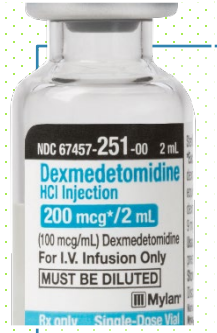

*Spreading Knowledge – Improving Outcomes*

# Sedative Agents

# Sedatives Pharmacology


Benzodiazepines

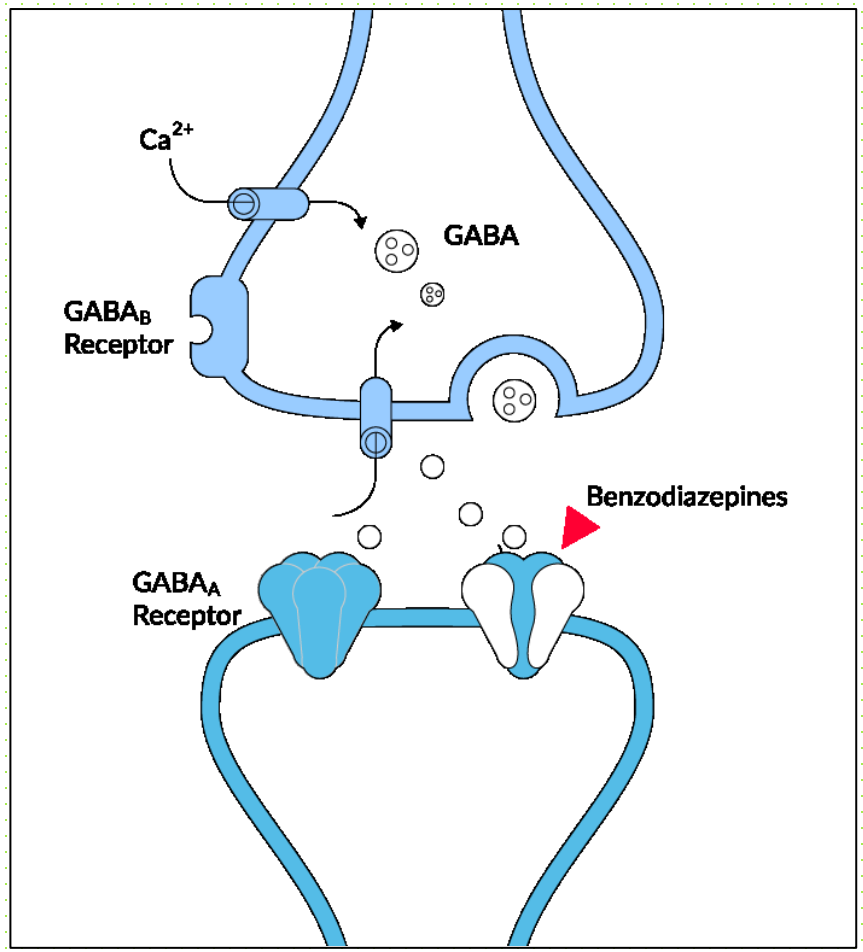

Propofol

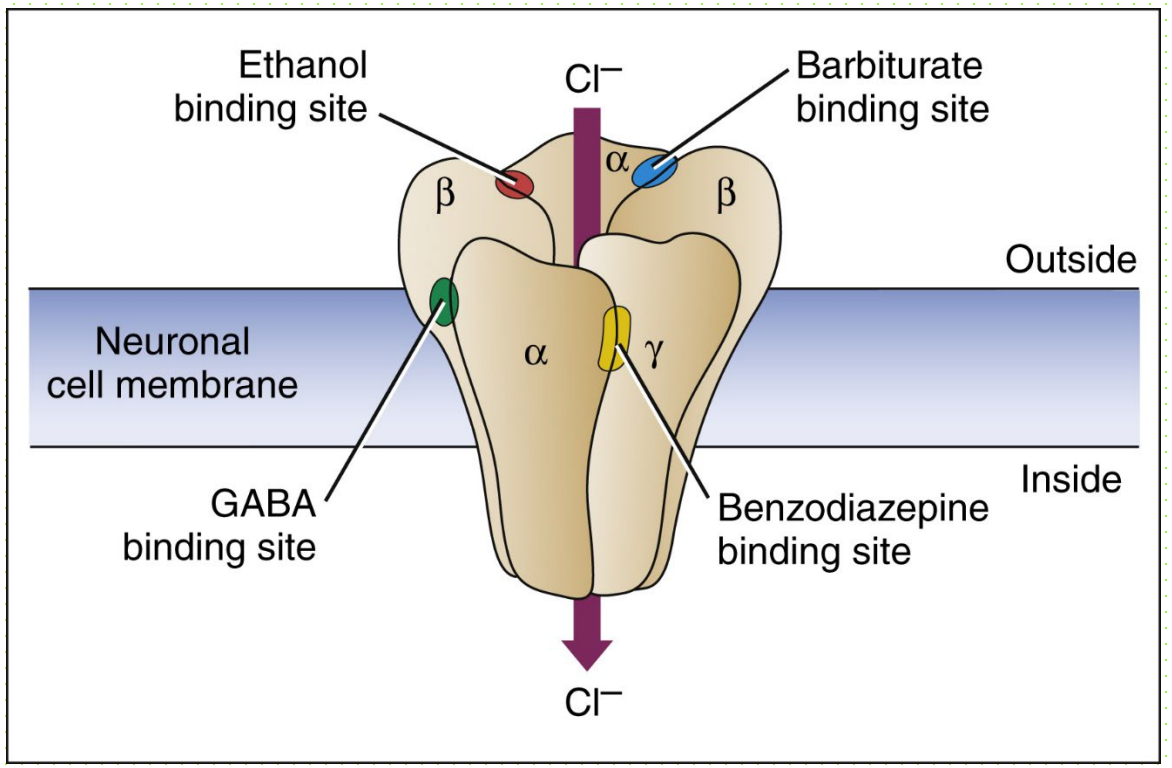



Dexmedetomidine


Ketamine

# Benzodiazepines Mechanism of Action



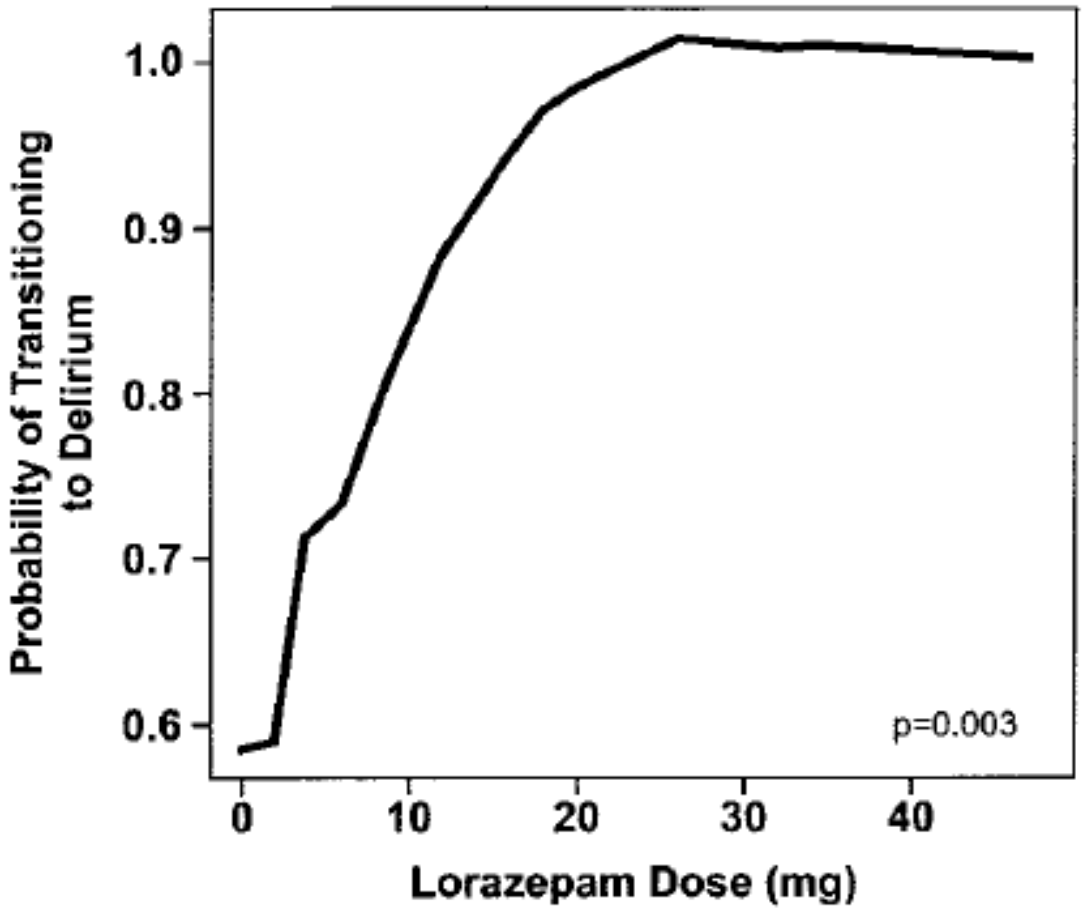

Griffin CE 3rd, et al. Ochsner J. 2013 Summer;13(2):214-23.

# Benzodiazepines Pharmacology

| Drug | MOA | Onset | Duration | Dose | Metabolism | Adverse Effect |
|---|---|---|---|---|---|---|
| **Midazolam**   | GABA receptor agonist | 3-5 min | 2-6 hr. | 0.02-0.1 mg/kg/hr. | Hepatically 3A4 substrate | Oversedation<br>Amnesia<br>Respiratory depression |
| **Lorazepam**   | GABA receptor agonist | 5-20 min | 4-8 hr. | 0.01-0.1 mg/kg/h<br>1-4 mg IV q 4-6 hr. | Direct glucuronidation | Oversedation<br>Propylene glycol toxicity<br>Respiratory depression |

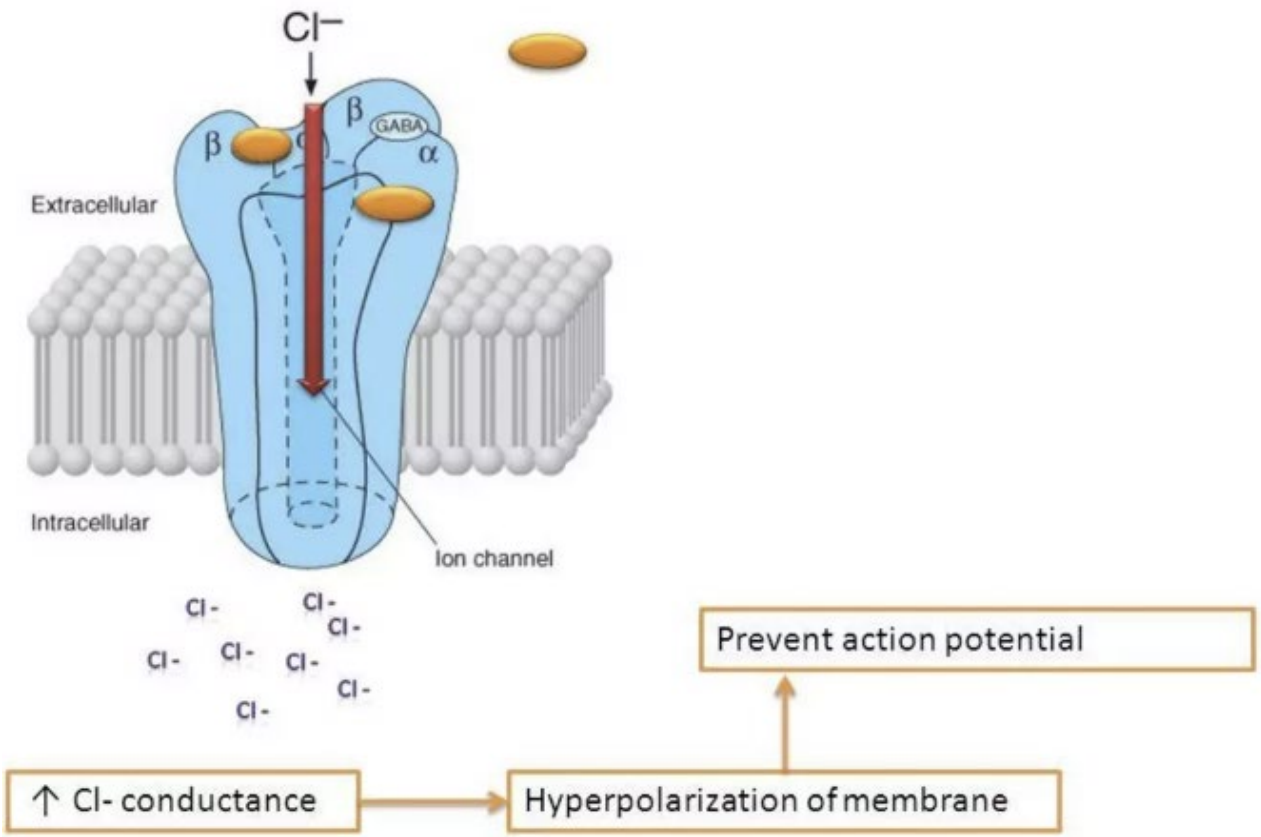
Griffin CE 3rd, et al. Ochsner J. 2013 Summer;13(2):214-23.

# Risk of Delirium Associated with Benzodiazepines




Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, Bernard GR, Ely EW. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006 Jan;104(1):21-6.

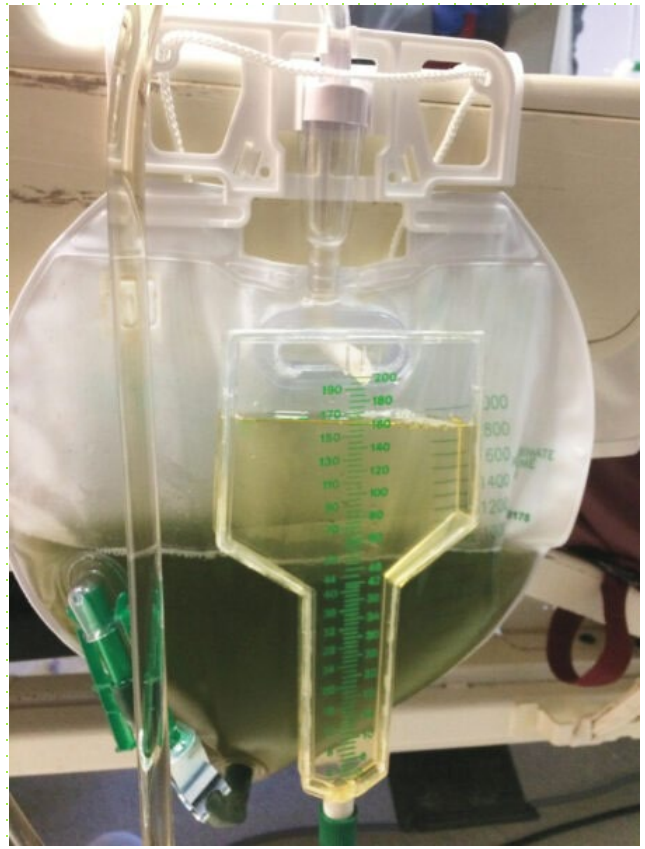
# Propofol Mechanism of Action


Antkowiak B, Rammes G. GABA(A) receptor-targeted drug development -New perspectives in perioperative anesthesia. Expert Opin Drug Discov. 2019 Jul;14(7):683-699.

# Propofol Pharmacology

| Propofol | |
|---|---|
| **MOA** | Binds to $GABA_A$, glycine, nicotinic, M1 muscarinic receptors |
| **Onset** | 1-2 min |
| **Duration** | 0.5-1 hr. |
| **Dose** | 0.3-3 mg/kg/hr.<br>5–50 mcg/kg/min |
| **Metabolism** | Hepatically |
| **Adverse Effect** | PRIS<br>Bradycardia<br>hypotension<br>Green discoloration of urine |



PRIS: Propofol-Related Infusion Syndrome

Folino TB, Muco E, Safadi AO, et al. Propofol. [Updated 2023 Jul 24]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-
J. Greenwood, RD, Clinical Dietitian Specialist, VCHA - VA. Reviewed by members of the ICU QI/QA Committee 11/7/08. Update 7/12/2009

# Propofol Related Infusion Syndrome

## Epidemiology

- The incidence of PRIS was 2.9% in a recent study
- PRIS-associated mortality rate of 36.8%

## Mechanism

- Alterations in the liver metabolism of the lipid emulsion→ accumulation of ketone bodies & lactate
- Disruptions in the mitochondrial respiratory chain and inhibition of oxidative phosphorylation.

## Risk Factors

- Doses > 50 mcg/kg/minute for 48 hours or more.
- Acute liver failure

## Characteristics

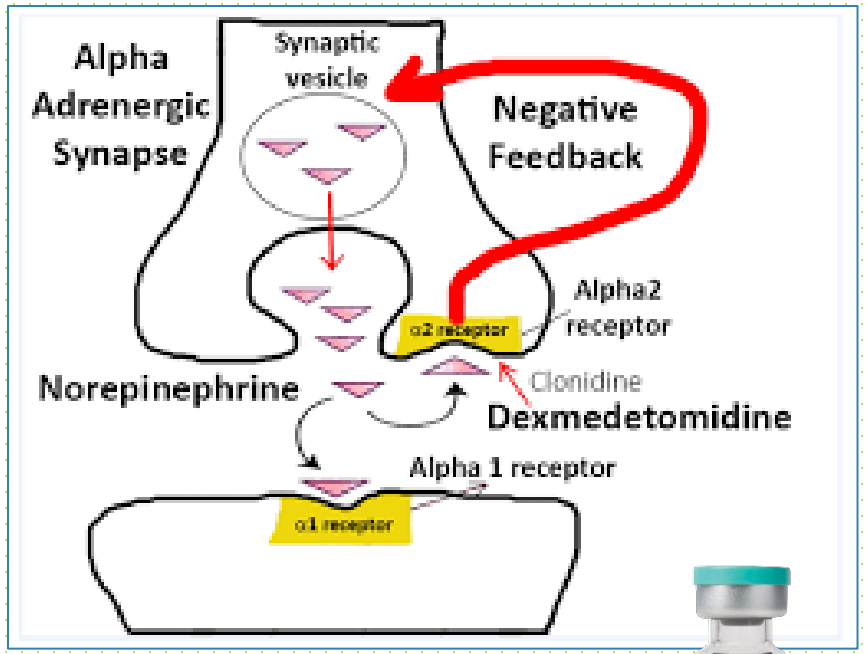
- Hypertriglyceridemia
- Metabolic acidosis
- Acute renal failure
- Cardiac arrhythmias
- Rhabdomyolysis
- Myoglobinuria
- Hyperkalemia
- Elevated creatine kinase conc.

Management of PRIS is the discontinuation of propofol infusion and supportive treatment

Li WK, et al. J Crit Care. 2022 Oct;71:154098
Stolllings et al. ACCP, 2020

# Dexmedetomidine

| Dexmedetomidine | |
|---|---|
| **MOA** | Selective alpha2 agonist |
| **Onset** | 5-10 min (with LD)<br>1-2 hr. (without LD) |
| **Half life** | 3 hours |
| **Dose** | LD: 0.5-1 mcg/kg<br><br>0.2-0.7 mcg/kg/hr.<br>*Trials used up to 1.5 mcg/kg/hr.* |
| **Adverse Effects** | Bradycardia<br>Hypotension<br>Transit hypertension with LD |





Reel B, Maani CV. Dexmedetomidine. 2023 May 1. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan

# Ketamine

| Ketamine | |
|---|---|
| **MOA** | Noncompetitive NMDA receptor antagonist |
| **Onset** | 30 seconds |
| **Half life** | Alpha 10-15 minutes; Beta 2.5 hours |
| **Dose** | LD 1-2 mg/kg<br>Maintenance infusion dose range is:<br>1-7.5 mg/kg/hr |
| **Adverse Effects** | Increased heart rate and blood pressure<br>Emergence reactions<br>Increased cerebral blood flow |


Barr J, et al. Crit Care Med 2013; 41: 263-306.

# Sedatives Pharmacology

| Drug | MOA | Onset | Duration | Dose | CYP substrate | Adverse Effect |
|---|---|---|---|---|---|---|
| **Dexmedetomidine*** | Selective alpha2 agonist | 5-10 min (with LD)<br>1-2 hr. (without LD) | 1-2 hr. | 0.2-0.7 mcg/kg/hr.<br>*Trials used up to 1.5 mcg/kg/hr.* | 2A6 | Bradycardia<br>Hypotension<br>Transit hypertension with LD |
| **Propofol** | GABA receptor agonist | 1 min | 0.5-1 hr. | 0.3-3 mg/kg/hr. | 2B6 | Bradycardia<br>hypotension<br>PRIS |
| **Midazolam #** | GABA receptor agonist | 3-5 min | 2-6 hr. | 0.02-0.1 mg/kg/hr. | 3A4 | Oversedation |
| **Lorazepam #** | GABA receptor agonist | 5-20 min | 4-8 hr. | 1-4 mg IV q 4-6 hr. | NA | Oversedation<br>Propylene glycol toxicity |
| **Ketamine** | NMDA receptor antagonist | 30 seconds | -2 hrs | 1-7.5 mg/kg/hr | NA | Increased HR and BP<br>Emergence reactions<br>Increased cerebral blood flow |

* Use of dexmedetomidine beyond 24 hours has been associated with tolerance (reduction in response after a longer duration), increase in adverse effects

# Benzodiazepines are first-line agents for status epilepticus, alcohol withdrawal, benzodiazepine dependence or withdrawal, and the need for deep sedation or amnesia and with the use of neuromuscular blockade.

PRIS: Propofol-Related Infusion Syndrome
NMDA = N-methyl-d-aspartate

Stolllings et al. ACCP, 2020

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# Thank you