

# **Repurposing flumazenil for prehospital intramuscular treatment of coma due to unintentional overdose – the RUFUS trial**

**Michael Eddleston**

**Pharmacology, Toxicology & Therapeutics, University of Edinburgh**

**National Poisons Information Service - Edinburgh**



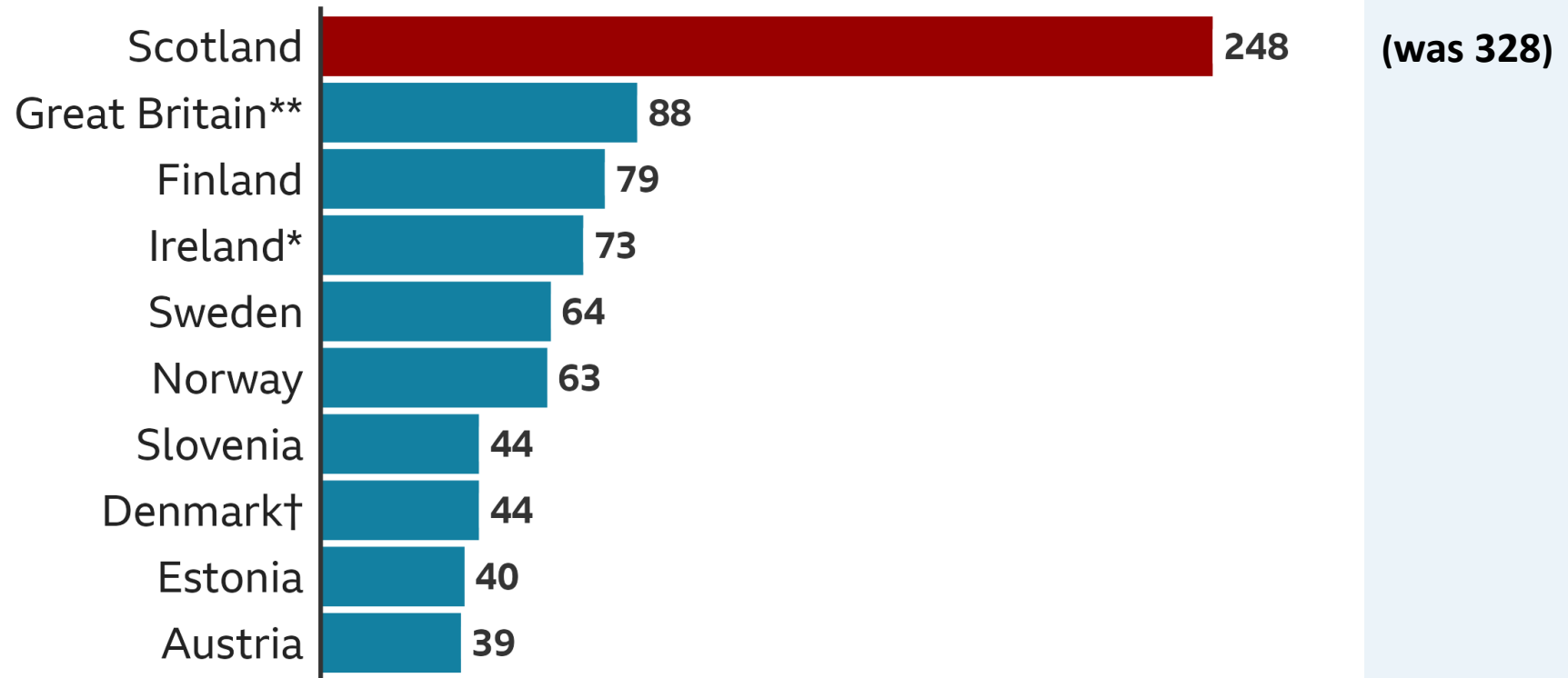
**Edinburgh  
Clinical  
Toxicology**





# Drug deaths in Scotland higher than other European countries

European countries with highest deaths per million aged 15-64, latest available data



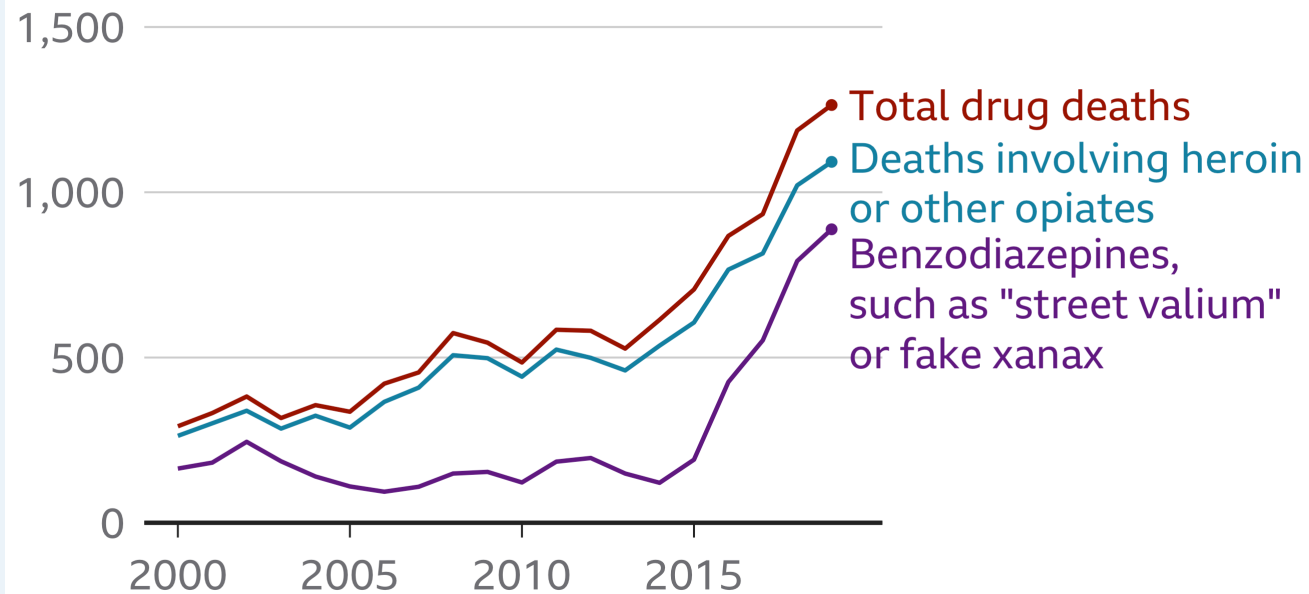
Note: Scotland data to 2022. Other countries' data to 2021 unless marked:  
\*2017, \*\*2018, †2020

Source: EMCDDA, National Records of Scotland

# Why ?? - Benzo + opioid OD

## Record number of drug deaths in Scotland

There were more than 1,200 drug-related deaths in 2019, with cases involving benzodiazepines increasing rapidly



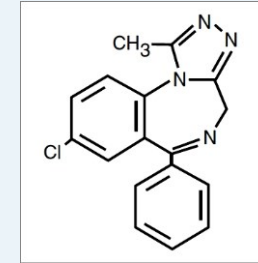
Note: Many cases involve more than one type of drug

Source: National Records of Scotland

BBC



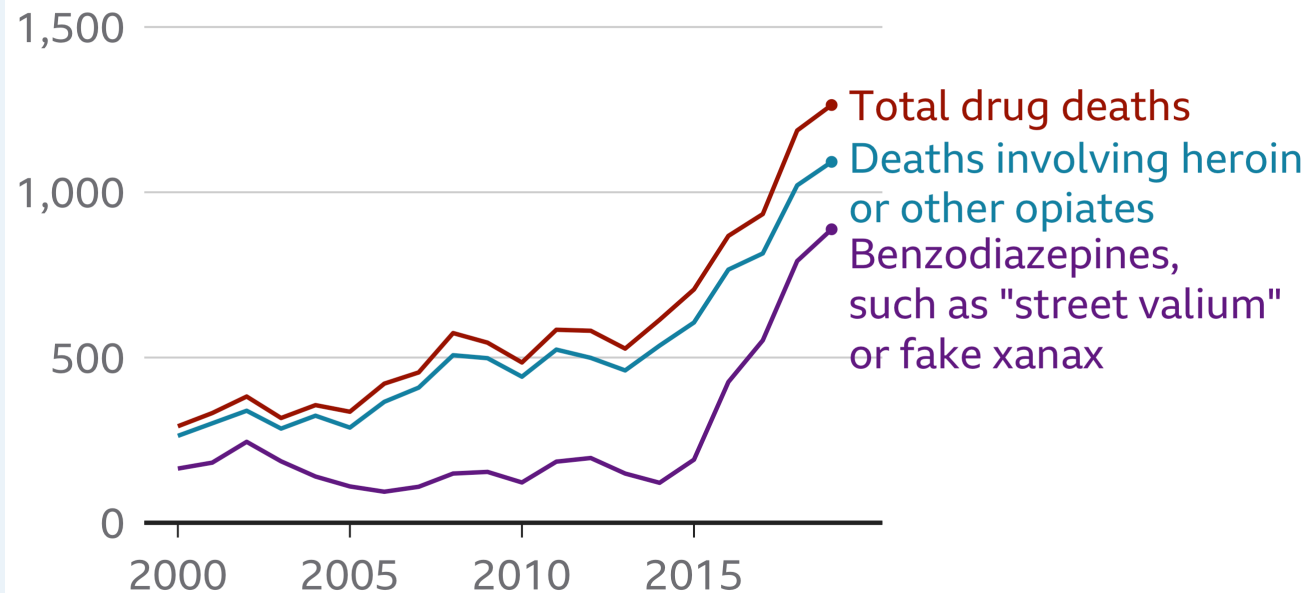
# Why ?? - Benzo + opioid OD



Alprazolam

## Record number of drug deaths in Scotland

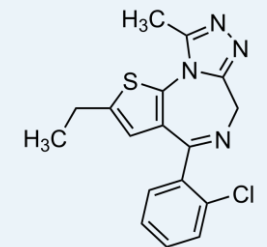
There were more than 1,200 drug-related deaths in 2019, with cases involving benzodiazepines increasing rapidly



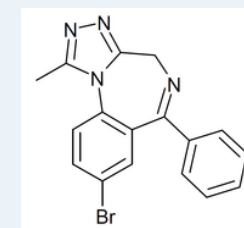
Note: Many cases involve more than one type of drug

Source: National Records of Scotland

BBC



Etizolam



Bromazolam



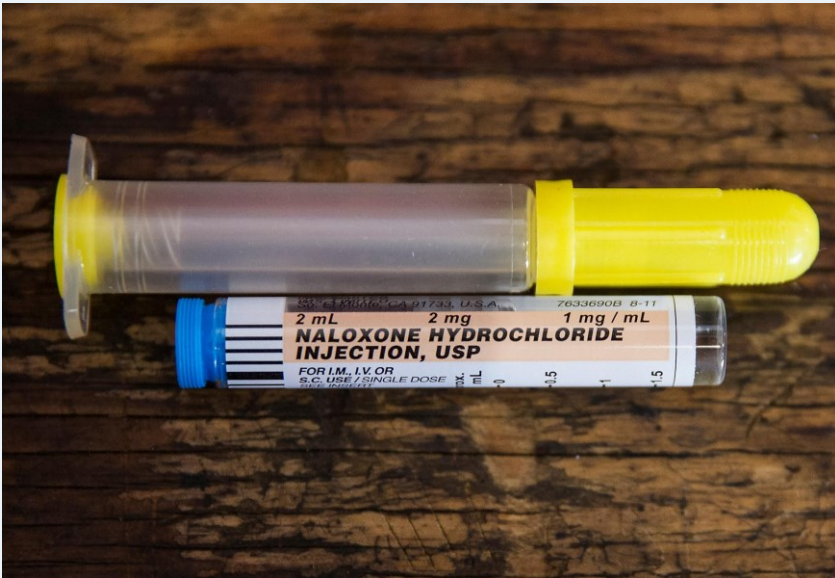
# Antidotes for unintentional overdose



**Naloxone**  
highly effective  
Now used in the community



# Antidotes for unintentional overdose

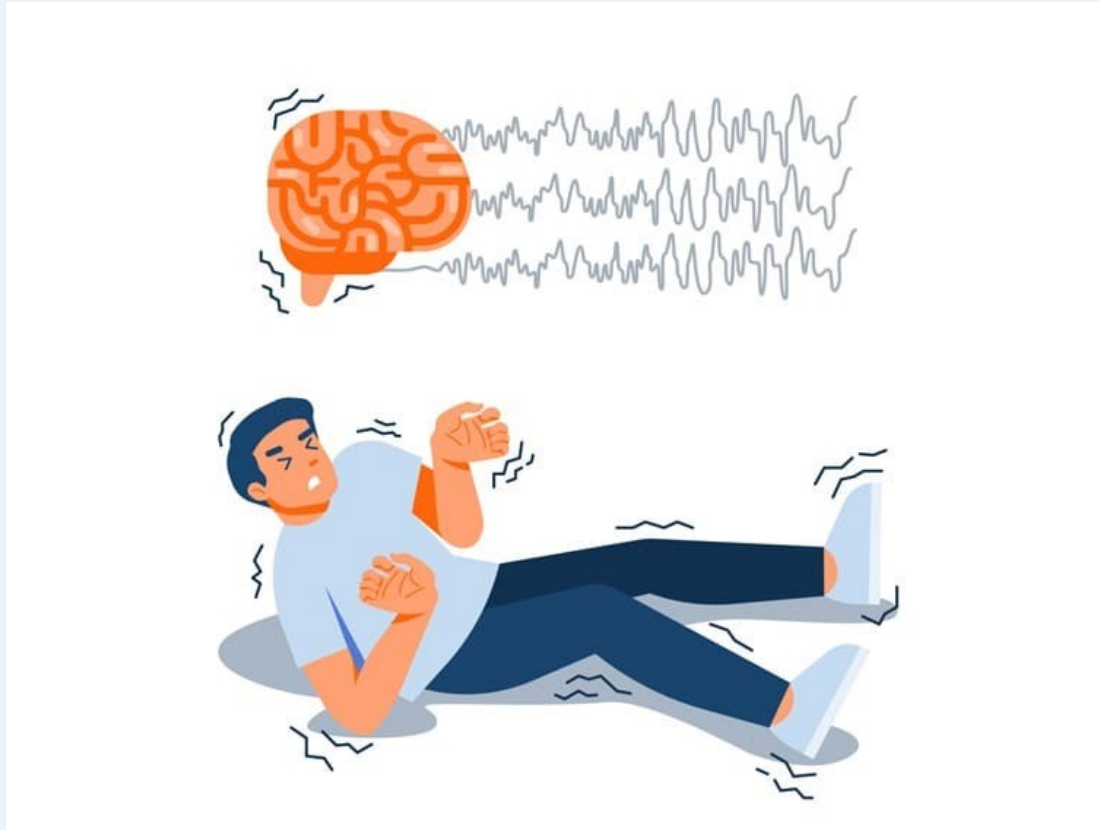


**Naloxone**  
highly effective  
Now used in the community



But  
Flumazenil is not used

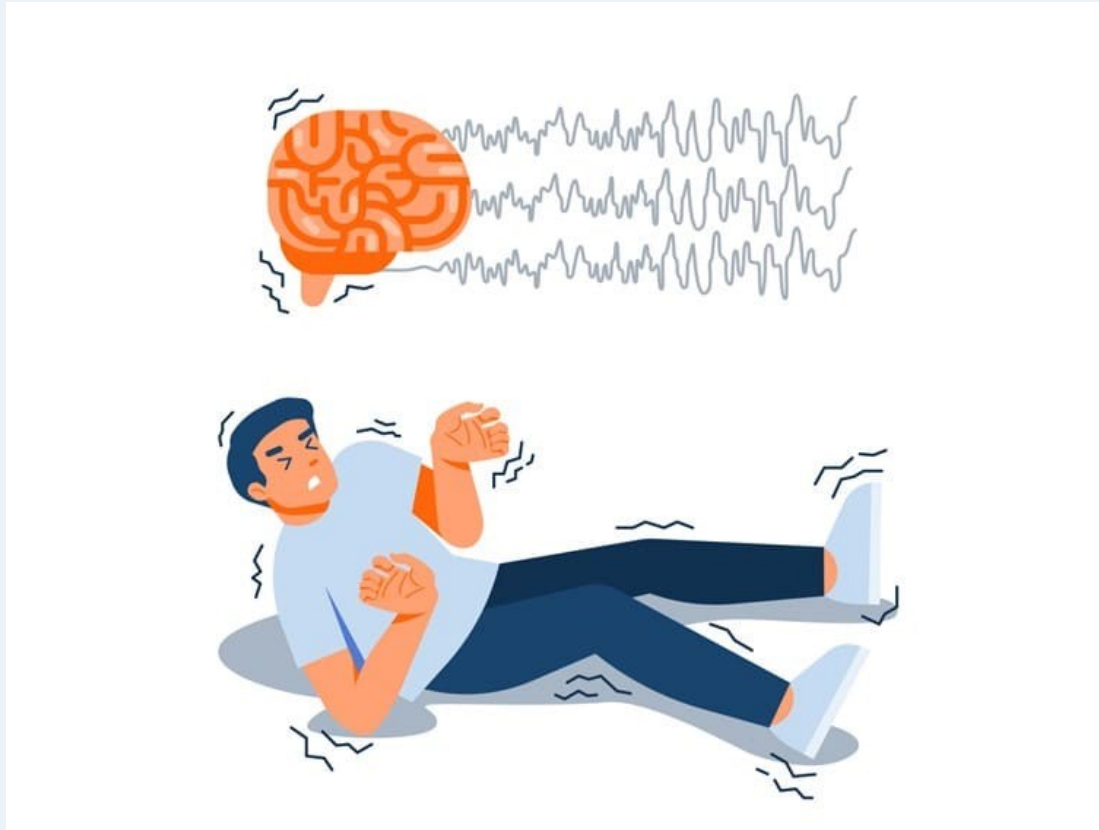
# Why? Fear of complications





# Why? Fear of complications

But incidence in literature is  
~0.6% and linked to TCAs

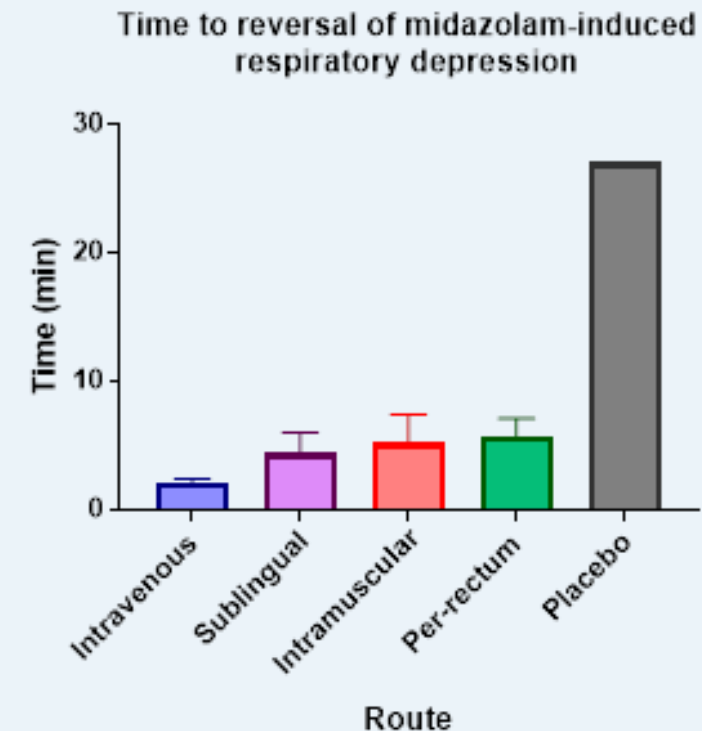


# Current issues

- Flumazenil will need to be given by **IM (or IN) route** to work in community where lives might be saved (only licensed for IV in hospital)
- We don't know whether  
**IM flumazenil reverses coma**

# Current issues

- Flumazenil will need to be given by IM (or IN) route to work in community where lives might be saved (only licensed for IV in hospital)
- We don't know whether IM flumazenil reverses coma
- Very little human experience (mostly France 1990s)



# Current issues

- Flumazenil will need to be given by IM (or IN) route to work in community where lives might be saved (only licensed for IV in hospital)
- We don't know whether IM flumazenil reverses coma
- Or the **incidence of tonic-clonic seizures** (or status epileptics)  
Literature suggests seizures <1.0% (even in high risk patients). No SE.
- If flumazenil works safely and effectively IM, then lives **might be** saved from pre-hospital use ....

# PICO Summary for RCT



- Population:** Patients with reduced GCS (RASS scores: -5 to -3) due to suspected BZD overdose after adequate naloxone administration.
- (Patients with no BZD detected in their blood on retrospective laboratory analysis will be excluded from secondary per-protocol analysis.)
- Intervention:** IM flumazenil (stage 1: up to 6 dose levels; stage 2: 2 doses; stage 3: 1 dose).
- Comparator:** Equal volume of 0.9% sodium chloride for infusion.
- Outcomes:**
- Safety** - incidence of seizures
  - Efficacy** - proportion improving RASS score to greater than -3



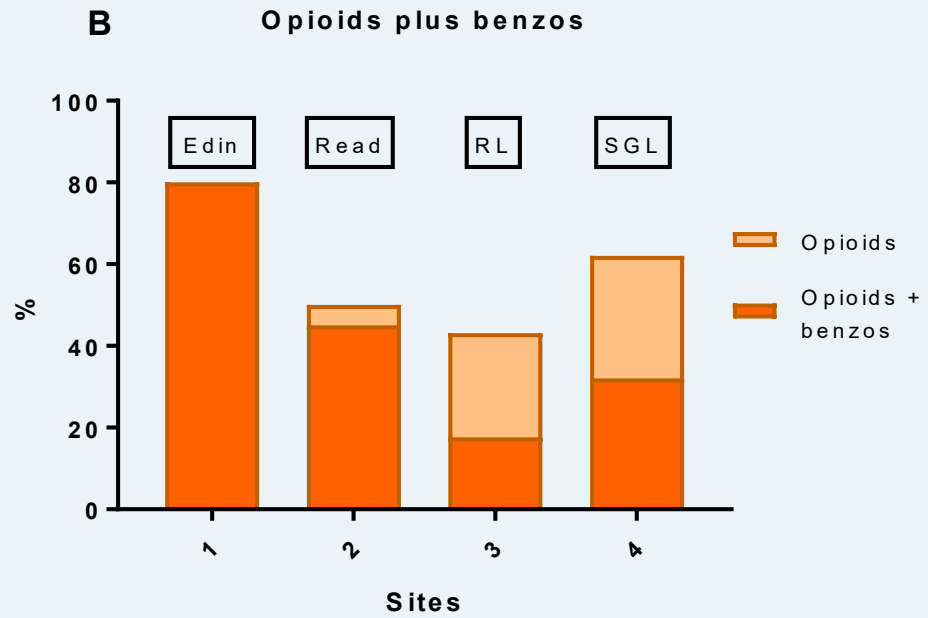
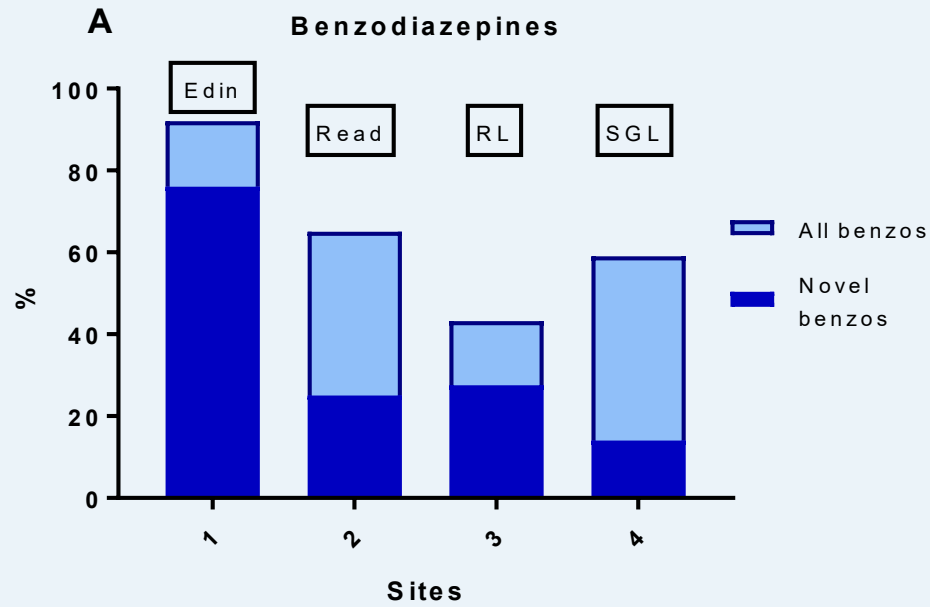
# RCT – 3 stages

- **Stage 1** – dose response efficacy & safety (6 cohorts, 10+2 placebo)  
**Aim** – identify two effective (& safe) doses of IM flumazenil (n=72)
- **Stage 2** – more precise estimates of efficacy for 2 IM doses  
**Aim** – select one dose for larger study (n=189)
- **Stage 3** – get precise estimate for incidence of tonic-clonic seizures after IM flumazenil  
**Aim** – estimate safety of 1 efficacious dose of IM flumazenil (n=374)

# Inclusion criteria

1. **Acute suspected unintentional BZD overdose** presenting to hospital with reduced consciousness after adequate administration of naloxone. Mixed overdoses suspected to include BZDs can be included.
2. **Other common causes** of unconsciousness (such as hypoglycaemia) will have been **excluded**.

# % with benzos - Scotland vs England



# Inclusion criteria

1. Acute suspected unintentional BZD overdose presenting to hospital with reduced consciousness after adequate administration of naloxone. Mixed overdoses suspected to include BZDs will be included.
2. Other common causes of unconsciousness (such as hypoglycaemia) will have been excluded.
3. **RASS score** of -5 (unrrousable) to -3 (moderate sedation).
4. Adult ( $\geq 16$ -yrs-old).

# Richmond Agitation-Sedation Scale

Target RASS Value		RASS Description
+4	Combative	Combative, Violent, Immediate Danger to Staff
+3	Very Agitated	Pulls or Removes Tube(s) or Catheter(s); Aggressive
+2	Agitated	Frequent non-Purposeful Movement, Fights Ventilator
+1	Restless	Anxious, Apprehensive but Movements are not Aggressive or Vigorous
0	Alert and Calm	
-1	Drowsy	Not Fully Alert, but has Sustained Awakening to Voice (Eye Opening & Contact >10sec)
-2	Light Sedation	Briefly Awakens to Voice (Eye Opening & Contact <10sec)
-3	Moderate Sedation	Movements or Eye Opening to Voice (BUT NO Eye Contact)
-4	Deep Sedation	No Response to Voice, BUT has Movement or Eye Opening to Physical Stimulation
-5	Unarousable	No Response to Voice or Physical Stimulation



**REBEL  
REVIEWS**



# Primary outcomes

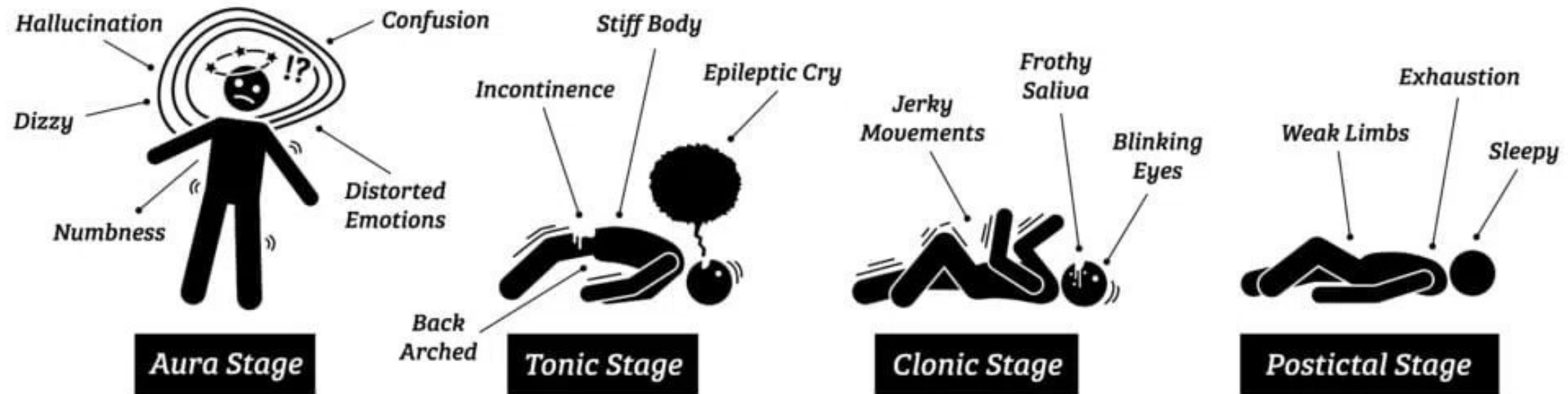
- **Primary Endpoint (safety)**

Occurrence of a tonic-clonic seizure (Dx by clinician) by **1 h**

- **Primary Endpoint (efficacy)**

RASS score in the -2 [light sedation] to 0 [alert, calm] range at **15 min**

# Stages of a Seizure



# Secondary outcomes

- Reversal of respiratory depression (falling PaCO<sub>2</sub> on V/ABG at 15 and 30 min)
- RASS, GCS, AVPU scores & standard Obs (HR, BP, etc) for 30 min.
- Need for/duration of intubation, death
- AEs/SAEs occurring from the time of administration of flumazenil or placebo until hospital discharge.

If a safe and efficacious dose of IM flumazenil  
can be found .....

# Future

1. Ambulance-based cluster RCT



2. Community-based stepped wedge cRCT



? Take-home  
flumazenil





# Conclusions

1. We urgently need to understand whether pre-hospital IM flumazenil can save lives
2. The first step is an ED-based study assessing safety of efficacious dose
3. The study started in Q1 2025 (n=8 so far).

We will collaborate widely with EDs across the UK in stages 2 and 3





# Exclusion criteria

1. RASS score above -3
2. PMHx of epilepsy or chronic brain injury
3. Seizure pre-hospital or after hospital admission, before recruitment
4. Apparent pregnancy (urine-HCG test not possible in unconscious patients)
5. Prolonged QRS duration (>120 msec, unless due to pre-existing RBBB/LBBB)
6. Prisoner or under arrest
7. Detained under the Mental Health Act
8. HIV +ve with detectable virus load (from recent [<1 year] blood tests)
9. Previous participation in the study
10. (For stage 1, unknown patients, no medical Hx)

# Study process

