# Clinical Pharmacology & Toxicology Pearl of the Week

## "Benzos, Benzos, Benzos"

**Case**

- ✓ A 19 year-old female presents to the ED after ingesting an unknown amount of venlafaxine in a suicide attempt
- ✓ She presents three hours post-ingestion with a GCS of 15, HR 108, BP 142/79. QRS duration on ECG is 173 ms. No clonus or rigidity, 3+ reflexes to lower extremities
- ✓ During observation in the ED, the patient develops dilated pupils and spontaneous clonus to her legs
- ✓ 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).

**GABA-A receptor (from Goldfrank 11th ed.)**

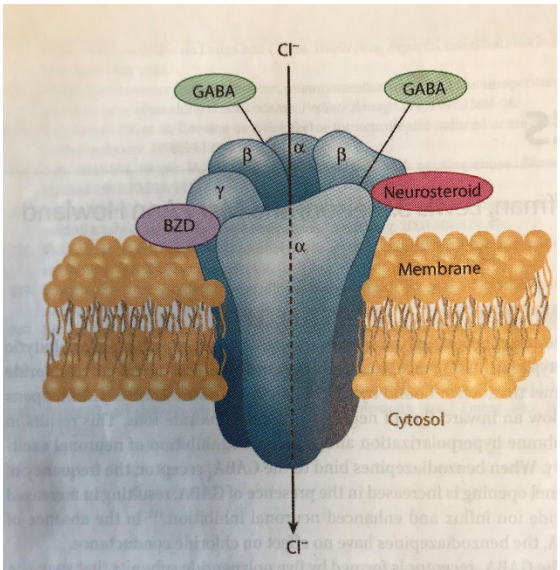


**FIGURE A26–2.** The γ-aminobutyric acid type A ($GABA_A$) chloride ($Cl^-$) channel. The figure demonstrates a typical configuration of the $GABA_A$ $Cl^-$ channel, which consists of two α, two β, and one γ isoforms. The benzodiazepine (BZD) receptor is located between an α and a γ subunit. Neurosteroid binding at the opposite side of the α isoform is a positive allosteric modulator.

**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.

**Pharmacodynamic profile and typical dosing strategy for common IV benzodiazepines (from Goldfrank 11th ed.). Note that these dosing intervals are only suggestions.**

| | **Diazepam IV** | **Midazolam IV** | **Lorazepam IV** |
|---|---|---|---|
| **Onset of action** | | | |
| Anticonvulsant | Rapid (minutes) | Rapid (minutes) | Rapid (minutes) |
| Sedation | 1-2 minutes | 1-2 minutes | 5 – 20 minutes |
| **Duration of action** | | | |
| 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 |
| **Equivalency** | 5 mg | 2 mg | 1 mg |
| **Typical starting dose** | 5 – 10 mg | 2 – 5 mg | 1 – 2 mg |
| **Dosing interval** | Q5 – 10 min | Q5 – 10 min | Q15 – 20 min |
| **Conditions where this drug is preferred** | Sedative-hypnotic/ethanol withdrawal, rapid control of agitation | Rapid control of agitation, seizure cessation | Seizure cessation, patient with hepatic failure |

**Treatment endpoints**

- ✓ If used for agitation, the goal is rapid sedation equivalent to a Richmond Agitation Sedation Scale (RASS) of 0 to -2 (i.e. alert and calm to light sedation, briefly awakens to voice for less than 10 seconds)
- ✓ If used for seizure, the goal is termination of seizure
- ✓ Avoid benzodiazepine orders that are written only for treating a specific heart rate or specific beats of clonus as this may lead to oversedation and unnecessary treatment

| Richmond Agitation and Sedation Scale (RASS) | | |
|---|---|---|
| +4 | 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 not aggressive or vigorous |
| 0 | Alert & calm | |
| -1 | Drowsy | Not fully alert, but has sustained awakening to *voice* (eye opening & contact ≥ 10 sec) |
| -2 | Light sedation | Briefly awakens to *voice* (eye opening & contact < 10 sec) |
| -3 | Moderate sedation | Movement or eye-opening to *voice* (but no eye contact) |
| -4 | Deep sedation | No response to voice, but movement or eye opening to *physical* stimulation |
| -5 | Unarousable | No response to *voice or physical* stimulation |

Pbrainmd.wordpress.com

**Case resolution**

- ✓ The patient receives 250 mg of diazepam over several hours in the ED
- ✓ ICU is called to assess because of concerns about airway protection from oversedation
- ✓ ICU determines the patient is stable to admission to the medical ward. Patient is admitted to medicine and makes a full recovery

**The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm, excluding stat holidays. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral, Specialist Link, and RAAPID. You can also find us in the Alberta Referral Directory (ARD) by searching "Pharmacology" from the ARD home page. Click HERE for more details about the service.**

**The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in Alberta Referral Directory (ARD) by searching "Toxicology" from the ARD home page.**

**More CPT Pearls of the Week can be found HERE.**

**Created: December 20, 2024**

**Reviewed: March 17, 2025**