Other Sedatives-Anxiolytics

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[Sedatives in Critical Care 1](#_Toc296240214)

[Dexmedetomidine (Precedex®) 1](#_Toc296240215)

[Propofol 1](#_Toc296240216)

[Etomidate 1](#_Toc296240217)

[Midazolam (Versed®) 1](#_Toc296240218)

[Lorazepam (Ativan®) 2](#_Toc296240219)

[Ketamine 2](#_Toc296240220)

[Others 2](#_Toc296240221)

[Clomethiazole (s. chlormethiazole) 2](#_Toc296240222)

[Buspirone (BuSpar®) 2](#_Toc296240223)

[Chloral hydrate 2](#_Toc296240224)

[Paraldehyde 3](#_Toc296240225)

[Glutethimide 3](#_Toc296240226)

[Ethanol (ethyl alcohol) 3](#_Toc296240227)

[Meprobamate 3](#_Toc296240228)

[Methocarbamol (Robaxin®) 3](#_Toc296240229)

[Nonbenzodiazepine Hypnotics 3](#_Toc296240230)

[Zolpidem (Ambien®, Zolpimist®) 3](#_Toc296240231)

[Zaleplon (Sonata®) 3](#_Toc296240232)

[Zopiclone 3](#_Toc296240233)

[Eszopiclone (Lunesta®) 3](#_Toc296240234)

[Ramelteon (Rozerem®) 3](#_Toc296240235)

[Antihistamines 3](#_Toc296240236)

Sedatives in Critical Care

Muscular blockers – see [p. 3905 >>](http://www.neurosurgeryresident.net/USMLE%202%5CIntensive%20Care%20%283901-3950%29%5C3905.%20Anesthesia%2C%20Pain%20management.pdf#Muscular_blockers)

Opioids, neuroleptanalgesia – see [p. 3905 >>](http://www.neurosurgeryresident.net/USMLE%202%5CIntensive%20Care%20%283901-3950%29%5C3905.%20Anesthesia%2C%20Pain%20management.pdf#Opioids)

**Sedation holidays** – to evaluate ability to wean from ventilation.

Dexmedetomidine (Precedex®)

- relatively selective α2-adrenoceptor agonist with sedative properties.

* used for sedation of intubated (mechanically ventilated) patients in ICU
* does not affect respiratory drive – can easily extubate! (helps patients tolerate endotracheal tube without sedatives/narcotics to facilitate extubation)
* no effect on neuro examination – ideal in awake neurosurgery!
* administered by continuous IVI not to exceed 24 hours (longer use may cause withdrawal\* if stopped abruptly). \*similar to clonidine withdrawal
* may cause bradycardia & hypotension (hypertension during loading dose may be observed).

Propofol

* exact mechanism of action unknown.
* short half life with no active metabolites.
* popular for *ambulatory surgery* and in *neurointensive care* – rapid-acting (30-40 sec), short-acting (5-10 min), with smooth, nausea-free emergence and clarity of mental status thereafter.
* excellent **bronchodilation** (via block of vagally mediated bronchoconstriction).
* **decreases cerebral metabolism**.
* disadvantages:
1. pain on injection.
2. dose dependent **BP↓** (caution in severe CAD, hypovolemia).
3. **poor analgesia** (add opioids).
4. if administered for > 48 hours – great risk of **PRIS (propofol-induced syndrome)** - rhabdomyolysis
* contraindications: liver injury.
* **propofol infusion syndrome**:
* first identified in children but can occur in adults as well.
* hyperkalemia, metabolic acidosis, hepatomegaly, lipemia, myocardial failure, rhabdomyolysis, and renal failure, resulting in death.
* extreme caution must be taken when using doses greater than 5 mg/kg/hour, or when usage of any dose exceeds 48 hours in critically ill adults

Etomidate (Amidate®)

* benzodiazepine derivative - anesthetic and amnestic but no analgesic properties
* rapid *onset* of action (30-60 sec); ultra-short *duration* of action (4-6 min)
* **absent hemodynamic changes** – useful in cardiovascular disease.
* **cerebrovasoconstrictor** - reduces CBF and ICP. Does not suppress brainstem activity.
* initial hopes for use as a cerebral protectant were abandoned based on experimental studies.
* disadvantages:
1. burning pain on injection
2. no analgesia → abnormal muscular movements (myoclonus – may be confused with seizures)
3. adrenal suppression (when given as prolonged sedation for critically ill patients).
4. impairs renal function
* contraindicated in children & pregnancy (embryocidal), renal failure

Midazolam (Versed®)

* benzodiazepine with rapid *onset* of action (1-5 min); *duration* of action much shorter (≈ 30 min) than diazepam.

N.B. catabolism in elderly may take 2-3 days!

* **minimal hemodynamic changes** - often selected in cardiovascular surgery.
* powerful **anxiolysis & antegrade amnesia** (3-4 times more potent than diazepam) – used:
	+ 1. to premedicate anxious patients
		2. for anesthesia induction
		3. as component of multidrug anesthetic.



Lorazepam (Ativan®)

* adverse effects: *propylene glycol (1,2-propanediol) toxicity* (esp. in doses > 5-7 mg)
* propylene glycol is ***solvent used to deliver*** lorazepam and diazepam IV.
* incidence unknown
* manifestations: unexplained anion gap / metabolic acidosis / hyperosmolality.

Ketamine

* onset in ≈ 1 min; duration 10-20 min.
* the only intravenous induction agent that:
	+ **increases sympathetic tone** → **BP & heart rate↑** - useful in hypovolemic patients; avoid in CAD, hypertension, stroke.
	+ **increases cerebral blood flow** → **ICP↑**.
* **no respiratory depression, bronchomotor tone↓** (via block of vagally mediated bronchoconstriction) - appropriate agent for asthmatics, respiratory failure patients (administer drying agent [e.g. glycopyrrolate] or premedicate with atropine because of copious oropharyngeal secretions).
* NMDA receptor antagonist - produces **dissociative anesthesia** (catalepsy, catatonia, **profound amnesia** and **potent somatic analgesia**, but not necessarily complete unconsciousness) – patient appears awake but is unconscious, immobile (muscle tone↑) and feels no pain.
* can be used as sole anesthetic for brief, superficial procedures (esp. in children and young adults).
* laryngeal reflexes are maintained.
* produces ***no muscular relaxation***, does not control visceral pain, and may not completely control patient movement - not useful for abdominal cases or delicate surgery.
* clinically important side effect - ***emergence delirium*** (H: supplemental benzodiazepines or volatile agents); contraindicated in psychiatric disorders.

Others

Clomethiazole (s. chlormethiazole)

* structurally related to thiamine (vit. B1) but acts like sedative, hypnotic, muscle relaxant and anticonvulsant.
* mechanism of action:
1. positive allosteric modulator at barbiturate/picrotoxin site of **GABA-A receptor**.
2. inhibits **alcohol dehydrogenase** - helps to relieve sudden effects of alcohol withdrawal in alcoholics.
* uses:
1. widely used in treating and preventing symptoms of **acute alcohol withdrawal**.
2. management of agitation, restlessness, short-term insomnia and **Parkinson's disease** in elderly.
* forms: 192 mg capsule, syrup.
* adverse effects: tolerance and physical dependence (abrupt withdrawal → apnoeic-tonic seizures).
* overdose (*particularly toxic*) - potentially fatal.

Buspirone (BuSpar®)

- unique chemically **azaspirone** (not chemically and pharmacologically related to benzodi­azepines or barbiturates or other sedatives!).

|  |  |
| --- | --- |
| * partial agonist at **serotonin 5-HT1A receptors**; some affinity for **D2** and **5-HT2 receptors**.
* used as **anxiolytic** in long-term therapy of general­ized anxiety disorders (efficacy comparable to benzo­diazepines!).
* only ***minimal sedation***! (+ does not potentiate CNS depression of ethanol) – most useful anxiolytic in elderly patients!
* effectively eliminates episodic outbursts of aggression and agitation in brain-damaged patients.
* ***minimal psy­chomotor*** and ***cognitive dysfunction***.
* no respiratory depression.
* because ***higher doses cause dysphoria***, patients do not escalate dose (dependence is unlikely, ***low addiction potential***).

N.B. *buspirone is not CNS depressant* - cannot be directly substituted for benzodiazepines and does not suppress benzodiazepine withdrawal.* at doses > 45 mg/d has **antidepressant effect** (but also at high doses may cause dysphoria).
* no anticonvulsant, hypnotic-sedating, myorelaxant properties.
* disadvantageous ***slow onset of action*** – must be given for 1 month before it is effective.
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* adverse effects (rare) - headaches, nervousness, dizziness, lightheadedness.

Little potential for abuse!

Chloral hydrate

*-* trichlorinated derivative of acetaldehyde.

* must be metabolized by alcohol dehydrogenase to active metabolite **trichloroethanol**.
* weak but safe **sedative-hypnotic** - induces sleep in 30 minutes and lasts 6 hours (T1/2 = 4-10 hrs).
	+ relatively safe;
	+ little reduction in REM sleep;
	+ has anticonvulsant properties;
	+ mostly used for 1-3 nights to treat transient insomnia.
* adverse effects - unpleasant taste, GI tract irritat­ion.
* CNS depressant effect potentiated by ethanol (combination chloral alcoholate is dubbed “Mickey Finn”); addiction can occur!
* also used externally as rubefacient, anesthetic, and antiseptic.
* chloral betaine is slowly hydrolyzed in GI tract to chloral hydrate.

Paraldehyde

*-* trimer of acetaldehyde (resembles chloral hydrate).

* potent **sedative-hypnotic** - induces sleep in 15 minutes and lasts 4-8 hours.
* has anticonvulsant properties.
* can be administered **orally** (*strong offensive odor* and *disagreeable taste* + *GI tract irritat­ion*!), **parenterally**, **rectally**.
* *eliminated via lungs* – does not depend on liver / kidney status!
* used exclusively for alcoholics undergoing withdrawal from alcohol.

Do not use with disulfiram!

Glutethimide

* *very narrow therapeutic index* - formerly used as **hypnotic** and as daytime **sedative**.

Ethanol (ethyl alcohol)

*-* CNS depressant\* with **anxiolytic & sedative** effects.

\*synergizes with many other sedative agents and can produce severe CNS depression!

N.B. *toxic potential* outweighs benefits!

* shallow dose-response curve (sedation occurs over wide dosage range with ultimately hypnosis and coma).
* about **metabolism** and disulfiram – see [p. 702 >>](http://www.neurosurgeryresident.net/USMLE%202%5CBiochemistry%2C%20Metabolic%20Disorders%20%28501-900%29%5C702.jpg)

Meprobamate

- propyl alcohol derivative (propanediol carbamate): hypnotic, muscle relaxant

* depresses CNS as shorter acting **barbiturates** (≈ phenobarbital).
* was widely used antianxiety agent → largely been replaced by benzodiazepines.
* well absorbed from GI tract.

Methocarbamol (Robaxin®)

- carbamate derivative of guaifenesin (expectorant).

* CNS depressant with **musculoskeletal relaxant** properties (related to sedative properties, because drug has no direct action on contractile mechanism, motor end plate or nerve fiber).
* indication - as adjunct to rest, physical therapy, and other measures in acute painful musculoskeletal conditions.
* mode of action - not been clearly identified.
* may inhibit effect of anticholinesterase agents (pyridostigmine) - use with caution in myasthenia gravis.

Nonbenzodi­azepine Hypnotics

Zolpidem (Ambien®, Zolpimist®)

 - **imidazopyridine**.

* selective for **subtype 1 of benzodiazepine receptor** (as quazepam).
* used as **sedative**-**hypnotic** (advantageous over ben­zodiazepines!)
* preserves sleep architecture!
* does not cause memory disturbances (as benzodiazepines do);
* minimal rebound insomnia;
* no tolerance, no withdrawal effects with prolonged use.
* no anticonvulsant, no myorelaxant properties.
* rapidly absorbed from GI tract, rapid onset of action, T1/2 ≈ 1,5-3 hours.

Zolpimist® - FDA approved oral spray for short-term treatment of difficulty with sleep initiation.

* adverse effects - nightmares, agitation, headache, GI upset, dizziness, daytime drowsi­ness.

Zaleplon (Sonata®)

- **pyrazolopyrimidine**; ≈ zolpidem.

* rapid onset of action with ultra-short duration.

Zopiclone

- **cyclopyrrolone**.

Eszopiclone (Lunesta®)

- **cyclopyrrolone**.

* mechanism of action - interaction with GABA-receptor at binding domains close to (or allosterically coupled to) **benzodiazepine receptors**.
* used as **hypnotic**; likely to become first choice agent for treatment of insomnia.
* shows continued efficacy at 12 months of continued use.
* less addictive than benzodiazepines.
* T1/2 ≈ 6 hr.
* higher doses (2-3 mg) are more effective for *sleep maintenance*, whereas lower doses (1-2 mg) are suitable for difficulty in *falling asleep*.

Ramelteon (Rozerem®)

- chemically related to **melatonin**.

* **melatonin receptor** agonist (high affinity and selectivity for MT1 and MT2 receptors, vs. MT3 receptors).
* T1/2 ≈ 1-2,6 hrs.
* metabolized by liver.
* decreases [testosterone] and increases [prolactin] in serum.
* used as **hypnotic** for sleep-onset insomnia (8 mg within 30 minutes of going to bed).
* does not cause rebound insomnia.
* does not cause dependence (drug is not controlled substance!).
* adverse effects: headache, somnolence, etc.
* should not be used with fluvoxamine (ramelteon concentration↑↑↑).

Antihistamines

**Nonprescription sedating antihistamines** (diphenhydramine, doxylamine) are effective only in *mild forms of situational insomnia*.

* anticholinergic side effects make them less useful than benzodiazepines.

hydroxyzine *-* antihistamine with antiemetic activity.

* low tendency for habituation - useful for *anxiety with history of drug abuse*.
* also used for *sedation prior to dental procedures*.

Bibliography for “Sedatives, Hypnotics” → follow this [link >>](http://www.neurosurgeryresident.net/Rx.%20Treatment%20Modalities%5CRx.%20Bibliography.pdf)

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