



## Clinical Pharmacology & Toxicology Pearl of the Week

### “Benzos, Benzos, Benzos”

#### Case

- ✓ A 43 year-old female presents to the ED after ingesting 2 grams of amitriptyline in a suicide attempt
- ✓ She presents three hours post-ingestion with a GCS of 9, HR 130, BP 90/70. QRS duration on ECG is 150ms
- ✓ Appropriate treatment is started and the patient seizes
- ✓ You decide to use benzodiazepines to treat this patient. Which benzo would you use and why?
- ✓ Is there any benefit to switching benzos in the same patient?
- ✓ How would your management change if this patient was in ethanol withdrawal or liver failure? What if they didn't have IV access?

#### Background

- ✓ Benzodiazepines increase inhibitory GABAergic neurotransmission by binding to their site on the GABA-A receptor, which is a ligand-gated chloride channel (see Figure).
- ✓ While the most common benzos are often used interchangeably, they have different onsets, peak effects and kinetics that render some more beneficial than others for various conditions (see Table below).
- ✓ Knowledge of time to onset of action and duration of action of various benzodiazepines allows safe and rapid dosing titration without over-sedation (see Table below).

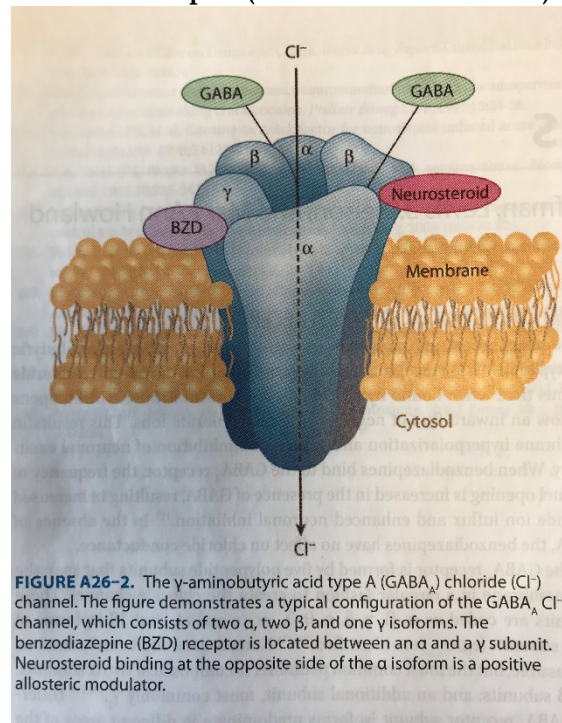
#### Kinetics

- ✓ Hepatic failure results in decreased clearance of benzos requiring hepatic metabolism (e.g. diazepam, midazolam).
- ✓ Active metabolites may prolong the clinical effect of some benzos (e.g. diazepam, midazolam), whereas others have no active metabolites (e.g. lorazepam).

#### Special considerations

- ✓ If IV access is not available, midazolam is the preferred benzodiazepine to use IM as it has the quickest onset of action (3 – 10 minutes) when given IM.
- ✓ Diazepam has erratic absorption when given IM and is therefore not preferred if the patient has no IV access.
- ✓ Lorazepam has a slower peak effect when used for sedation because of its decreased lipophilicity.
- ✓ Switching from one benzodiazepine to another is rarely indicated, and increases the risk of an adverse drug event from unpredictable peak effects and different dosing intervals.
- ✓ Paradoxical reactions to benzos can occur, in which some patients become more agitated after benzodiazepine administration, particularly children.

GABA-A receptor (from Goldfrank 11<sup>th</sup> ed.)



**FIGURE A26-2.** The  $\gamma$ -aminobutyric acid type A (GABA<sub>A</sub>) chloride (Cl<sup>-</sup>) channel. The figure demonstrates a typical configuration of the GABA<sub>A</sub> Cl<sup>-</sup> channel, which consists of two  $\alpha$ , two  $\beta$ , and one  $\gamma$  isoforms. The benzodiazepine (BZD) receptor is located between an  $\alpha$  and a  $\gamma$  subunit. Neurosteroid binding at the opposite side of the  $\alpha$  isoform is a positive allosteric modulator.

**Pharmacodynamic profile and typical dosing strategy for common IV benzodiazepines (from Goldfrank 11th ed.)**

	<b>Diazepam IV</b>	<b>Midazolam IV</b>	<b>Lorazepam IV</b>
<b>Onset of action</b>			
Anticonvulsant	Rapid (minutes)	Rapid (minutes)	Rapid (minutes)
Sedation	1-2 minutes	1-2 minutes	5 - 20 minutes
<b>Duration of action</b>			
Anticonvulsant	1 - 2 hours	30 - 80 minutes	Many hours
Sedation			
Single dose	Short	Short	Long
Repeat dose	Long (from active metabolites)	Intermediate (from active metabolites)	Long
<b>Equivalency</b>	5 mg	2 mg	1 mg
<b>Typical starting dose</b>	5 - 10 mg	2 - 5 mg	1 - 2 mg
<b>Dosing interval</b>	Q5 - 10 min	Q5 - 10 min	Q15 - 20 min
<b>Conditions where this drug is preferred</b>	Sedative-hypnotic/ethanol withdrawal, rapid control of agitation	Rapid control of agitation, seizure cessation	Seizure cessation, patient with hepatic failure

**References**

1. Goldfrank's Toxicologic Emergencies, 11<sup>th</sup> ed., 2019.



The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Click [HERE](#) for more details.



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