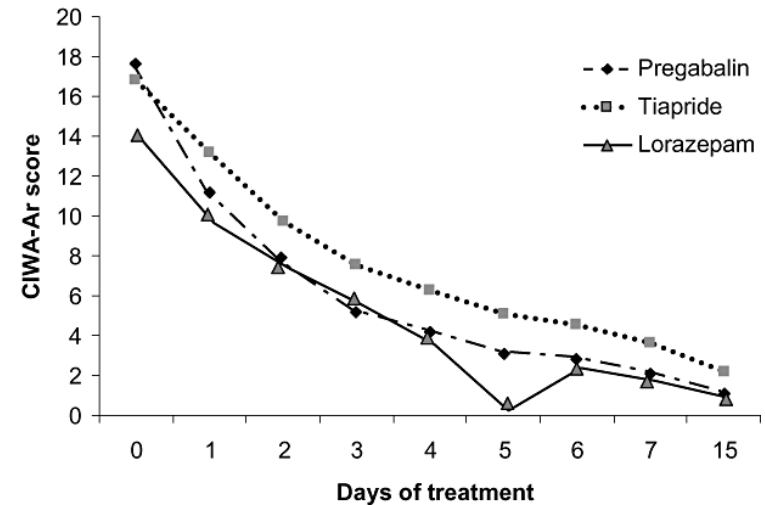
- People prescribed benzo for GAD (Hadley et al 2012)
 - Double-blind RCT, n=106
 - Pregabalin 75-300mg bd vs placebo.
 - Reduced 25% / week over 6 weeks.
 - More people ceased alprazolam:
 - 51% vs 37% on placebo (non-significant)
 - OR=1.39; 0.87-2.16

Pregabalin as a benzo withdrawal treatment

- Uncontrolled trial for benzodiazepine withdrawal (Bobes et al 2012)
 - n=282 with benzodiazepine dependence
 - 12 weeks of pregabalin 25-600mg/day
 - Other substance use disorders not exclusion criterion
 - 52% successful taper (70% in completers at 12 weeks)
 - Improved anxiety symptoms as well as reducing withdrawals
- Reduces consumption of benzodiazepines in people with long-term prescriptions (n≈13,000) (Bramness et al 2010)
 - Dispensing rates 182 days before vs after initiation of pregabalin
 - 15-28% stopped benzos after starting pregabalin
 - People with psychiatric disorders mean decrease in benzo use ~50%

Pregabalin as an alcohol withdrawal treatment

- Pregabalin vs tiapride vs lorazepam
- Single blind RCT, n=111
- Alcohol-free for 14 days
 - pregabalin 62%
 - lorazepam 57%
 - tiapride 38%
- Pregabalin = lorazepam > tiapride for completing treatment
 - Martinotti et al 2010 Addiction 105(2)



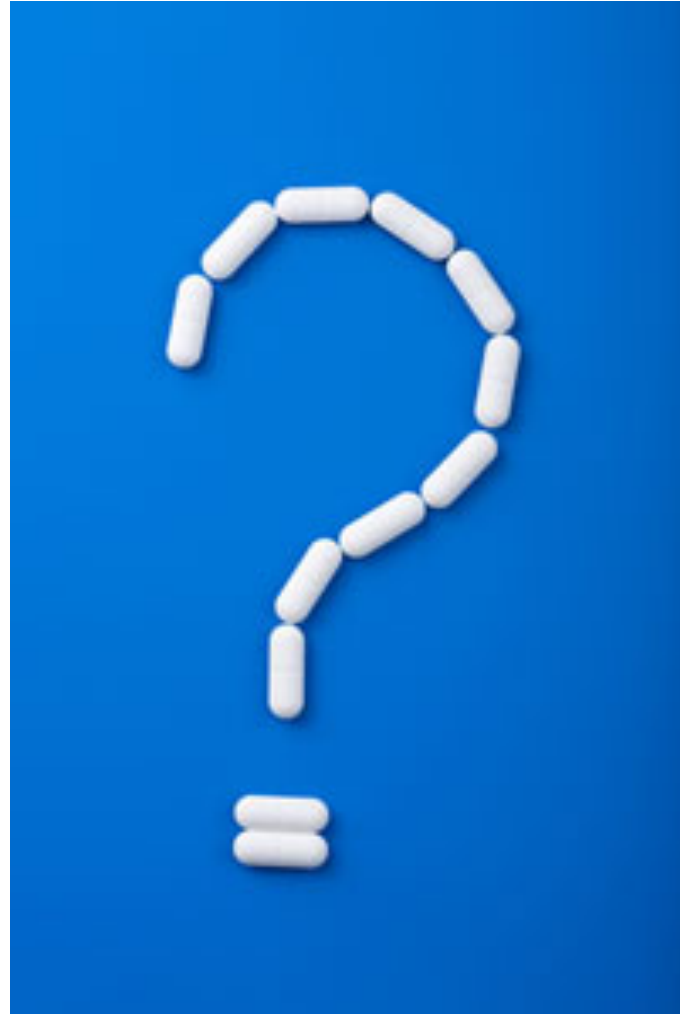
Pregabalin as an alcohol withdrawal treatment

- Reduces withdrawal seizures and attenuated sensitisation over repeated withdrawal episodes in mice (Becker et al 2006)
- Pregabalin vs placebo (Förg et al 2012)
 - Double-blind RCT, n=42, 83% completion
 - pregabalin (150 bd -> 50mg) vs placebo
 - Rescue diazepam ≤ 60 mg/day, symptom-triggered
 - No difference for alcohol withdrawal or required diazepam over 6 days

Monitored Medicines...

- Coming soon
- Real time monitoring of dispensing
- Available to prescribers & dispensing pharmacists
 - Optional initially
 - Will be mandatory
- Enacted in legislation
- List of medicines controlled by regulation
- Likely list
 - All S8
 - All S4 benzos
 - Gabapentinoids
 - Z-drugs
 - Quetiapine
 - Tramadol
 - CACC (e.g. panadeine forte)

Any questions?



Thanks for joining us today!

Join us again next week for

Gemma Nevin & Alan Gude

‘Evolution of an AOD workforce to include Peer Workers as an integrated multidisciplinary team’

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Centre for alcohol and other drug
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The Australasian Professional Society
on Alcohol and other Drugs