

Hennepin Healthcare Integrated Opioid and Addiction Care ECHO: “Designer Drugs in 2022”

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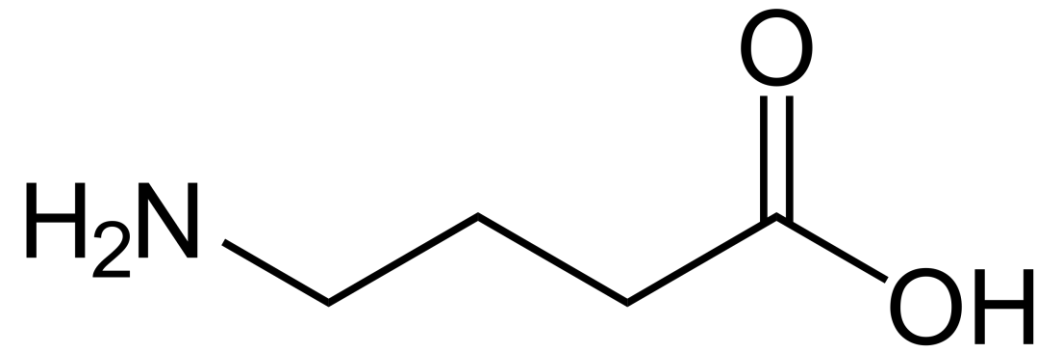
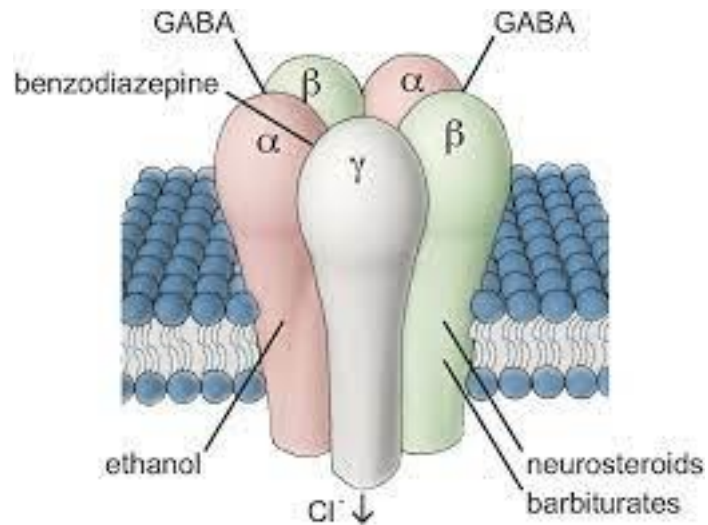


Objectives

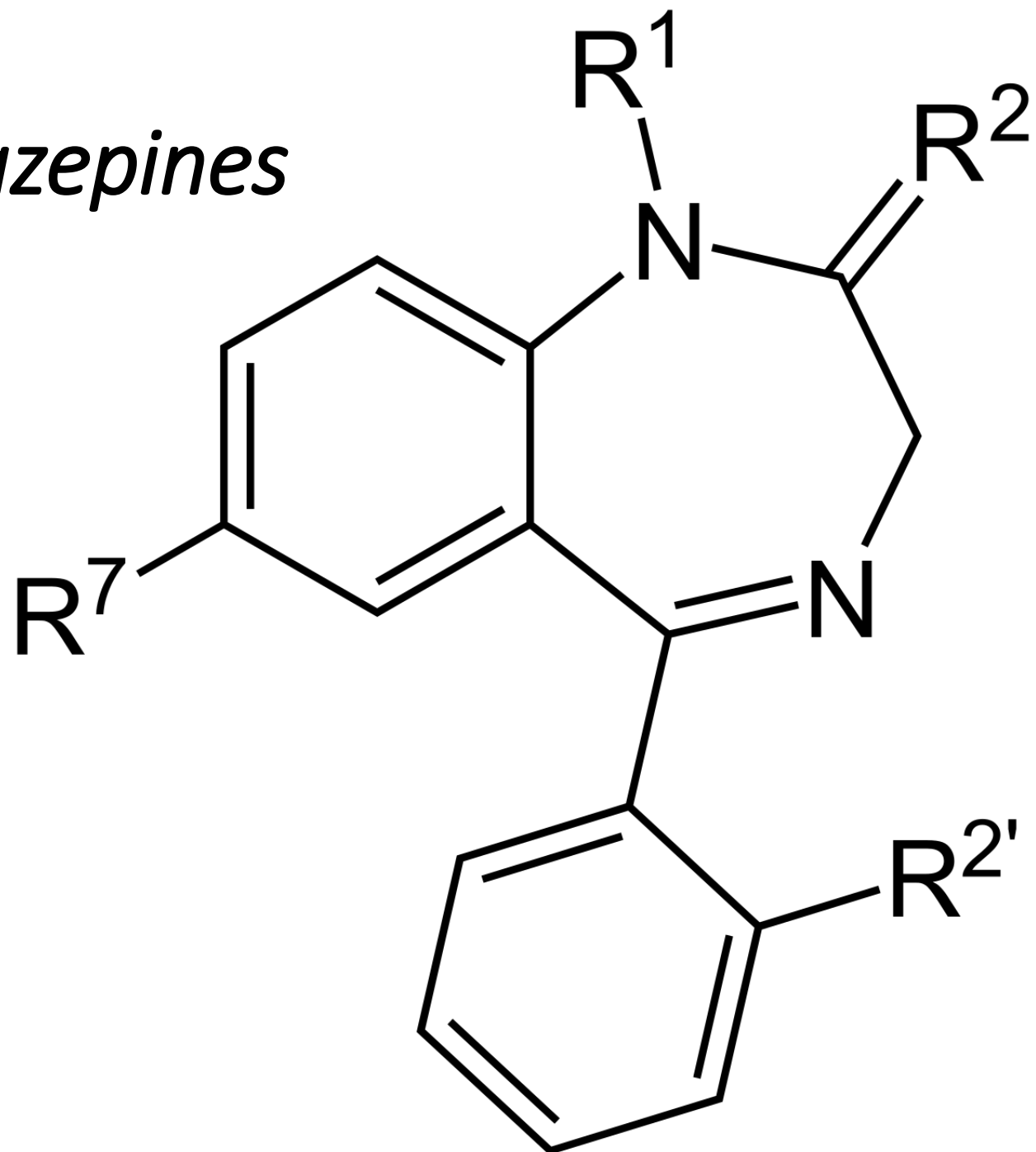
- Understand the pharmacology of novel designer drugs such as:
 - Etizolam
 - Phenibut
 - Tianeptine
 - Xylazine
- Use new pharmacology knowledge to make educated guesses on symptomology from novel drug intoxications

Neurotransmitters – Brief Review

- **GABA (γ -Aminobutyric acid)** is the main inhibitory neurotransmitter
- GABA binds voltage-gated chloride (Cl^-) channels
- Hyperpolarizes membrane, preventing transmission

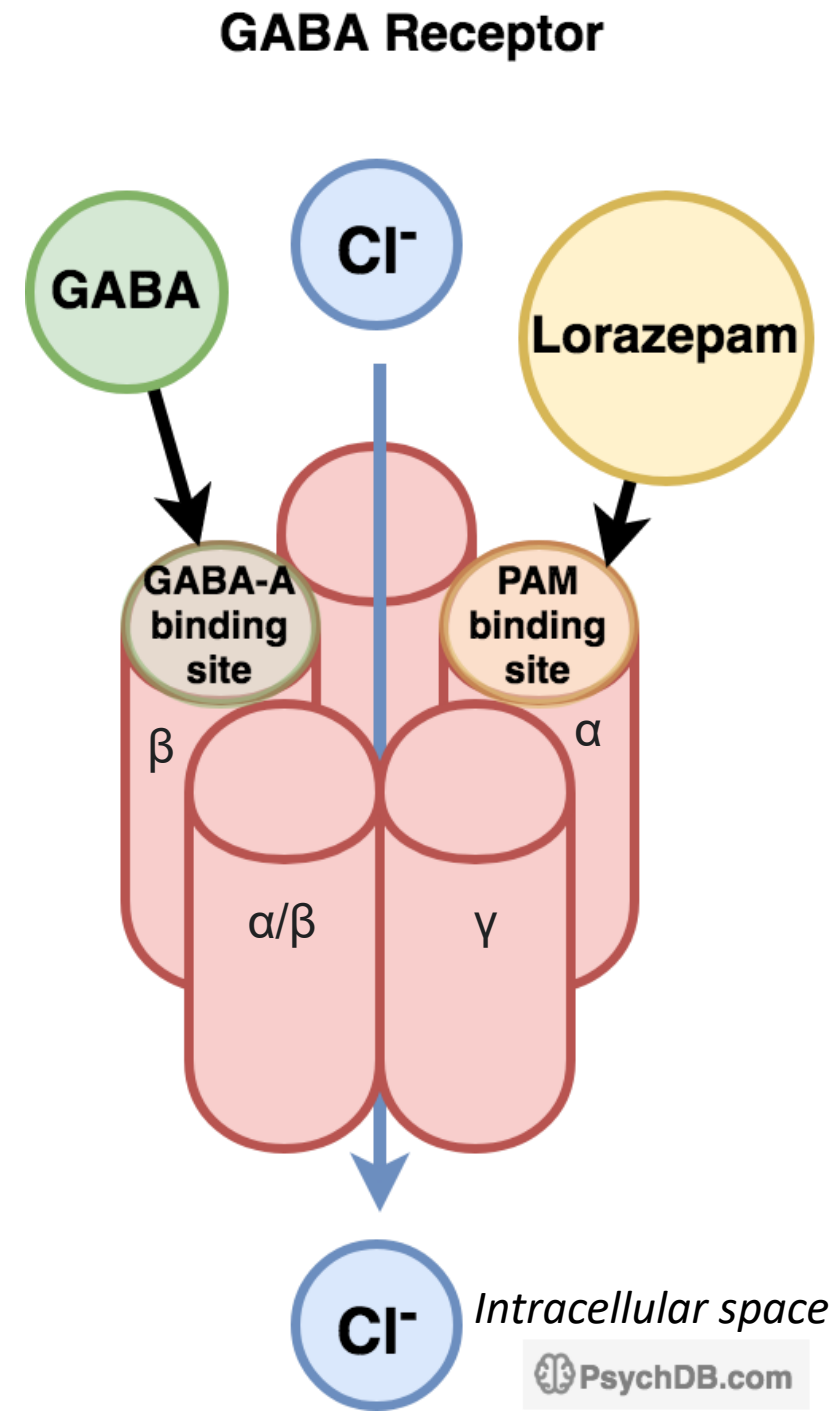


Novel *benzodiazepines*



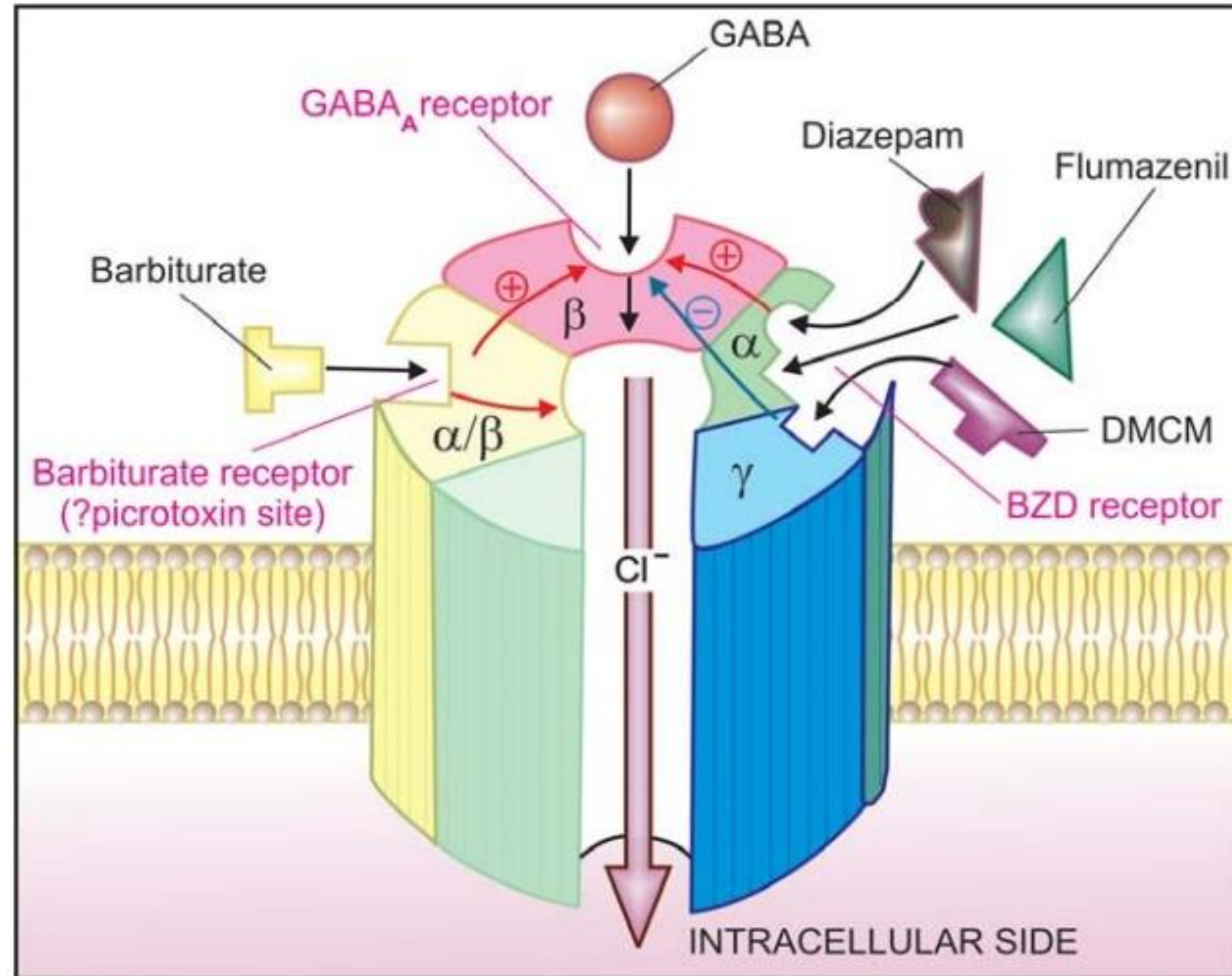
Benzodiazepines: pharmacology

- Mechanism of action:
 - Enhance function of GABA-mediated chloride channels via agonism at GABA_A receptor
 - Bind and increase the affinity of GABA for its receptor and *increase the frequency* of Cl⁻ channel opening in response to GABA binding
- Different subunits give different properties
 - α_1 = anxiety, sleep, amnesia
 - α_2 & α_3 = anxiolysis



Benzos vs. Barbs

- Benzodiazepines:
 - increase Cl⁻ channel opening *frequency*
 - require the presence of GABA
- Barbiturates:
 - increase Cl⁻ channel opening *duration*
 - do not require presence of GABA

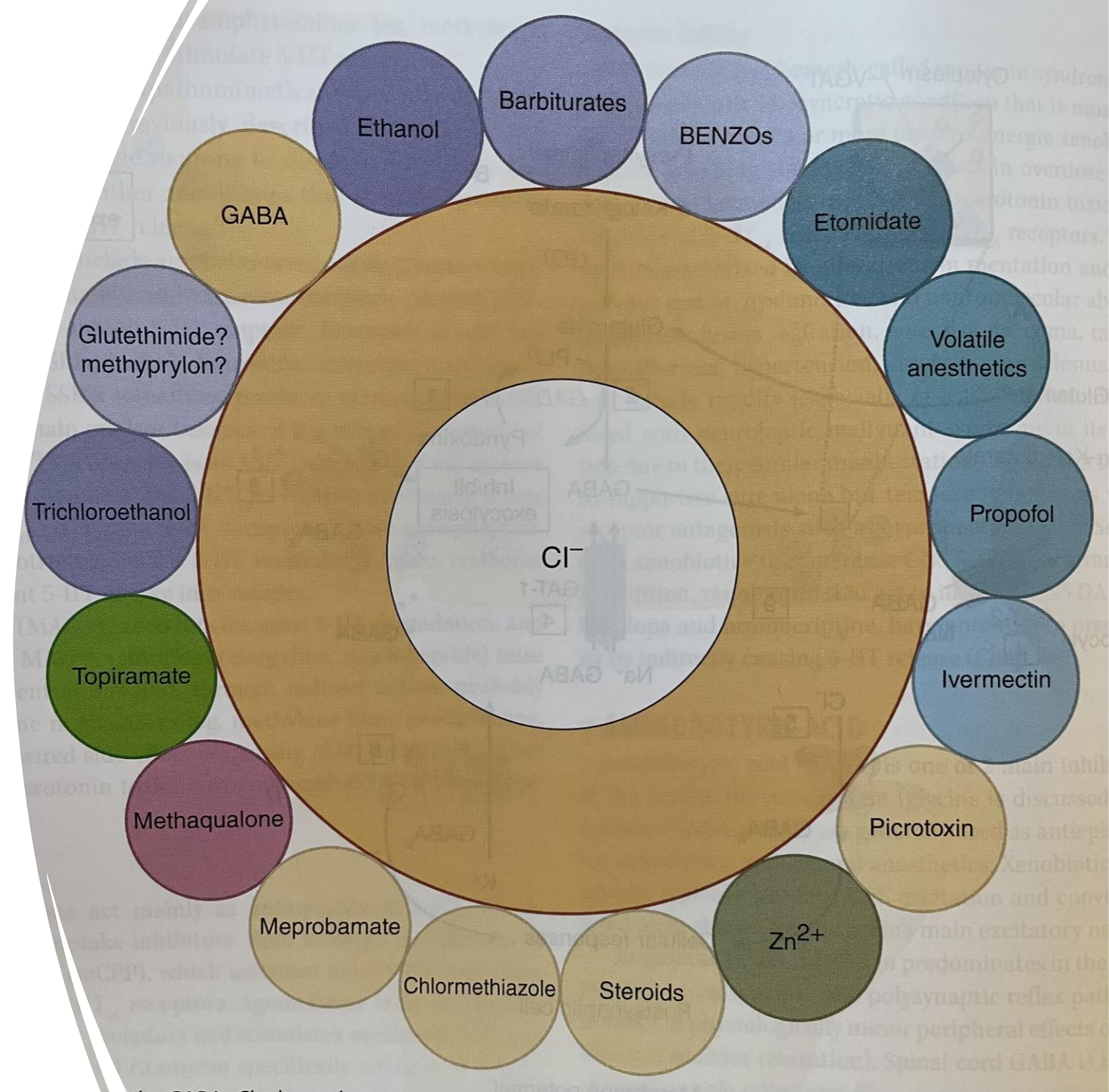


Benzo Intoxication: Signs & Symptoms

- Toxidrome:
 - “coma with normal vital signs”
- Common findings
 - Slurred speech/ataxia
 - Sedation
 - Hypnosis
 - Miosis (mild)
- Rare(er) findings
 - Hypopnea (rare, beware synergism with co-ingestions)
 - Hypothermia (rare)
 - Skin blisters

Lots of drugs work on GABA_A

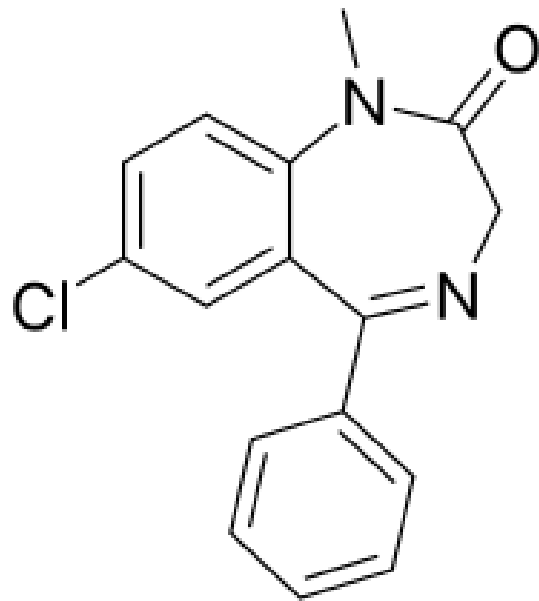
End goal of all of them is more chloride inside the cell



Structure (different) vs. Function (same...mostly)

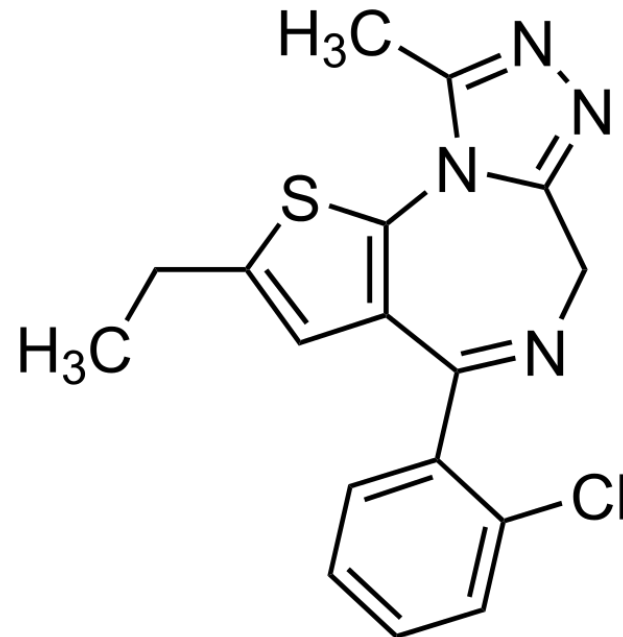
Benzodiazepine

- diazepam



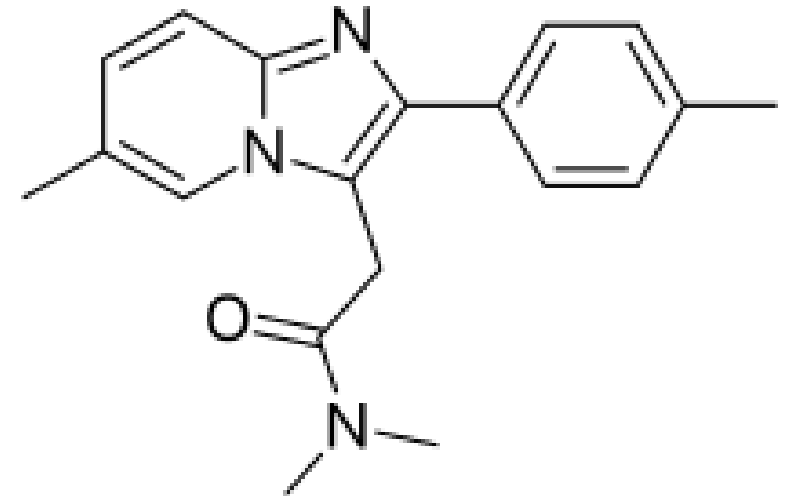
Thienodiazepine

- etizolam

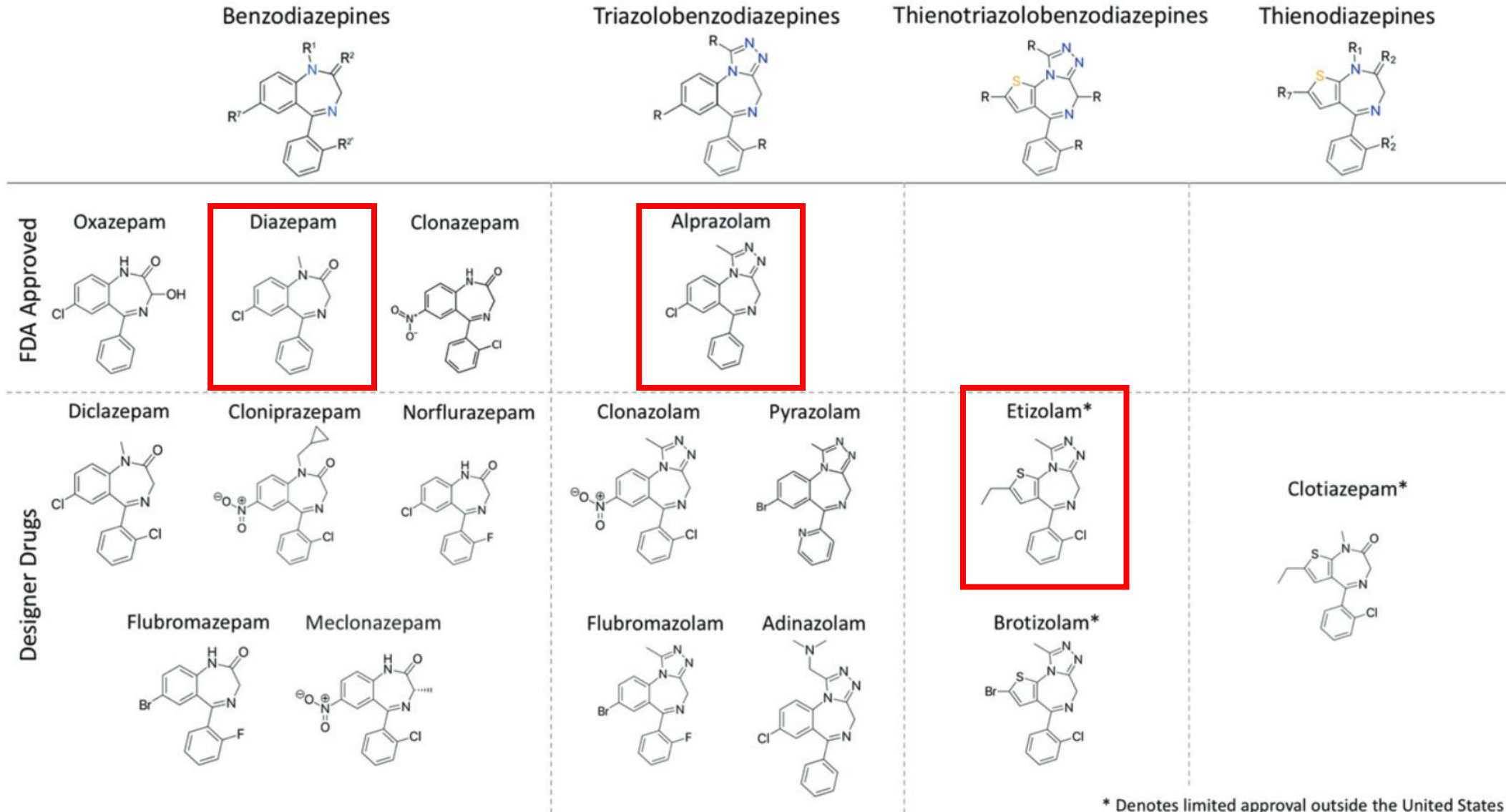


“Z-drugs” for sleep

- zolpidem



Structure vs. Function: Further Detail



* Denotes limited approval outside the United States

Novel benzodiazepines: clinical effects

- Similar to FDA-approved benzodiazepines

CLINICAL TOXICOLOGY

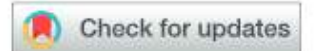
2019, VOL. 57, NO. 3, 203–212

<https://doi.org/10.1080/15563650.2018.1506130>



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POISON CENTRE RESEARCH



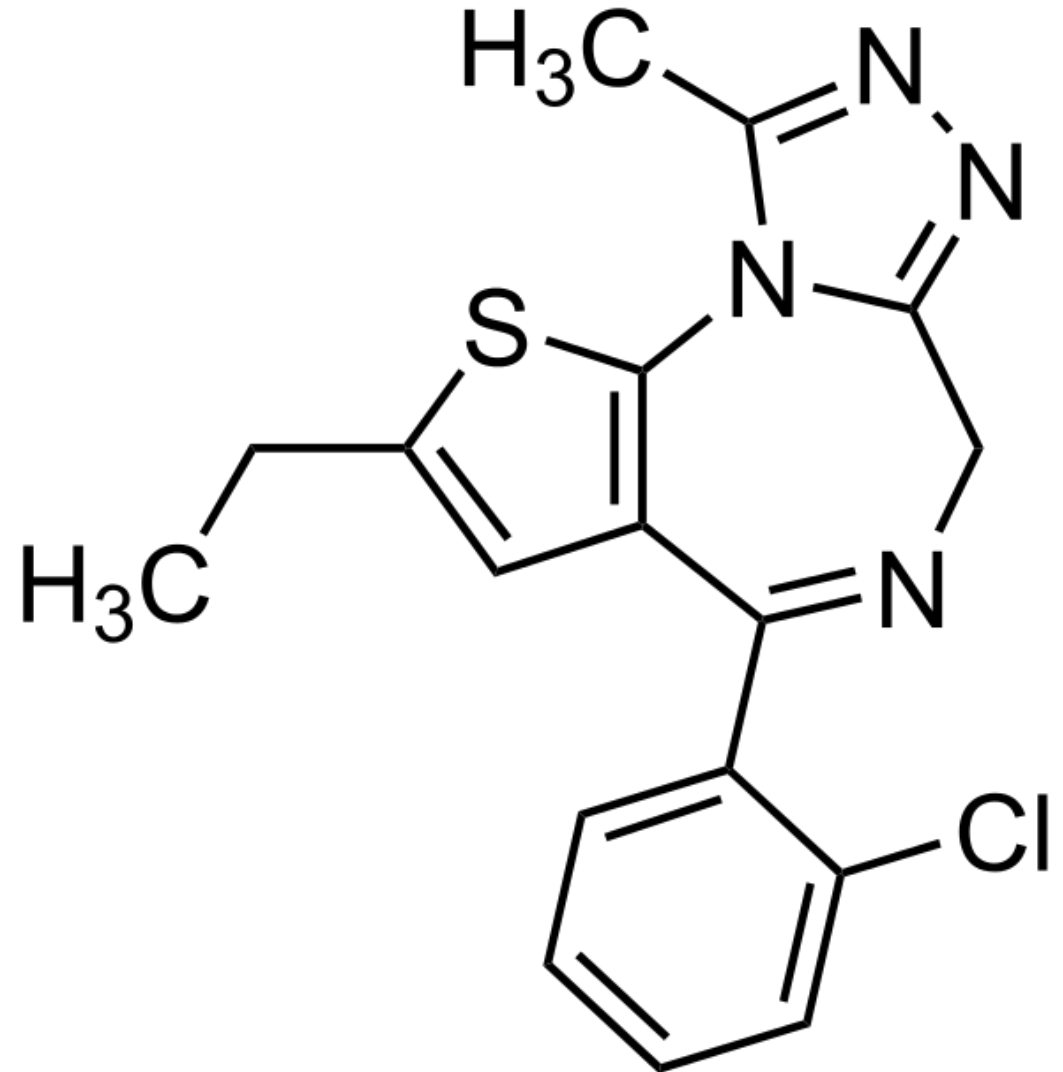
Occurrence and time course of NPS benzodiazepines in Sweden – results from intoxication cases in the STRIDA project

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^aThe Swedish Poisons Information Centre, Stockholm, Sweden; ^bDepartment of Laboratory Medicine, Division of Clinical Pharmacology,

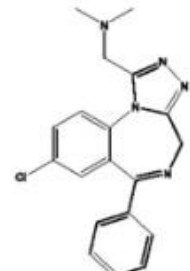
First Project STRIDA case: etizolam

- Patient found down next to 100 etizolam tablets/pellets
- Normally takes 3-4 tablets/day
- Today also drank alcohol
- Brought to hospital for CNS depression, “woke quickly”
- Observed and discharged
- Biologic samples positive for:
 - Ethanol, etizolam, methoxetamine, mitragynine

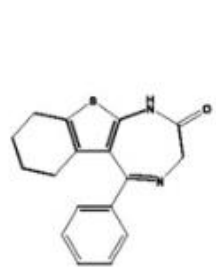


novel benzos ad nauseum

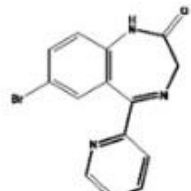
- Project STRIDA
- 2012-2016



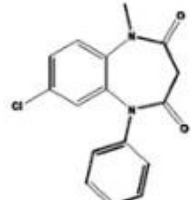
Adinazolam



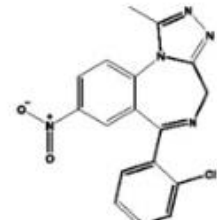
Benzazepam



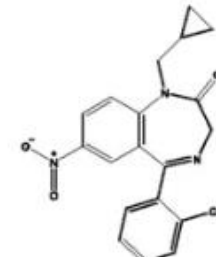
Bromazepam



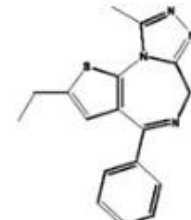
Clobazam



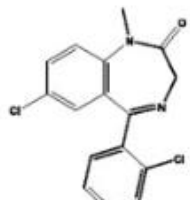
Clonazolam



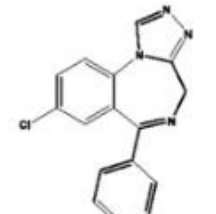
Cloniprazepam



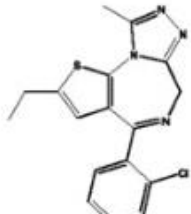
Deschloroetizolam



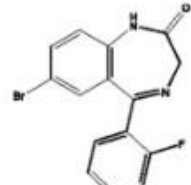
Diclazepam



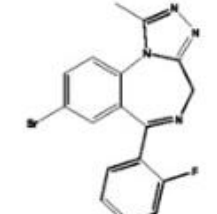
Estazolam



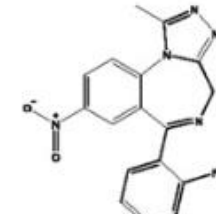
Etizolam



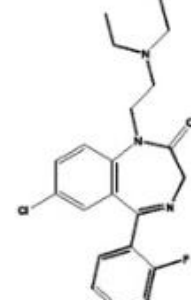
Flubromazepam



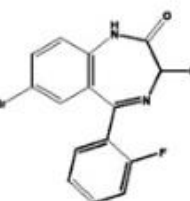
Flubromazolam



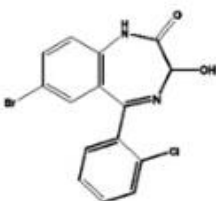
Flunitrazolam



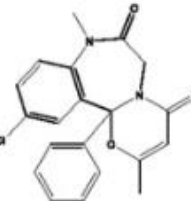
Flurazepam



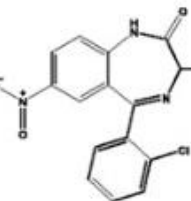
3-Hydroxy-flubromazepam



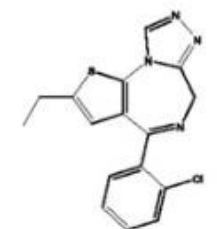
3-Hydroxy-phenazepam



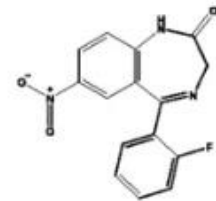
Ketazolam



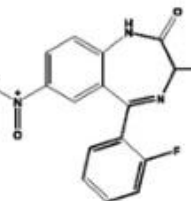
Meclonazepam



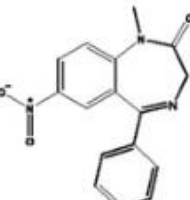
Metizolam



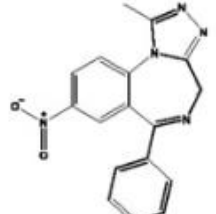
N-Desmethylflunitrazepam/Fonazepam



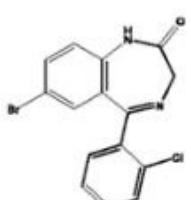
Nifoxipam



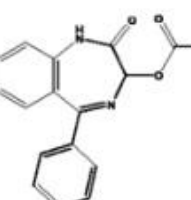
Nimetazepam



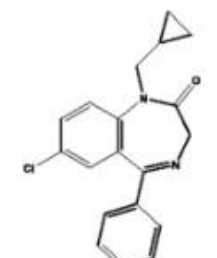
Nitrazolam



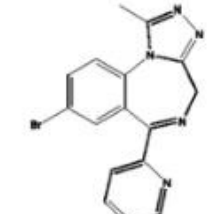
Phenazepam



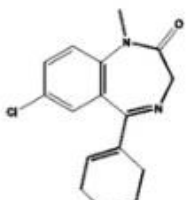
Pivoxazepam



Prazepam



Pyrazolam



Tetrazeepam

Novel benzos: etizolam common

Table 1. Subject demographics and exposure characteristics.

	Etizolam (n = 162)	Clonazolam (n = 50)	Flubromazolam (n = 13)	Total (n = 234)
Age				
Median (Range)	25 (13–63)	26 (15–50)	24 (18–36)	25 (13–63)
Gender				
Male	141 (88%)	42 (84%)	11 (85%)	201 (86%)
Female	20 (12%)	8 (16%)	2 (15%)	32 (14%)
Exposure Reason				
Misuse	24 (15%)	6 (12%)	1 (8%)	31 (13%)
Abuse	93 (57%)	30 (60%)	10 (77%)	138 (59%)
Suspected suicide	28 (17%)	10 (20%)	2 (15%)	42 (18%)
Intentional–Unknown	17 (11%)	4 (8%)	0 (0%)	23 (10%)
Exposure Type				
Acute	107 (77%)	35 (78%)	10 (77%)	158 (77%)
Acute-on-chronic	21 (15%)	3 (7%)	3 (23%)	29 (14%)
Chronic	11 (8%)	7 (16%)	0 (0%)	19 (9%)

Table 2. Single-agent exposures to designer benzodiazepines reported to NPDS, 2014–2017.

Substance	2014	2015	2016	2017	2014–2017
Etizolam	26	30	46	60	162
Clonazolam	*	*	14	36	50
Flubromazolam	*	*	2	11	13
Diclazepam	*	*	1	3	4
Flubromazepam	*	*	2	1	3
Meclonazepam	*	*	1	0	1
Norflurazepam	*	*	0	1	1
Total	26	30	66	112	234

*: Prior to 2016, exposure data was collected only for etizolam.

...but the dominant benzo can change over time

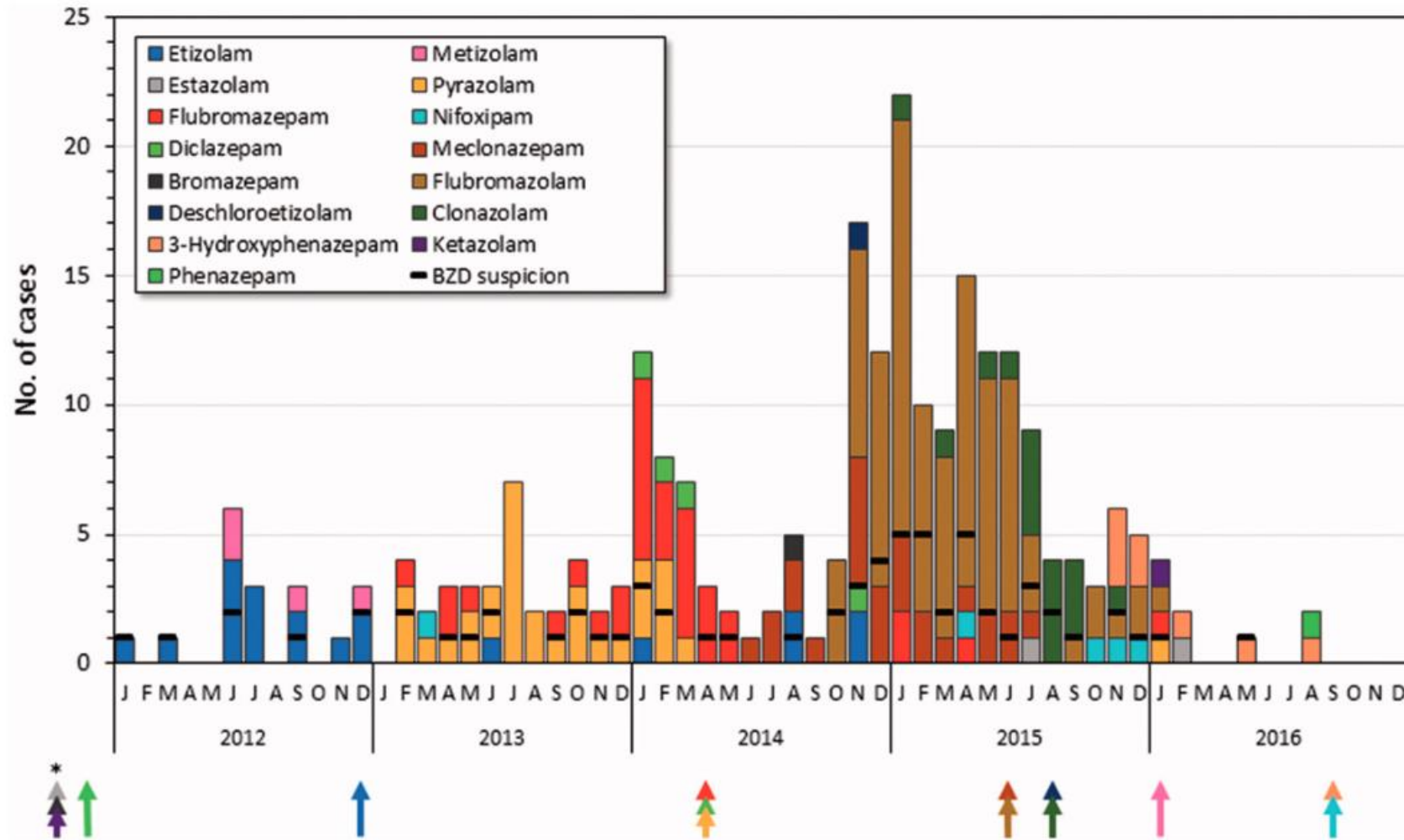


Figure 3. Analytical confirmation of cases testing positive for new psychoactive substance (NPS) benzodiazepines (BZD) in the STRIDA project in 2012–2016. Black markings represent number of suspected or claimed exposure to any BZD, and arrows represent the time for substance classification (* some substances were banned before the start of this study).

Regional variation, but beware data source

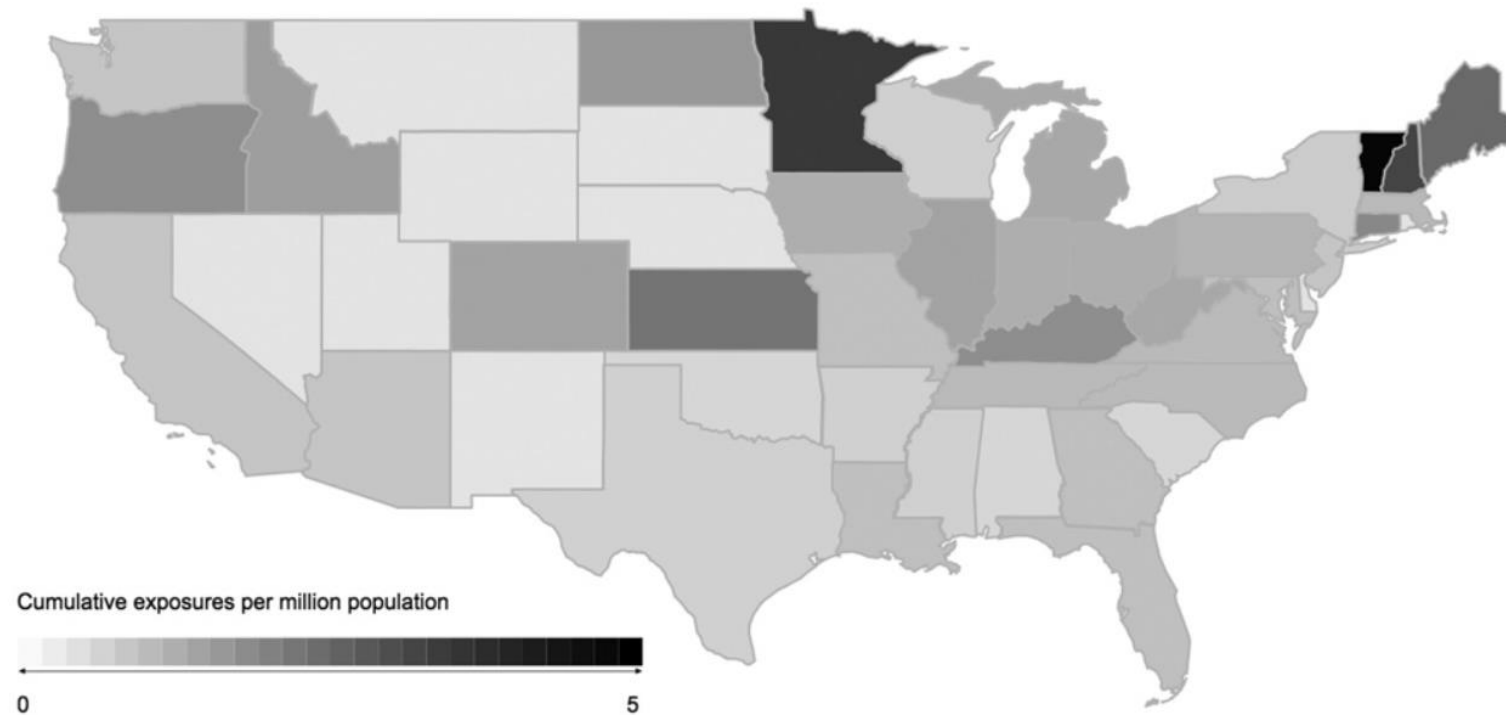


Figure 2. Cumulative designer benzodiazepines exposures reported to NPDS by state, 2014–2017. Darker shades indicate higher frequency of exposure.

Co-ingestion is the rule, not the exception

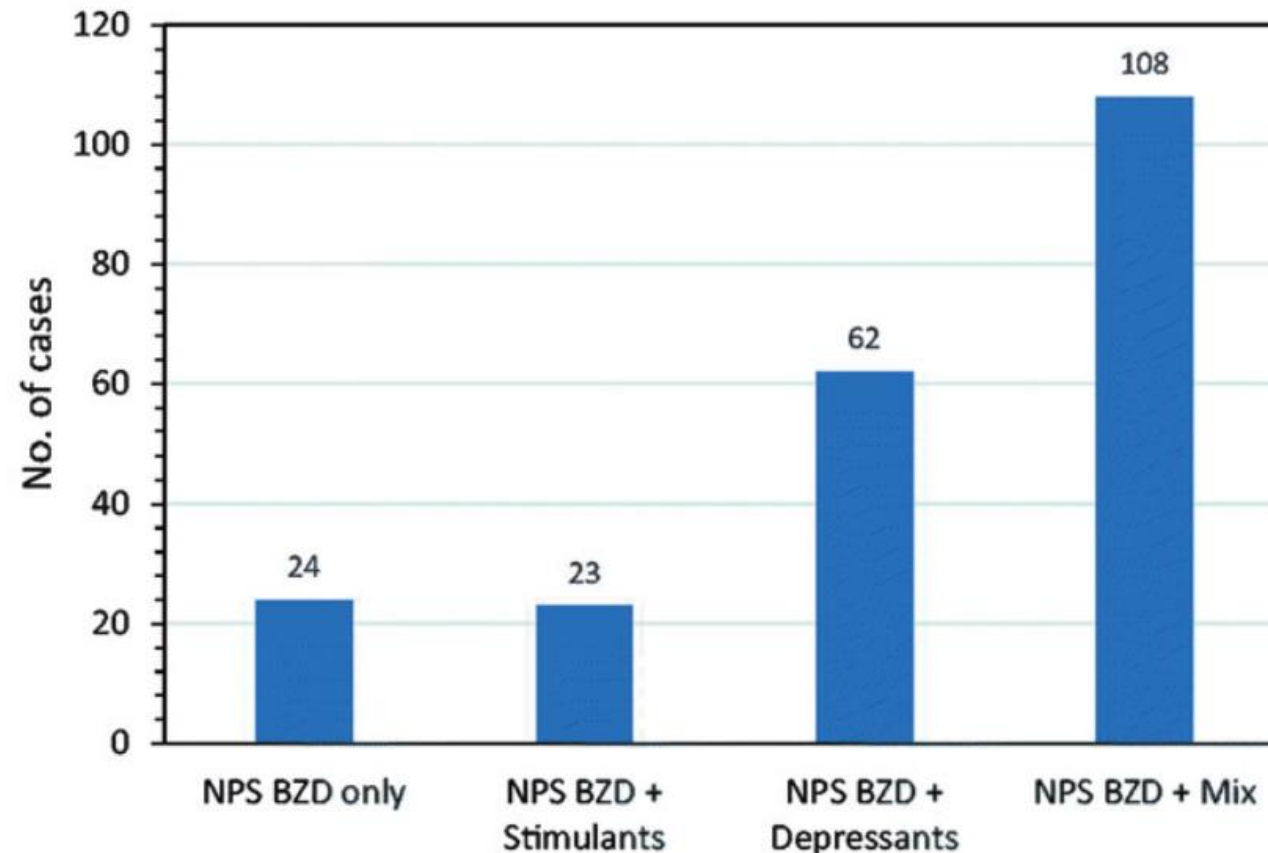
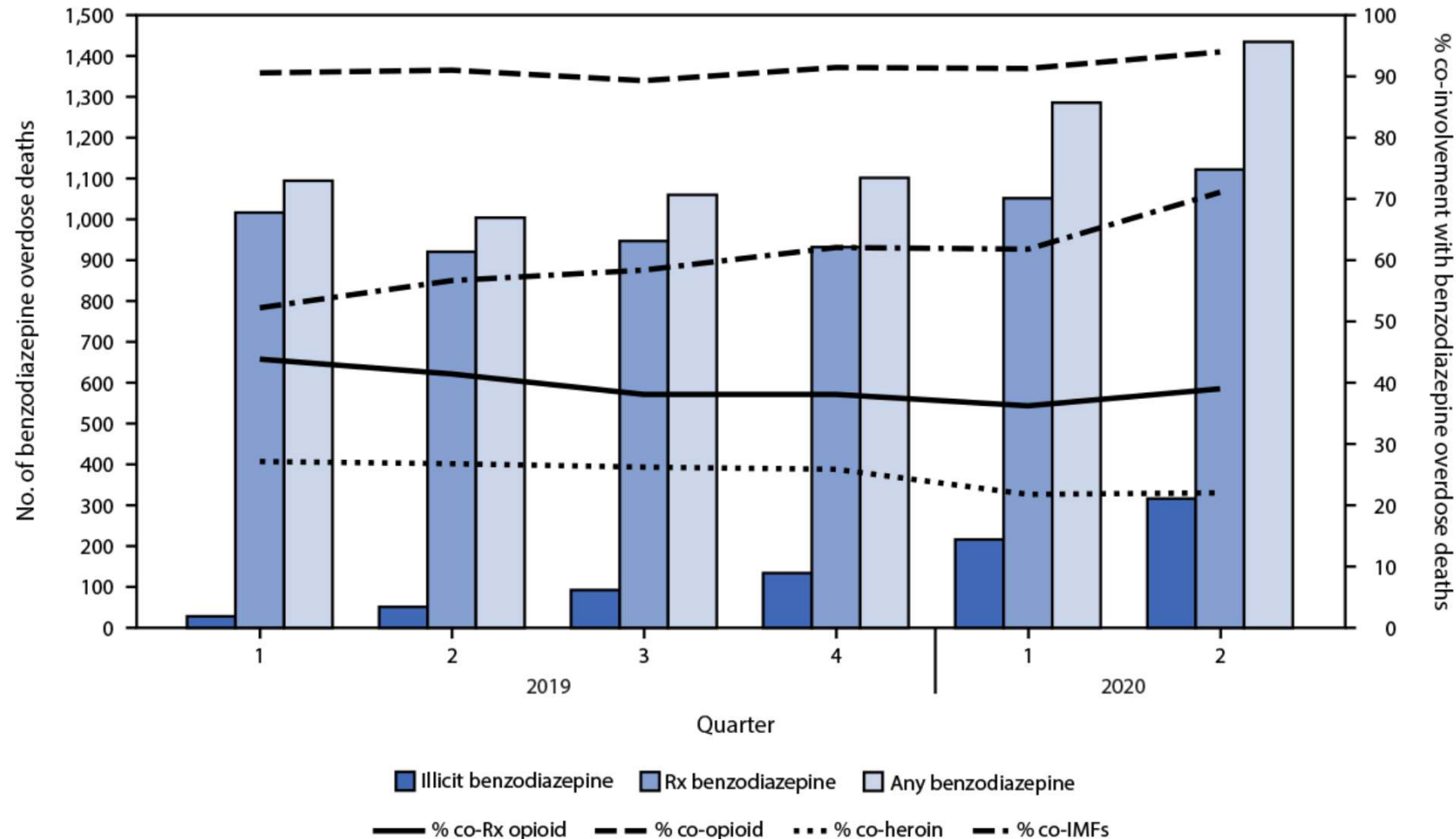


Figure 5. The concomitant use of new psychoactive substance (NPS) benzodiazepines (BZD) with other drugs, separated into stimulants, depressants, and a mixture of several drugs, in the 217 analytically confirmed intoxication cases involving NPS BZD.

benzo ODs increasing, largely from illicit

- Co-ingestion is common



Novel Benzos: Take Home Points

Use increasing

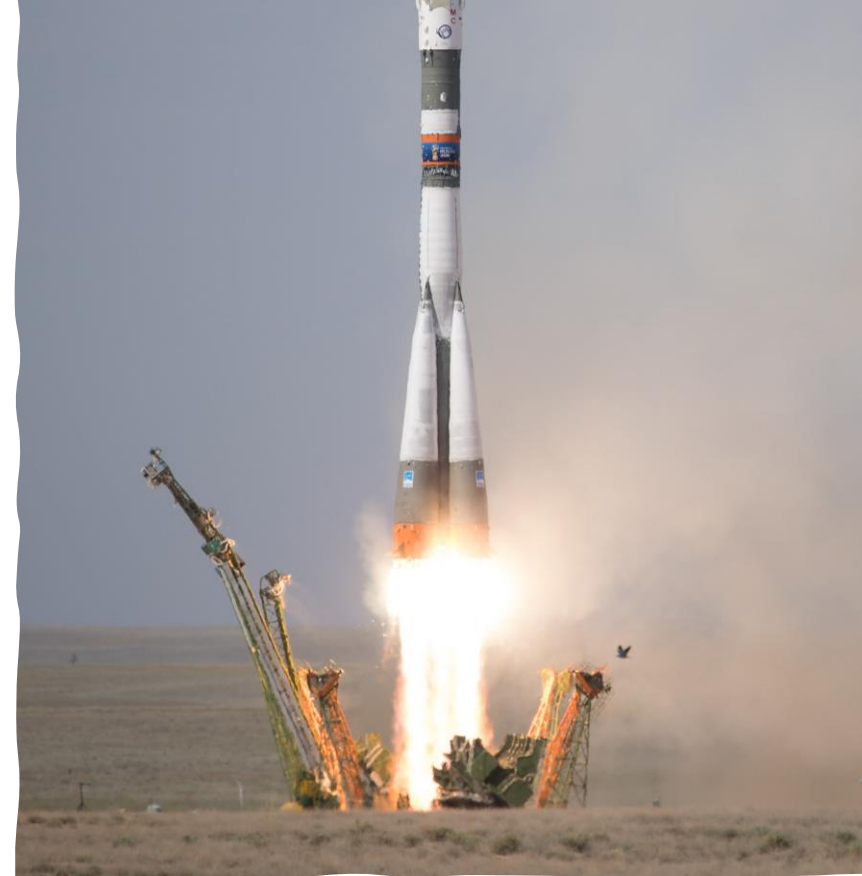
Symptoms like pharmaceutical
benzos

Co-ingestions common

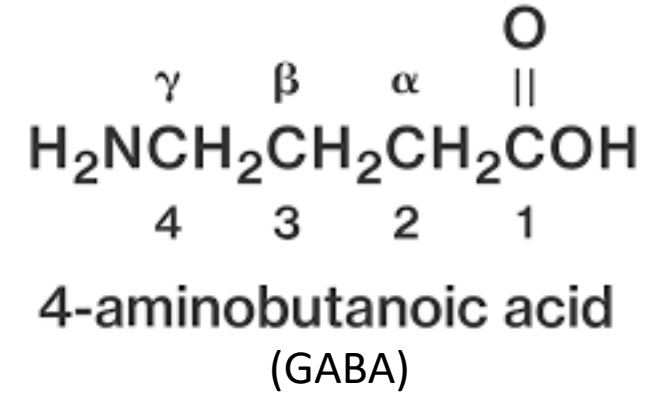
Death rare

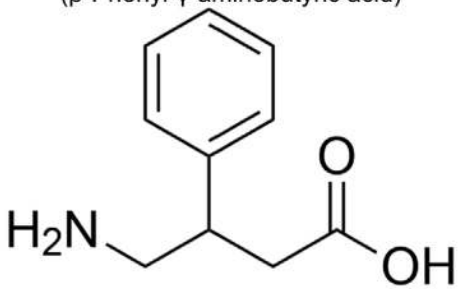
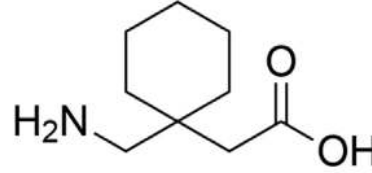
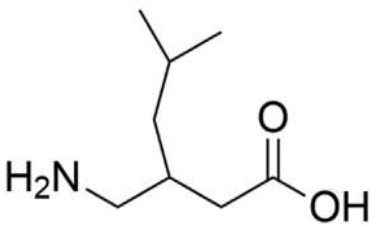
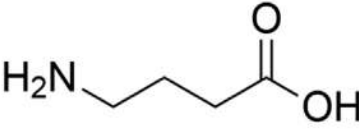
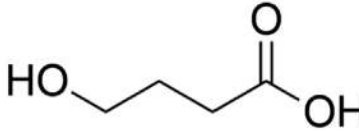
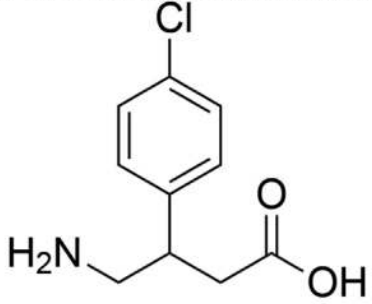
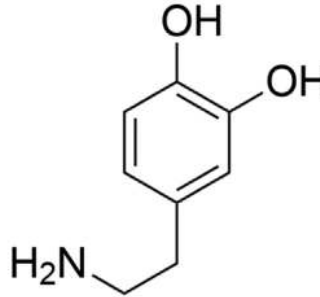
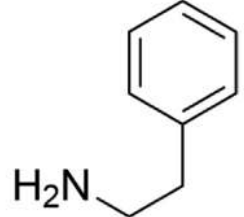
Phenibut – what is it?

- Synthetic CNS depressant
- Structurally similar to GABA
- Developed in 1960's Soviet Union to treat anxiety
- Not approved in U.S. (legal status dubious)
 - Nor in most of Europe
- Approved for use in:
 - Russia, Ukraine, Belarus, Latvia & Kazakhstan
 - To treat anxiety & insomnia



Phenibut – a complicated molecule

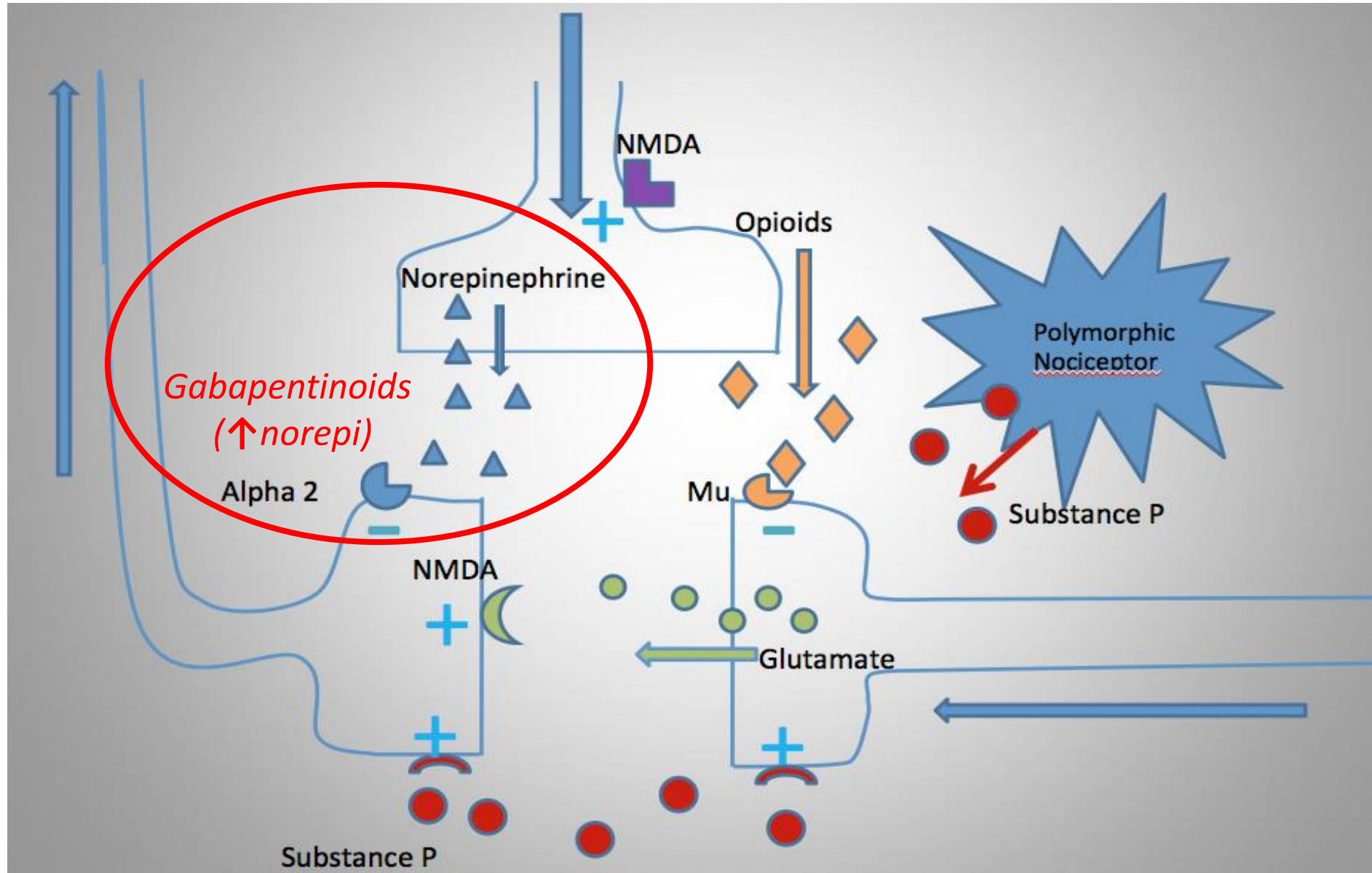


<p>Phenibut (β-Phenyl-γ-aminobutyric acid)</p> 			<p>Gabapentinoids/VGCC Inhibitors</p>	
			<p>Gabapentin</p> 	<p>Pregabalin</p> 
<p>GABA agonists</p>				
<p>GABA (γ-aminobutyric acid)</p> 	<p>GHB (γ-hydroxybutyric acid)</p> 	<p>Baclofen (β-(4-chlorophenyl)-γ-aminobutyric acid)</p> 	<p>Anxiogenics</p>	
			<p>Dopamine</p> 	<p>Phenethylamine</p> 

Gabapentinoids: Mechanism Review

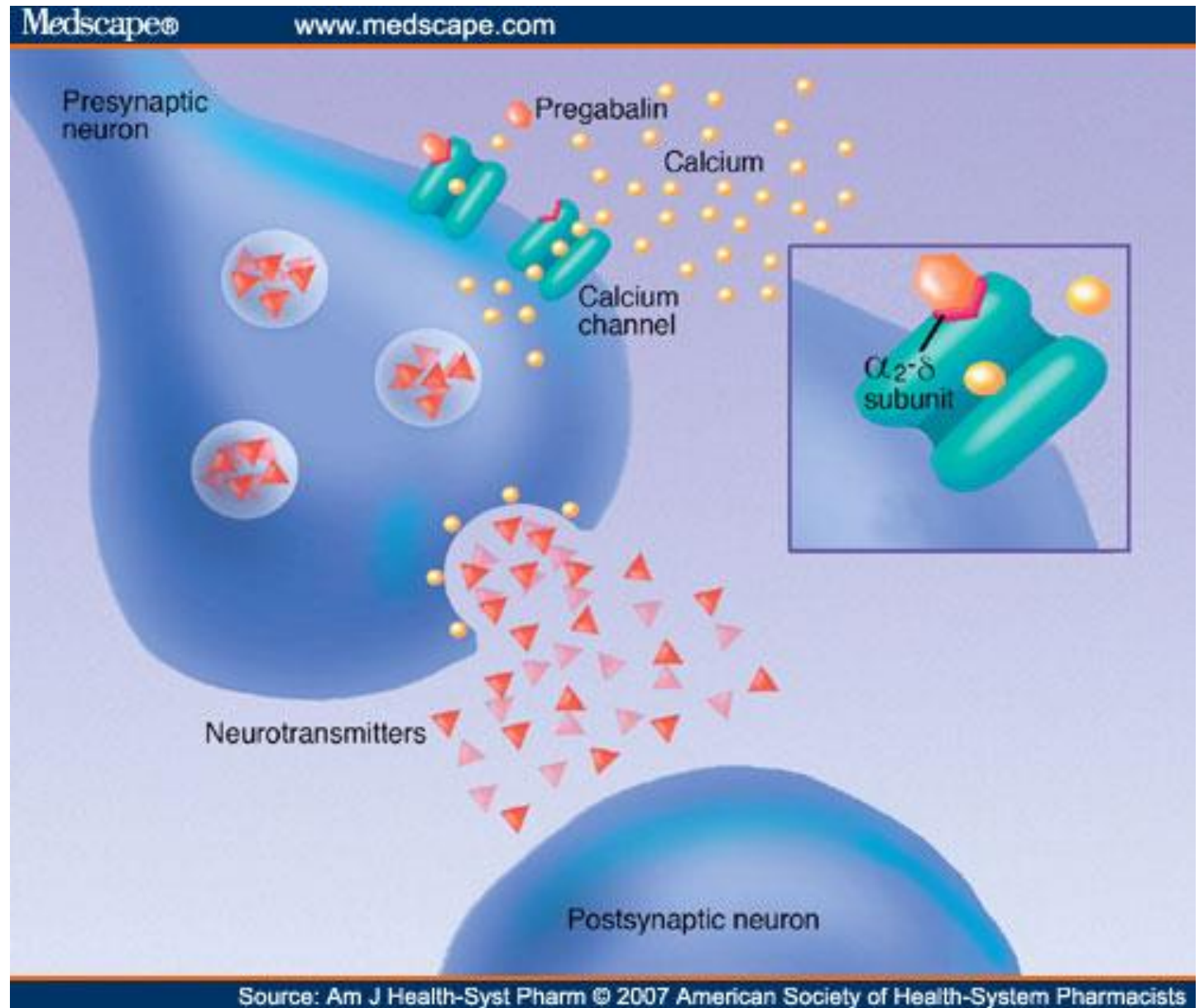
- Blocks neuro (N-type) calcium channels by binding $\alpha_2\delta-1$ subunit
- This leads to increased inhibitory tone in descending pathways.
- Calcium is probably also necessary for norepinephrine re-uptake
 - Gabapentin potentiates norepinephrine's α_2 agonism to decrease nociceptive transmission.

Gabapentinoids: Mechanism Review



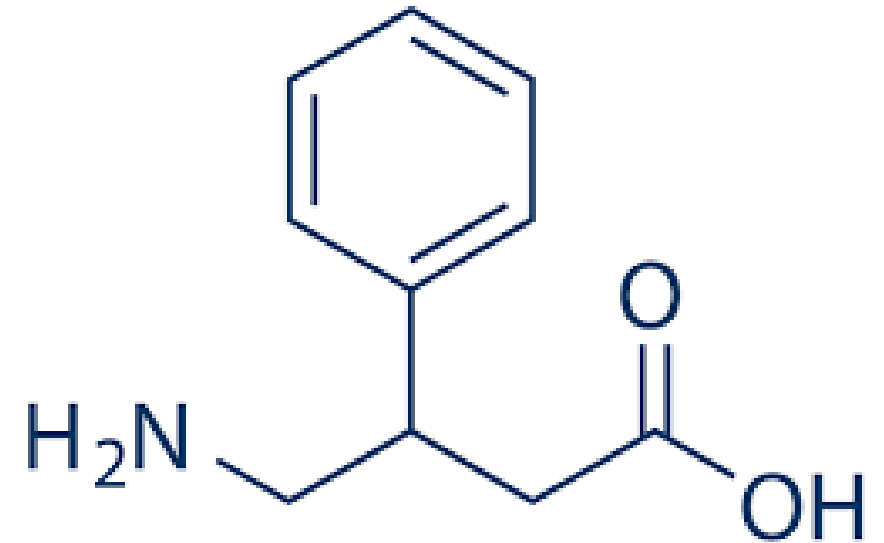
Gabapentinoids: Mechanism Review

- Blocks neuro (N-type) calcium channels by binding $\alpha 2\delta$ -1 subunit
- Increased inhibitory tone in descending pathways.
 - \uparrow norepinephrine

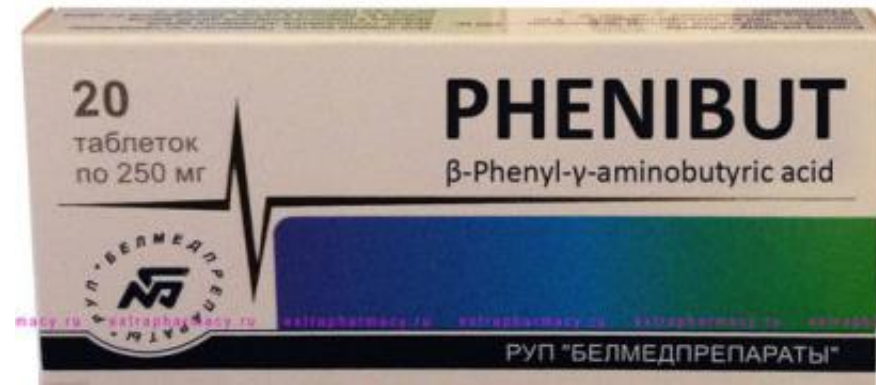


Phenibut: Pharmacology

- GABA_B agonism > GABA_A agonism
 - Similar to baclofen & GHB rather than benzos/barbs
- Antagonizing endogenous catecholamines
 - “Anxiogenics”
 - dopamine, phenethylamines
- Purported uses:
 - Nootropic
 - “supplement”
 - “anxiolytic”, “antidepressant”
- Large doses = paradoxical effects
 - Think ethanol



Phenibut overdose



- 30 YOM, GCS 13, found uncooperative, brought by ambulance
- Vitals: pulse 159, BP 164/89, SpO2 96%
- Exam: Pupils 3 mm, diaphoresis, agitated
- Treated with IV lorazepam (all given over 15 min)
 - 2 mg, 4 mg, 8 mg, 16 mg; no effect
- Intubated as he was uncooperative with care
- Mother arrives, brings 500 mg “phenibut” container (Cyrillic text)
- Extubated 2 days later, stated he took Phenibut to “get high” and “treat anxiety”

Phenibut – MN Poison Center Data 2000 - 2018

- 56 cases (48 from 2013-2018)
- 50% with CNS symptoms
- 10% complaining of withdrawal
- Reasons:
 - 48% abuse, 23% to treat anxiety
- 20% intubated

Table 3
Description of patients requiring intubation. LOC = level of consciousness.

Patient	Age/Gender	Indication for intubation	Listed coingestants	Reason for Use
1	31/M	Decreased LOC, airway protection		Abuse
2	30/M	Fluctuating mental status (somnia, agitation)	Ethanol	Abuse
3	22/M	Initial verbalized concern for “withdrawal”, hallucinations, anxiety Subsequent CNS depression and aspiration		Abuse
4	21/M	Unresponsive mental status		Abuse
5	31/M	Unresponsive mental status	Ephedra	Unknown/Chronic
6	20/F	Unresponsive mental status	Ethanol	Unknown
7	20/M	Initial depressive CNS effects Subsequent severe agitation requiring intubation	Kratom	Abuse
8	25/M	Unresponsive mental status		Abuse
9	31/M	Apneic episodes		Abuse
10	49/M	Unresponsive mental status	Ethanol	Abuse
11	27/M	Unresponsive mental status		Abuse

Phenibut: Take Home Points

GABA_B & gabapentinoid
pharmacology: (like baclofen/ethanol)

Intoxication unpredictable

Expect either agitation *or* respiratory
depression in critically ill patients

Withdrawal common and difficult to
treat

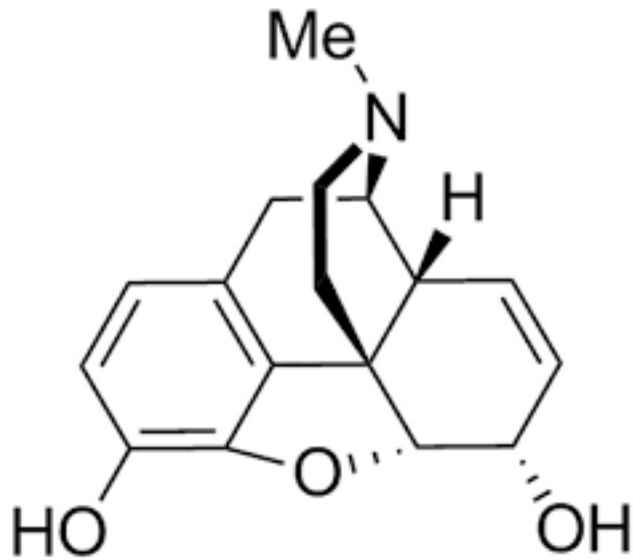
Tianeptine

- Tricyclic antidepressant (TCA) structure
- Prescribed as an antidepressant in Europe
 - Approved in France
 - Not approved in: USA, Canada, UK, Australia, NZ
 - Schedule I in Minnesota (MN Statute: 152.02)
- Sold as a nootropic & anxiolytic
- Therapeutic mechanism uncertain:
 - Initially thought to block serotonin reuptake, but...
 - ...probably works via μ and δ opioid agonism

Structure & Function

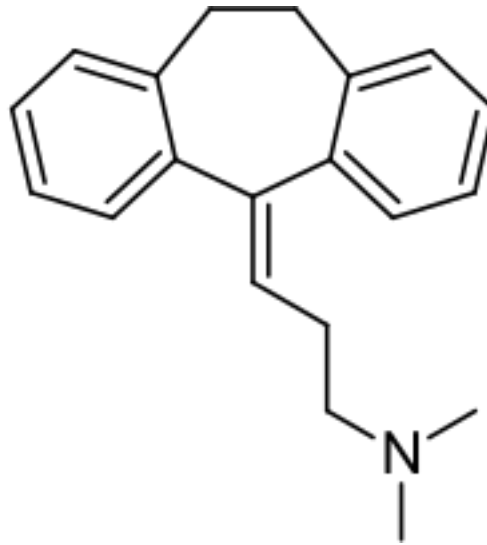
Morphine

- opioid



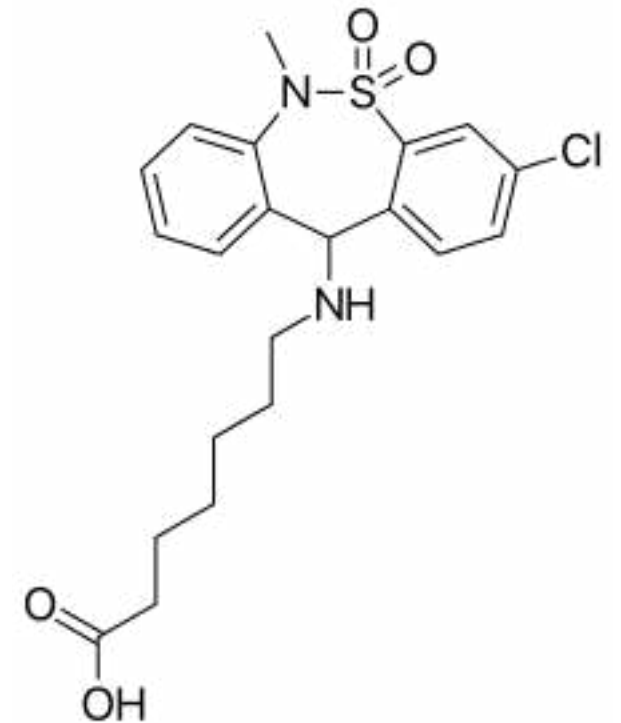
Amitriptyline

- TCA



Tianeptine

- TCA + opioid



TCA Poisoning: Review

TCA Mechanisms (7)	Clinical Effect	Treatment
<ul style="list-style-type: none">• Na⁺ channel blockade• K⁺ channel blockade• α₁-blockade• GABA-blockade• 5-HT/norepi reuptake• Antimuscarinic• Antihistamine	<ul style="list-style-type: none">• Wide QRS/♥-shock• QTc prolongation• Vasodilation/↓BP• Seizures• HTN, then ↓BP• Anticholinergic toxidrome/delirium	<ul style="list-style-type: none">• Na⁺ bicarb• Optimize electrolytes• Norepi• Benzos• Norepi• Benzos & (sometimes) physostigmine

Tianeptine: TCAs + Opioids all in one?

- 36 YOM injected white powder to “see into the future.”
- Became unresponsive, bystander 911, 1 mg empiric naloxone
- In ED, miosis, resp rate = 6, woke with IV naloxone 0.4 mg x 2
 - Naloxone infusion at 0.2 mg/hour
 - Vitals now: pulse 72/min, BP 94/43, resp 12/min, SpO2 98%
- ECG: QRS = 104 ms, QT = 461 ms
- Labs unremarkable (ethanol 133 mg/dL)
- Naloxone infusion x 9 hours, then 4 additional hours observation & d/c
- Urine: neg for TCAs, pos for tianeptine

Tianeptine: Poison Center Data

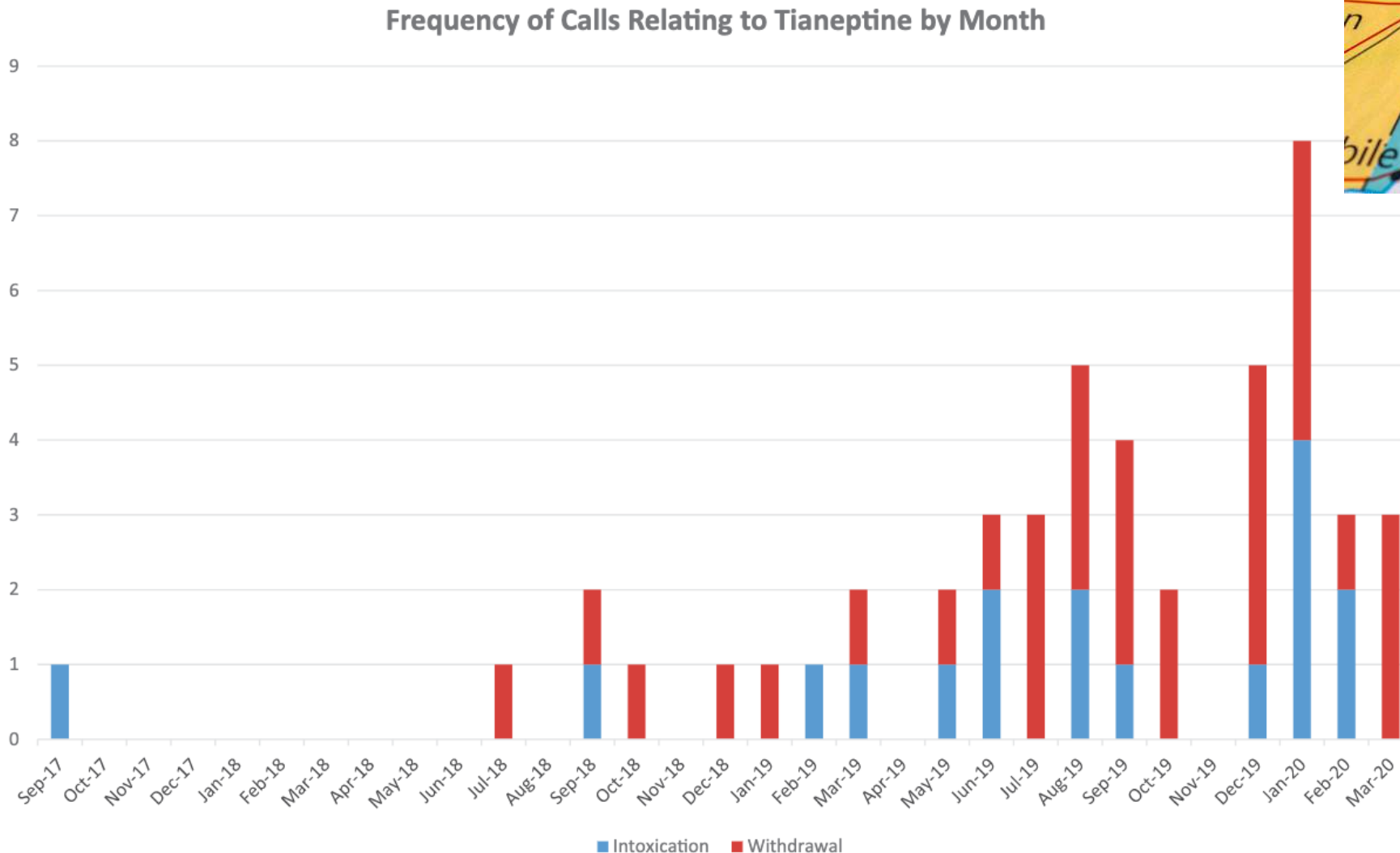


Figure 2. Frequency of calls to the poison center from January 1, 2015 to March 15, 2020. No calls regarding tianeptine were received prior to September 2017.

Tianeptine in 2015 - 2020



- 48 cases: 17 intoxication, 31 withdrawal
- 17 patients (35%) in ICU
 - 11 intoxication, 6 withdrawal
 - No deaths
 - Agitation most common reason for ICU in *both* intoxication & withdrawal
- Opioid effects common
 - 4 patients received naloxone
- TCA effects (except agitation) less common
 - No cases of QRS widening or seizures
 - No patients received vasopressors

Tianeptine: Take Home Points

Opioid and TCA pharmacology

Poisoning mostly opioid effects, TCA effects rare

Opioid effects respond to naloxone

Expect either agitation *or* respiratory depression in critically ill patients

Xylazine – “Tranq-dope”

- Not a controlled substance
- FDA-approved for veterinary use only as a sedative
 - Commonly administered with ketamine or barbiturates
- Pharmacology:
 - α_2 -agonist
 - Sedation
 - Hypotension
 - Vasoconstriction
- Combined with fentanyl
 - First common in Puerto Rico
 - Appeared in Philadelphia \approx 2019



Central α_2 agonists

Oral Meds

- clonidine (Catapres[®])
- guanfacine (Tenex[®])
- guanabenz
- methyldopa (Aldomet[®])
- tizanidine (Zanaflex[®])

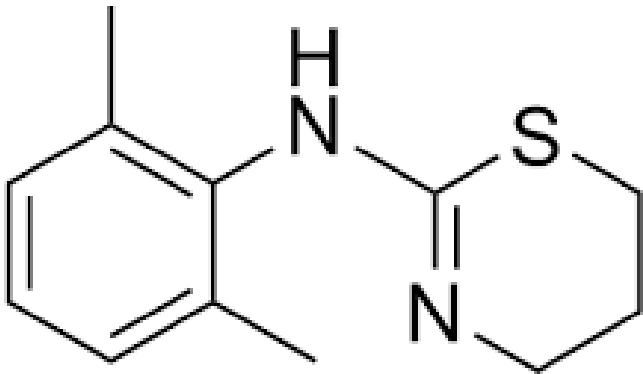
IV, Eye, Nasal, and Derm Meds

- dexmedetomidine (Precedex[®])
- apraclonidine (Iopidine[®])
- brimonidine (Mirvaso[®], Lumify[®], Alphagan P[®])
- dexmedetomidine (Precedex[®])
- xylazine – veterinary medicine only
- Imidazolines
 - oxymetazoline (Afrin[®])
 - naphazoline (Clear Eyes[®])
 - tetrahydrozoline (Visine[®])

Structure & Function

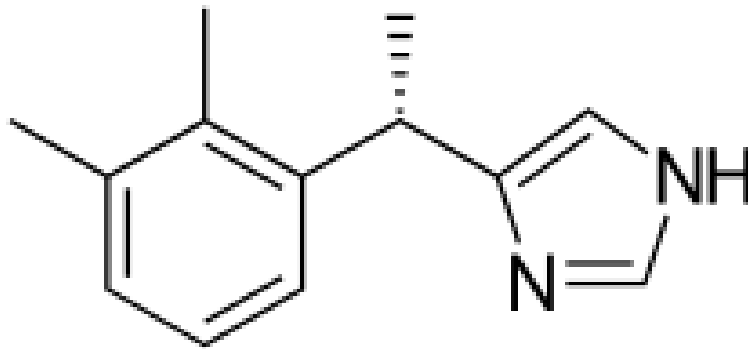
Xylazine

- Veterinary sedative



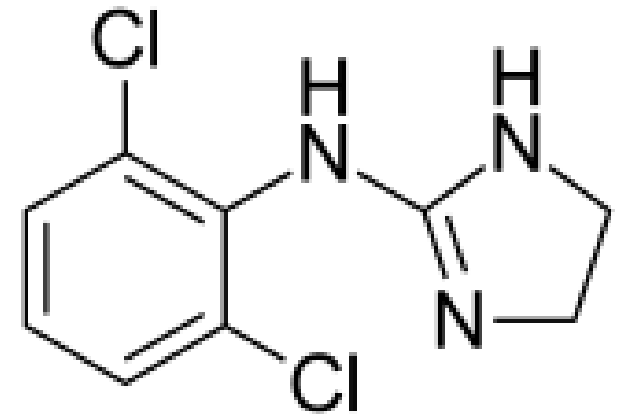
Dexmedetomidine

- ICU sedative

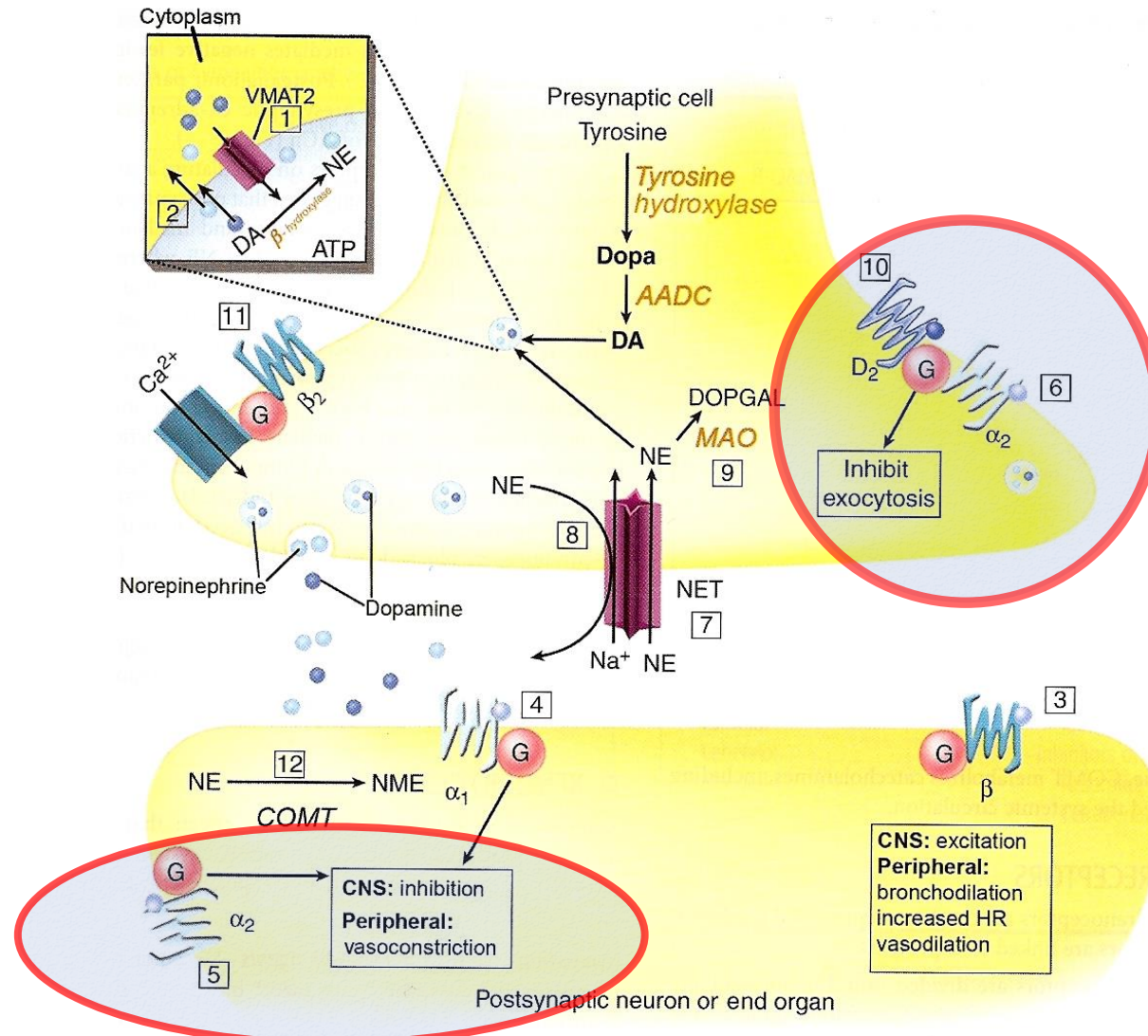


Clonidine

- antihypertensive



α_2 agonist mechanisms: sympatholysis & vasoconstriction



Central α_2 agonists - management

- Atropine for bradycardia
- Norepinephrine if pressors needed
- Consider *naloxone*
 - Endogenous CNS opioids may modulate sympathetic outflow, *high doses required*
 - Dose: 10 mg IV push, all at once
- α_2 antagonists (yohimbine and tolazoline) are not approved for human use in the USA

CLINICAL TOXICOLOGY
2018, VOL. 56, NO. 10, 873–879
<https://doi.org/10.1080/15563650.2018.1450986>

CLINICAL RESEARCH

Naloxone reversal of clonidine toxicity: dose, dose, dose

Donna L. Seger^{a,b} and Justin K. Loden^b

^aDepartment of Medicine, VUMC, Nashville, TN, USA; ^bTennessee Poison Center, Nashville, TN, USA

Unique Skin Findings... Maybe

- Ulcers purported to come from
 - Vasoconstriction
 - Hypotension (↓perfusion)
- Case reports often without confirmatory testing
- Adulterants also often not accounted for



We've seen skin lesions like this before

- “Krokodil,” an opioid, easily synthesized from codeine.
 - Only takes 30-60 min to prepare
 - 100,000 active users in Russia
- Name derived from α -chlorocodide, a precursor.
- Impurities (e.g., gasoline) may be cause phlebitis and gangrene
- Even published cases...
 - often not confirmed
 - Impurities not screened for



Fig 1. Krokodil-induced necrotic ulcerations of the bilateral forearms.



Fig 2. Krokodil-induced deep ulceration of the right forearm with nearly exposed tendon.

Regardless, Xylazine is becoming more common

J. Friedman et al.

Drug and Alcohol Dependence 233 (2022) 109380

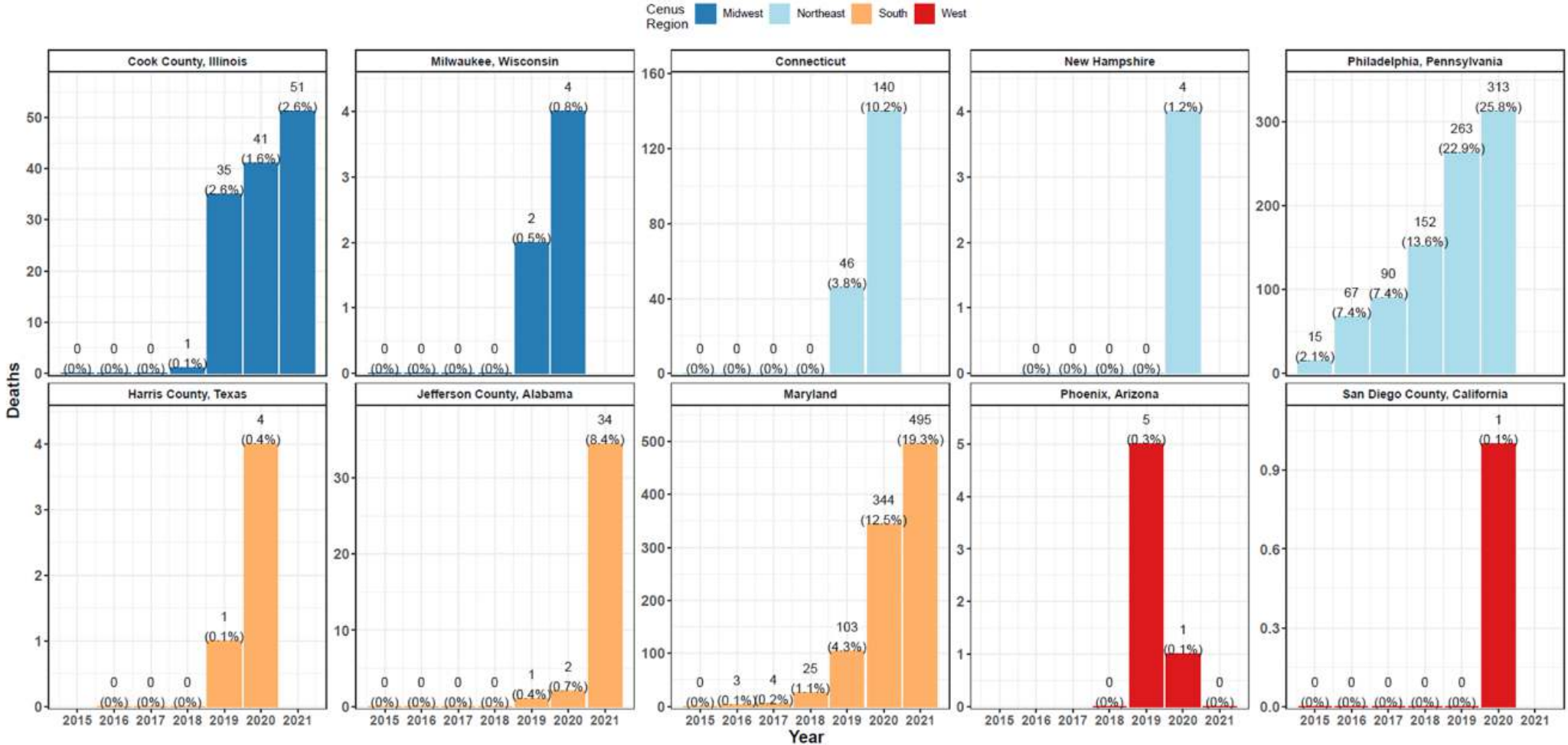
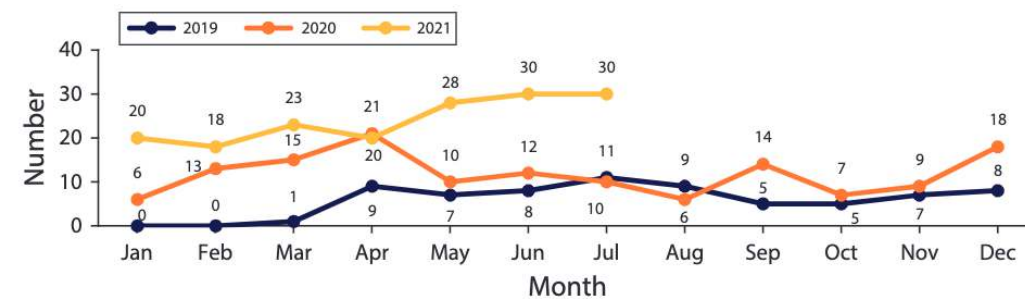
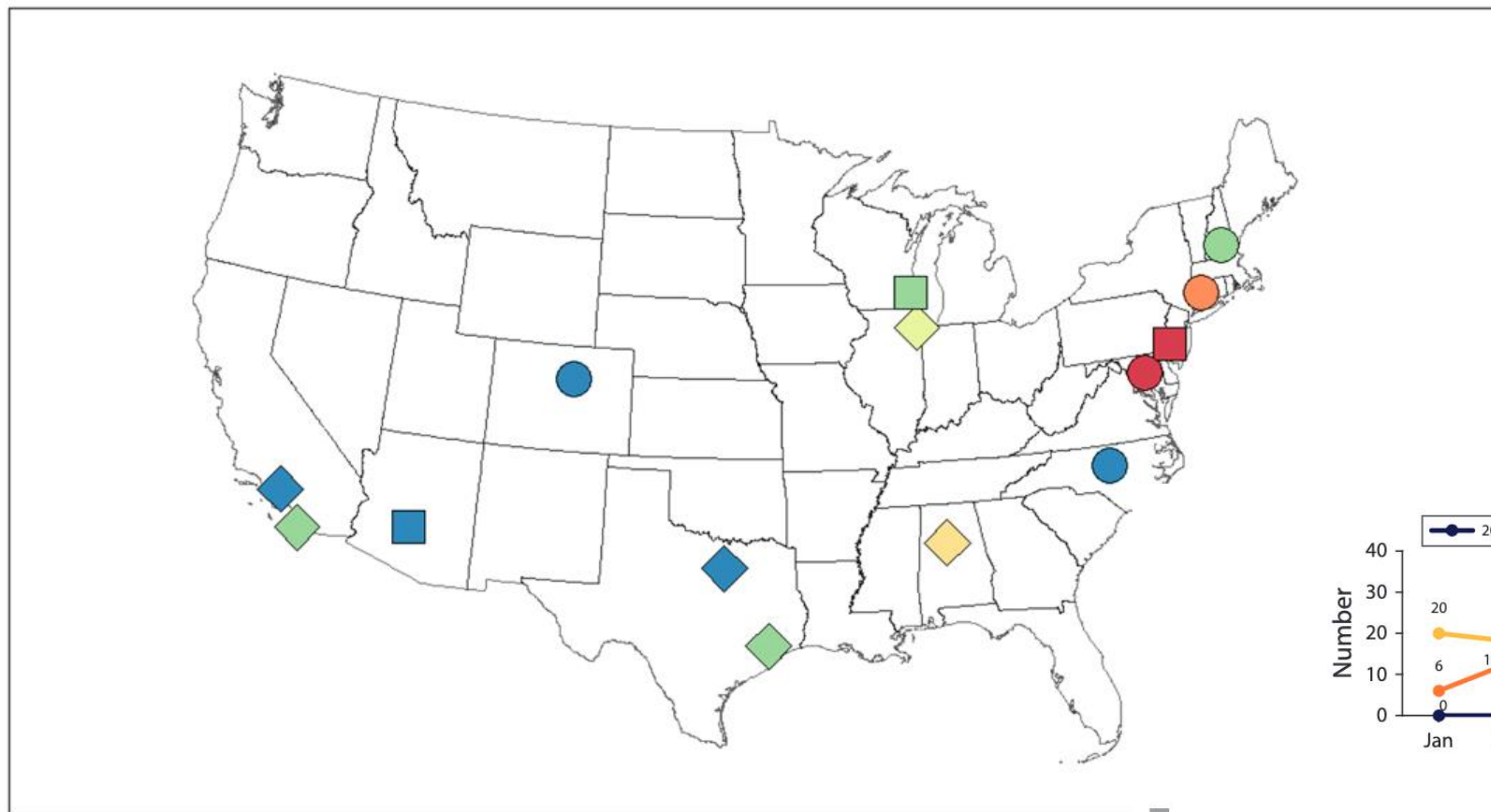


Fig. 1. Xylazine-Present Overdose Deaths by Jurisdiction and Year. Xylazine-present deaths are shown as counts and as a percent of all overdose deaths in text. Color indicates US census region. Values for 2021 represent estimates, should trends from the observed fraction of the year continue linearly.

Xylazine in overdose deaths: 2021 (regional variation)

Type of Jurisdiction: City (square), County (diamond), State (circle). Xylazine Positivity: 0% (blue), >0%-2% (green), 2%-5% (light green), 5%-10% (yellow), 10%-15% (orange), 15+% (red).



Friedman et al. *Drug Alcohol Depend.* 2022 Apr 1;233:109380.

FIGURE 1— Number of Xylazine-Involved Overdose Deaths, by Month: Connecticut, 2019-2021

Source. Adapted from the Connecticut Department of Public Health.¹⁴

Alexander et al. *Am J Public Health.* 2022 Aug;112(8):1212-1216.

Xylazine + fentanyl = ↑deaths?

Hot off the press! (NACCT 2022)

13. “Tranq dope” opioid overdose: clinical outcomes for emergency department patients with illicit opioid overdose adulterated with xylazine

- Multi-center (9 EDs), prospective cohort study of suspected opioid OD
 - Discarded biologics analyzed
- Outcomes:
 - Cardiac arrest requiring CPR (primary)
 - Coma within 4 hours of arrival
- Multivariable regression
- Findings:
- “Tranq-dope” (xylazine) patients (n=90) tended to have less severe outcomes (less risk of cardiac arrest or coma) than just opioids (n=271)
 - Xylazine odds of cardiac arrest (OR: 0.30; 95% CI: 0.10 – 0.92)
 - Xylazine odds of coma within 4 hours (OR 0.52; 95% CI: 0.29 – 0.94)

Xylazine: Take Home Points

α_2 -agonist pharmacology: Sedation, hypotension, vasoconstriction

Increasingly found in fentanyl supply & overdoses

Might be associated with ulcers

Unclear if xylazine-adulterated fentanyl causes worse outcomes

Travis's slides now

Just a slide to save this dopamine figure

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