Delirium Tremens

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PharmD Candidate 2019

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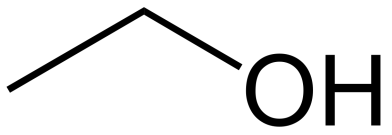
Objectives

1. Exemplify one possible treatment course from a recent patient with delirium tremens
2. Recognize the prevalence alcohol use disorders and the implications on patient care in the intensive care unit
3. Review the neurotransmitter pathways involved in acute and chronic alcohol consumption
4. Synthesize a treatment plan for a patient presenting with severe alcohol withdrawal symptoms or delirium tremens
5. Understand the benefits and limitations of various adjunctive therapies for delirium tremens and alcohol withdrawal syndrome

Background

- 86.4% of people report drinking alcohol at some point in their lifetime
  - 70.1% drank in the past year
  - 56.0% drank in the past month.
- 16 million people in US have alcohol use disorder
- 8 million alcohol dependent people in the United States
  - 500,000 episodes require pharmacologic treatment annually

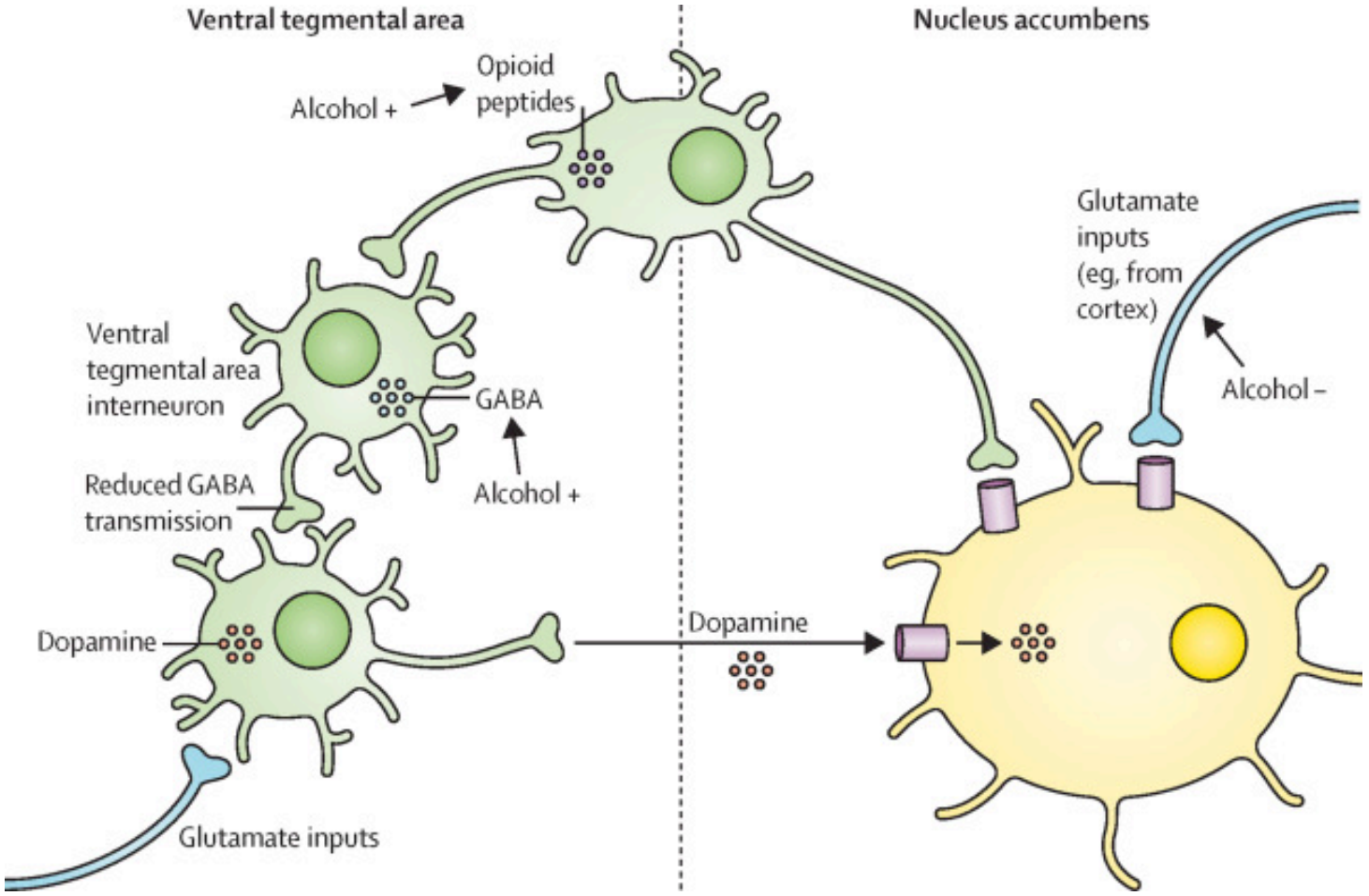


KEY POINT:

It is essential that clinicians know how to prevent, recognize, and treat these severe withdrawal states to minimize costly hospitalizations and avoidable deaths.

Physiology with Acute Exposure to Alcohol

- CNS Depressant
- ↑ in Reward Circuit Activity
  - Dopamine
  - Endogenous Opioids
- ↑ Inhibitory Tone
  - Modulation of GABA
- ↓ Excitatory Tone
  - Modulation of Glutamate

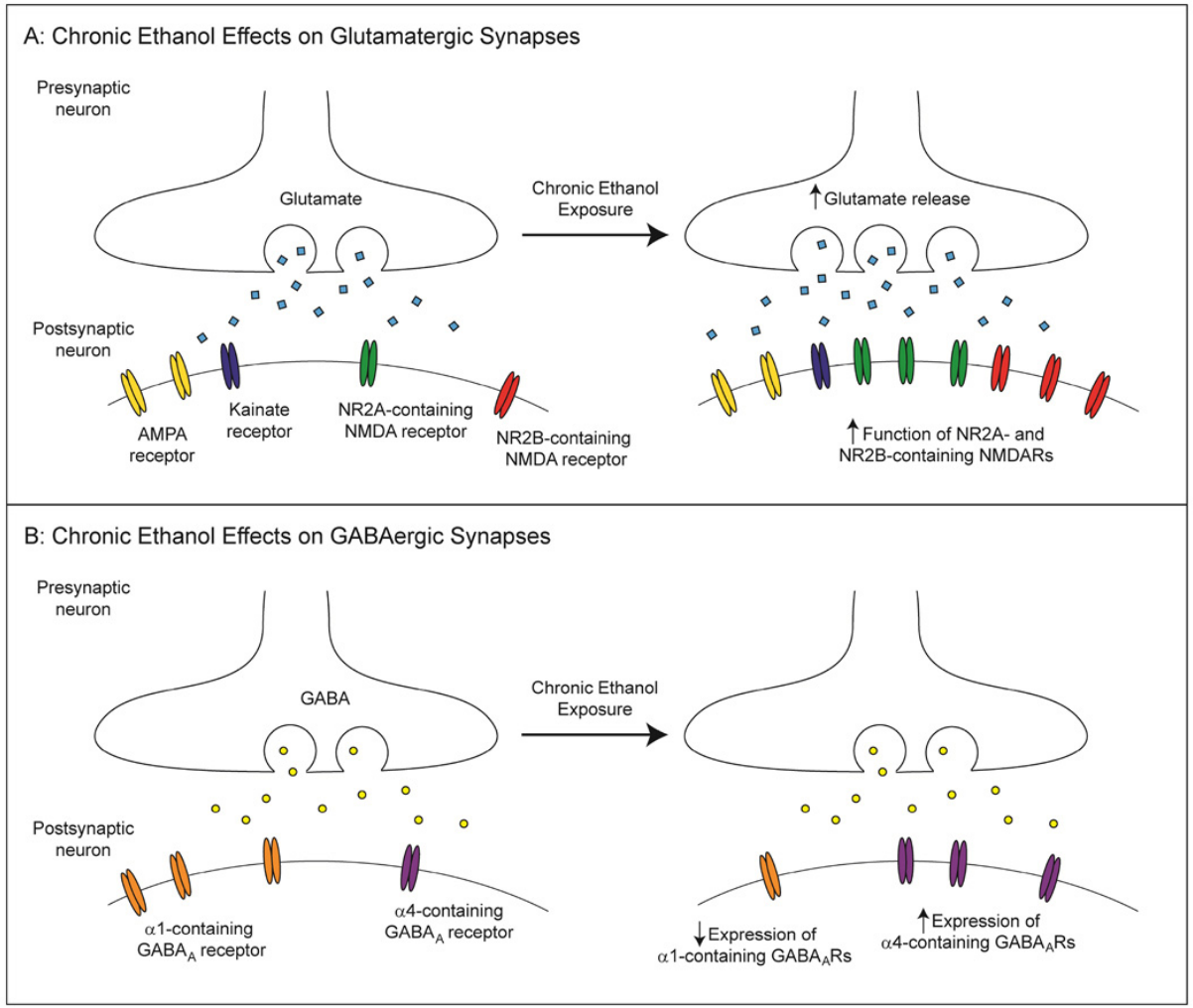



I'M NOT
SLURRING
I'M TALKING IN
CURSIVE
memegenerator.net

Physiology with Chronic Consumption of Alcohol

Chronic ethanol use induces:

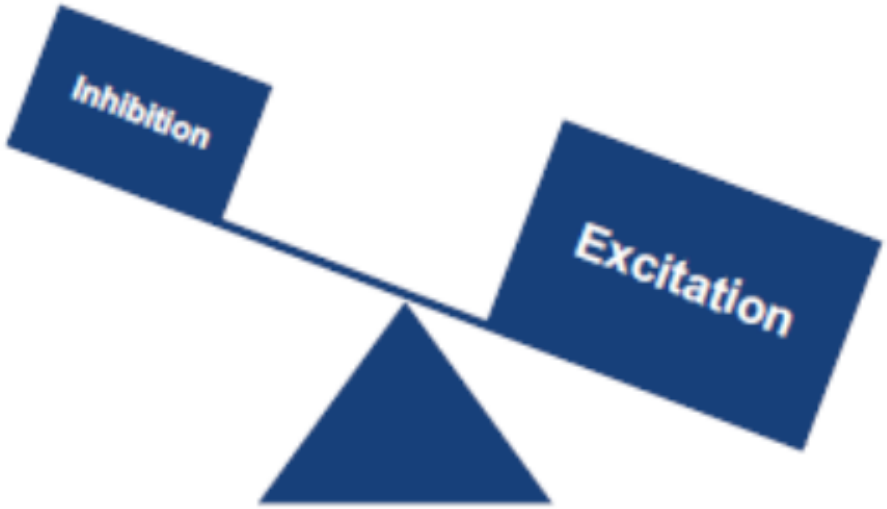
- Down-regulation and conformational changes of the GABA receptor
- Upregulation of the NMDA receptors



Physiology with Alcohol Withdrawal

On abrupt discontinuation of alcohol exposure, neuronal hyperactivity ensues:

- Overactivation of the NMDA pathway
- Decreased inhibitory activity due to downregulation of the GABA receptor.



These changes result in clinical manifestations of autonomic excitability and psychomotor agitation seen in AWS.

Valenzuela, C.F. (1997). Alcohol and neurotransmitter interactions. Alcohol Health and Research World, 21(2):144. Retrieved from, http://pubs.niaaa.nih.gov/publications/arh21-2/144.pdf

So, why do we care?

25% of ICU patients have an alcohol use disorder and are at risk for developing alcohol withdrawal syndrome (AWS).

44% of ICU patients with AWS are **rehospitalized** at least once or **experience death** within a year.

> "Patients admitted to the ICU with AWS have ***longer duration of mechanical ventilation***, ***higher costs***, and ***increased mortality"***

Albert Coholic

Al is a 46 y.o. male who states that he has hx of ETOH dependence and stopped drinking ETOH about 6 days ago because it is "ruining my life".

Per family, for the past 48 hours, pt has also had confusion and visual hallucinations

- some of pt's sx are similar to previous episodes of ETOH withdrawal.

N/V, shaking, upper abdominal pain a few hours after he stopped drinking ETOH

He notes that he underwent detox at The Brook about 4 years ago but left prematurely.

Psychiatric/Behavioral: Positive for confusion and hallucinations (visual hallucinations).

A/O x 3 at the moment

Appears tremulous

Allergies:	ASA
PMH:	Upper GI Bleed 2 years ago HTN
Social History:	EtOH: yes, '5th of vodka a day' Drug: yes, 'marijuana'
Vitals on Presentation	
Temp	98.2 F
HR	120
BP	149/110
RR	18
SpO2	94%

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Labs on Presentation			
Glucose	112	**Mg**	2.5
BUN	10	**Lipase**	72 (H)
SCr	0.89	**Ethanol**	< 10
Na	133	**WBC**	9.65
K	3.9	**RBC**	4.47 (L)
Cl	94 (L)	**HGB**	15
CO2	21.7 (L)	**HCT**	42.8
Ca	10.1	**MCV**	95.7
Protein, t	8.2	**MCH**	3.6 (H)
Albumin	5.2	**MCHC**	35
ALT/AST	87/68	**RDW**	11.7
Alk Phos	83	**Leukocytes**	WNL
Bili	1.2	**UA**	WNL
Anion Gap	17.3	**UDS**	Negative

DSM V: Alcohol Withdrawal Syndrome

Cessation or reduction in alcohol use that has been heavy and prolonged

Two or more of the following developing within several hours to a few days after cessation/reduction:	
Autonomic Hyperactivity	Transient visual/auditory/tactile hallucinations or illusions
Increased hand tremor	Psychomotor Agitation
Insomnia	Anxiety
N/V	Generalized tonic-clonic seizures

Appendix. Clinical Institute Withdrawal Assessment for Alcohol.*

Category	Range of Scores	Examples
Agitation	0–7	0=normal activity 7=constantly thrashes about
Anxiety	0–7	0=no anxiety, at ease 7=acute panic states
Auditory disturbances	0–7	0=not present 7=continuous hallucinations
Clouding of sensorium	0–4	0=oriented, can do serial additions 4=disoriented as to place, person, or both
Headache	0–7	0=not present 7=extremely severe
Nausea or vomiting	0–7	0=no nausea, no vomiting 7=constant nausea, frequent dry heaves and vomiting
Paroxysmal sweats	0–7	0=no sweat visible 7=drenching sweats
Tactile disturbances	0–7	0=none 7=continuous hallucinations
Tremor	0–7	0=no tremor 7=severe, even with arms not extended
Visual disturbances	0–7	0=not present 7=continuous hallucinations

Kosten TR, O'Connor PG. Management of Drug and Alcohol Withdrawal. *New England Journal of Medicine.* 2003;348(18):1786-1795.

Grading and Assessment

CIWA-Ar

Clinical Institute Withdrawal Assessment for Alcohol, revised

Mild Withdrawal	≤ 15
Moderate Withdrawal	16-20
Severe Withdrawal	> 20
Max Score	67

Target CIWA-Ar < 8

"patient in a calm arousable state"

Richmond Agitation-Sedation Scale (RASS)

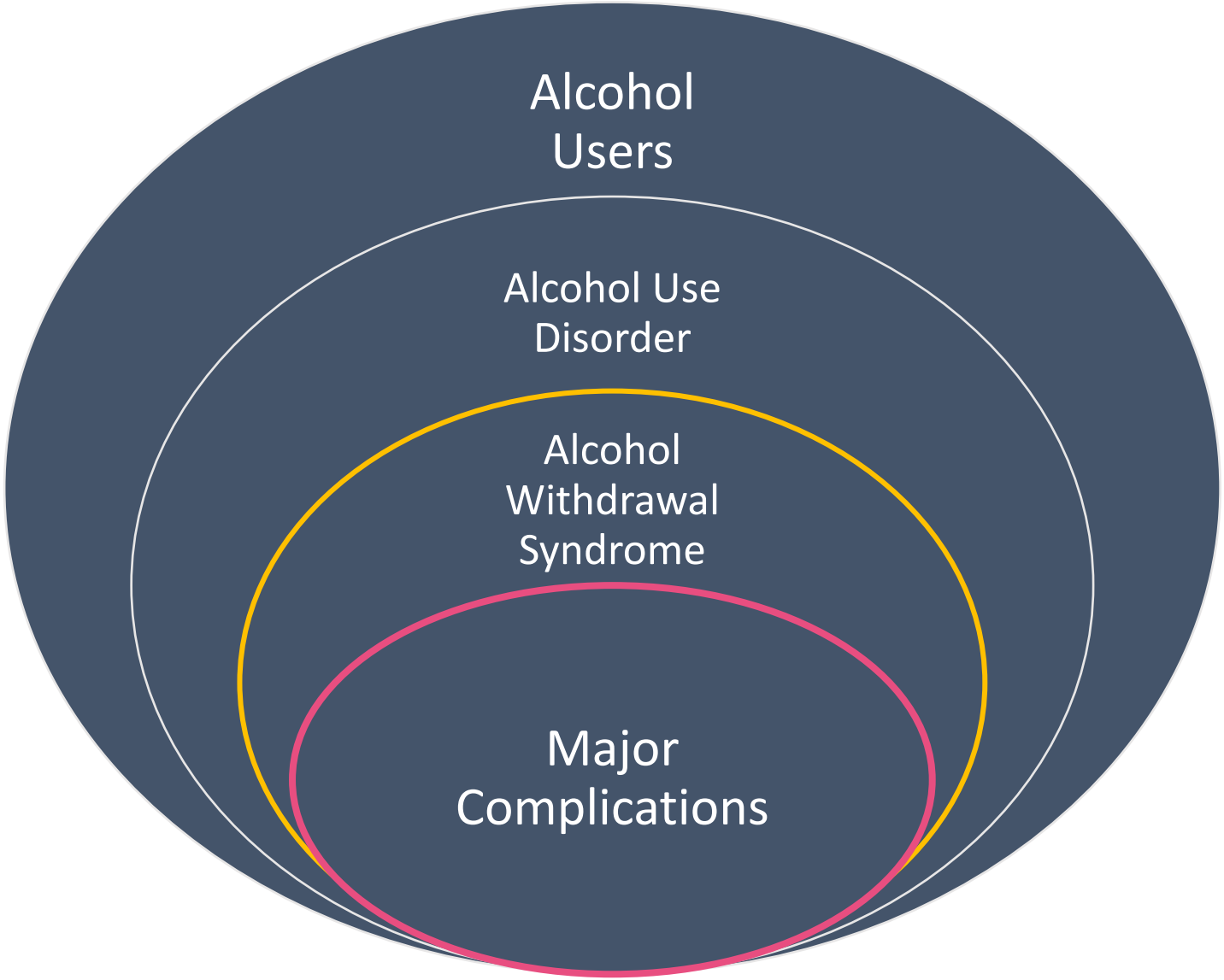
Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation
Procedure		
1.	Observe patient. Is patient alert and calm (score 0)?	
2.	Does patient have behavior that is consistent with restlessness or agitation?	
	Assign score +1 to +4 using the criteria listed above.	
3.	If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.	
	Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).	
	Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).	
	Patient has any movement in response to voice, excluding eye contact (score -3).	
4.	If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response.	
	Patient has any movement to physical stimulation (score -4).	
	Patient has no response to voice or physical stimulation (score -5).	

Richmond Agitation Sedation Score (RASS)

- Inherent limitation to CIWA-Ar is the requirement that the patient is able to communicate
- In severe withdrawal, intubation may be necessary

Target RASS 0 to -2

"patient in a calm arousable state"


Alcohol
Users
Alcohol Use
Disorder
Alcohol
Withdrawal
Syndrome
Major
Complications

Timing	6-8 hours	12-24 hours	12-48 hours	48-72 hours
Syndrome	Initial Symptoms	Alcoholic Hallucinations	Withdrawal Seizures	Delirium Tremens
Prevalence	100%	30%	10%	5%
Characteristics	Tachycardia Hypertension Hyperthermia Tremulousness Anxiety Nausea/Vomiting Headache Diaphoresis Palpitations	Tactile Hallucinations Visual Hallucinations Auditory hallucinations Possible Tremors/Other Initial Sx **Normal sensorium**	Generalized Tonic-Clonic Short in duration Short post-ictal period Some patients will progress to delirium tremens	Rapid-onset, Fluctuating Disturbance of Attention and Cognition + Initial Symptoms Autonomic Instability Lasts 1-8 days

Withdrawal Timeline

Arrival in ED at 1100

1203 “Ordered banana bag, IV fluids for hydration, and zofran for nausea. Ordered BAL, UDS, UA, magnesium level, blood work, and lipase for further evaluation.”

- **Banana Bag**
  - 10 mL MVI
  - Thiamine 100 mg
  - Folic Acid 1 mg
  - Magnesium Sulfate 2 g
  - 1000 mL of NS
- **Ondansetron** 4 mg IV x 1 for nausea
- 1000 mL **NS Bolus** (1st Bolus)

1310 now having active hallucinations (seeing family members in the room that are not present) and vomiting.

- **Famotidine** 20 mg IV x 1 for vomiting/possible alcoholic gastritis
- **Lorazepam** 1 mg IV x 1 for EtOH withdrawal/DT (1st Dose)

1326 “Patient reports seeing family member in room who are not there, states he is aware that no one is in the room, but still saw his sons briefly before they "disappeared"”

1430 agitated and attempting to get out of bed per family and was "thinking his kids are here but they aren't". PT is calling family member by wrong name appears agitated.

- **Lorazepam** 1 mg IV x 1 for EtOH Withdrawal/DT (2nd Dose)

Delirium Tremens (DT)

Alcoholic hallucinosis is distinguished from DTs by the presence of a *clear sensorium*

The hallmark of this phase of withdrawal is delirium combined with autonomic hyperactivity and alcohol hallucinosis

Schuckit MA. Recognition and management of withdrawal delirium (delirium tremens). *N Engl J Med.* 2014;371(22):2109-2113.

Table 2. DSM-5 Criteria for Withdrawal Delirium (Delirium Tremens).*

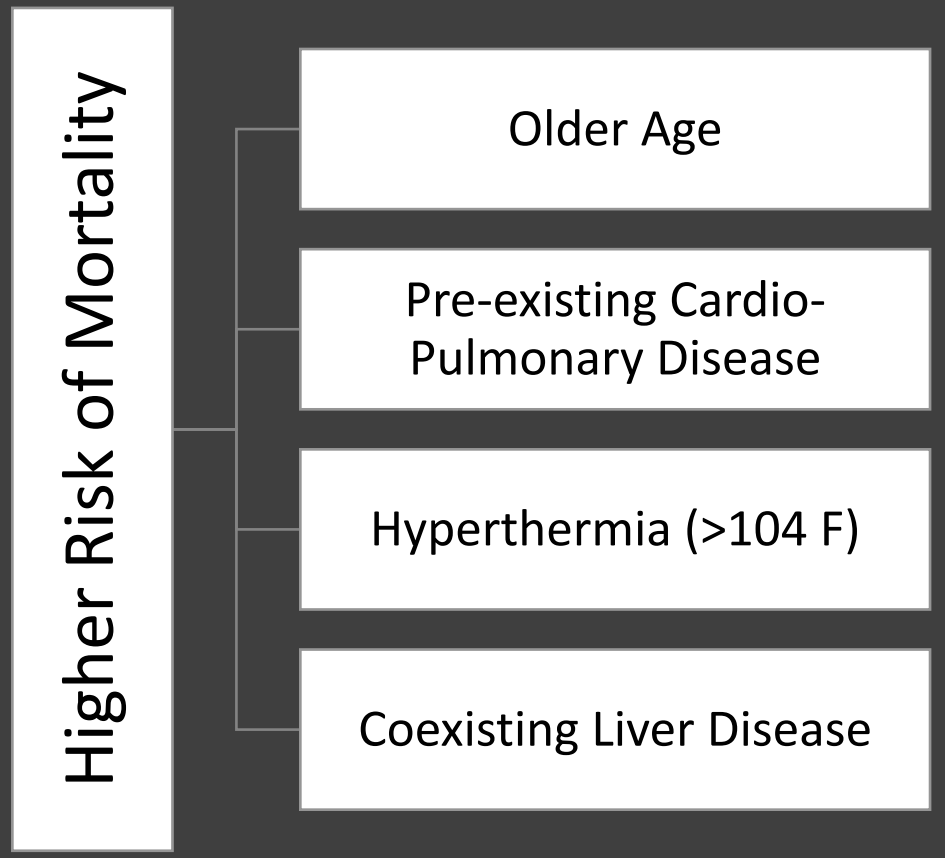
Criteria for alcohol withdrawal
Cessation of or reduction in heavy and prolonged use of alcohol
At least two of eight possible symptoms after reduced use of alcohol:
Autonomic hyperactivity
Hand tremor
Insomnia
Nausea or vomiting
Transient hallucinations or illusions
Psychomotor agitation
Anxiety
Generalized tonic–clonic seizures
Criteria for delirium
Decreased attention and awareness
Disturbance in attention, awareness, memory, orientation, language, visuospatial ability, perception, or all of these abilities that is a change from the normal level and fluctuates in severity during the day
Disturbances in memory, orientation, language, visuospatial ability, or perception
No evidence of coma or other evolving neurocognitive disorders

* The criteria are based on the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).[1] A patient who meets the criteria for both alcohol withdrawal and delirium is considered to have withdrawal delirium.

Kosten TR, O'Connor PG. Management of Drug and Alcohol Withdrawal. *New England Journal of Medicine.* 2003;348(18):1786-1795.

Prognosis

- Hospital Mortality 1-3%
  - 35% Prior to BZD use
- Ideally, DT prevented with appropriate treatment of AWS
- Death usually is due to:
  - Arrhythmia
  - complicating illnesses
  - failure to identify an underlying problem



Sarff M, Gold JA. Alcohol withdrawal syndromes in the intensive care unit. *Critical care medicine.* 2010;38(9 Suppl):S494-501.

Risk Factors for the Development of DT

- History of previous DT, AWS
- **CIWA-Ar ≥ 15**
- SBP > 150 mm Hg
- **HR > 100 beats/min**
- **Last alcohol intake > 2 days**
- **Age > 30 years**
- Recent misuse of other depressants
- Concurrent medical illness

Comparison of alcohol withdrawal patients with and without development of DTs.

	Delirium tremens		RR	CI 95%	*p*
	No ($n=156$)	Yes ($n=147$)			
Age*	46.3 (12.9)	45.3 (12.1)			0.48
Sex (male)	139 (89.1%)	128 (87%)	1.1	0.7–1.5	0.58
Cause of admission					
Withdrawal	105 (67.3%)	96 (65.3%)	1.03	0.8–1.3	
Other	51 (34.6%)	50 (34%)			0.77
Reason for stopping consumption					
Disease	61 (39.1%)	64 (43.5%)			
Voluntary	59 (37.8%)	49 (33.3%)			0.67
Hospitalization	36 (23%)	34 (23.1%)			
Liver disease					
No	102 (65.3%)	96 (65.3%)			
Steatosis	37 (23.7%)	35 (23.8%)			1
Cirrhosis	17 (10.9%)	16 (10.8%)			
Prior AWS admission(s)					
No	131(83.9%)	112 (76.2%)			
Yes	25 (16%)	35 (23.8%)	1.2	0.9–1.6	0.08
Withdrawal period (hours)*	56.2 (34.6)	48.6 (28.3)			0.1
Grams of alcohol per day*	225.8 (88.5)	236.5 (87.5)			0.03
BPs*,a	133 (18.2)	140 (19.1)			0.001
BPd*,b	76.4 (12.9)	80.6 (13.5)			0.006
HR*,c	94.8 (12.3)	95 (17.5)			0.3
T 24 h *,d	37.3 (0.6)	37.6 (0.6)			0.001
Tremor**	139 (97.8%)	122 (96.8%)	0.8	0.4–1.5	0.71
Sweats**	111 (91.7%)	82 (78.8%)	0.6	0.4–0.8	0.006
Hallucinations**	76 (56.3%)	51 (42.5%)	0.7	0.5–0.9	0.02
Epileptic seizures	49 (31.4%)	84 (57.1%)	1.7	1.3–2.1	<0.001
Number of seizures					
None	107 (69.4%)	63 (42.8%)			
1 or 2	40 (25.6%)	60 (40.8%)			<0.001
3 or more	9 (5.7%)	24 (16.3%)			
Psychomotor agitation	99 (61.1%)	63 (38.9%)	0.6	0.5–0.8	<0.001

Monte R, et al. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J of Int Med.* 2009;20(7)

Clinical Manifestations of Delirium Tremens

Neurologic Symptoms

- Severe Agitation
- Tremor
- Disorientation
- Persistent Hallucinations
  - Auditory
  - Visual

Autonomic Overdrive

- Tachycardia
- Hypertension
- Hyperthermia

Clinical Manifestations of Delirium Tremens

Hypermetabolic State

- Oxygen Consumption
- Respiratory Alkalosis
- Decreased Cerebral Perfusion

Dehydration and Electrolyte Abnormalities

- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia

1500 Decision Made to Admit to ICU

Pt continues to hallucinate but is not agitated. Ordered 2nd liter of IV fluids and 3rd dose of ativan.

- 1000 mL of **NS Bolus** (2nd Liter)
- **Lorazepam** 1 mg IV x 1 for EtOH withdrawal/DT (3rd Dose)

1500 He is still hallucinating but is not agitated. Ordered 4th dose of ativan for ETOH withdrawal/DTs.

- **Lorazepam** 1 mg IV x 1 for ETOH withdrawal/DTs (4th Dose)

1513 Pt is tremulous. HR is 106.

1530 Pt is now very agitated and combative. Ordered ketamine

- **Ketamine** 72.5 mg IV (1 mg/kg) x 1

1544 agitated and combative with ketamine. Increased agitation, combative. Six staff members unable to restraint patient. Pharmacy obtaining medications, patient head butting, scratching, yelling, order received for restraints

- Olanzapine 10 mg IM x 1 for combativeness and agitation

1552 Patient combative, agitated, unable to calm per family. Security called. Patient scratching, yelling, rushing staff, security blocking patient.

1555 IM Ketamine given, pharmacy at bedside, patient remains agitated. Struggling with staff, patient disoriented, patient fights again restraints and medications.

- **Ketamine** 50 mg IM x 1

1603 Patient remains agitated, verbally abusive, and, hallucinating, staff remains at bedside. Ordered ketamine drip.

- **Ketamine** 5 mcg/kg/min IV Infusion

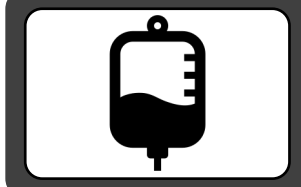
1630 left the ER after a ketamine drip started.

- **Lorazepam** 1 mg IV x 1 for ETOH withdrawal/DTs

Treatment Overview

Resuscitation and Stabilization

Benzodiazepines

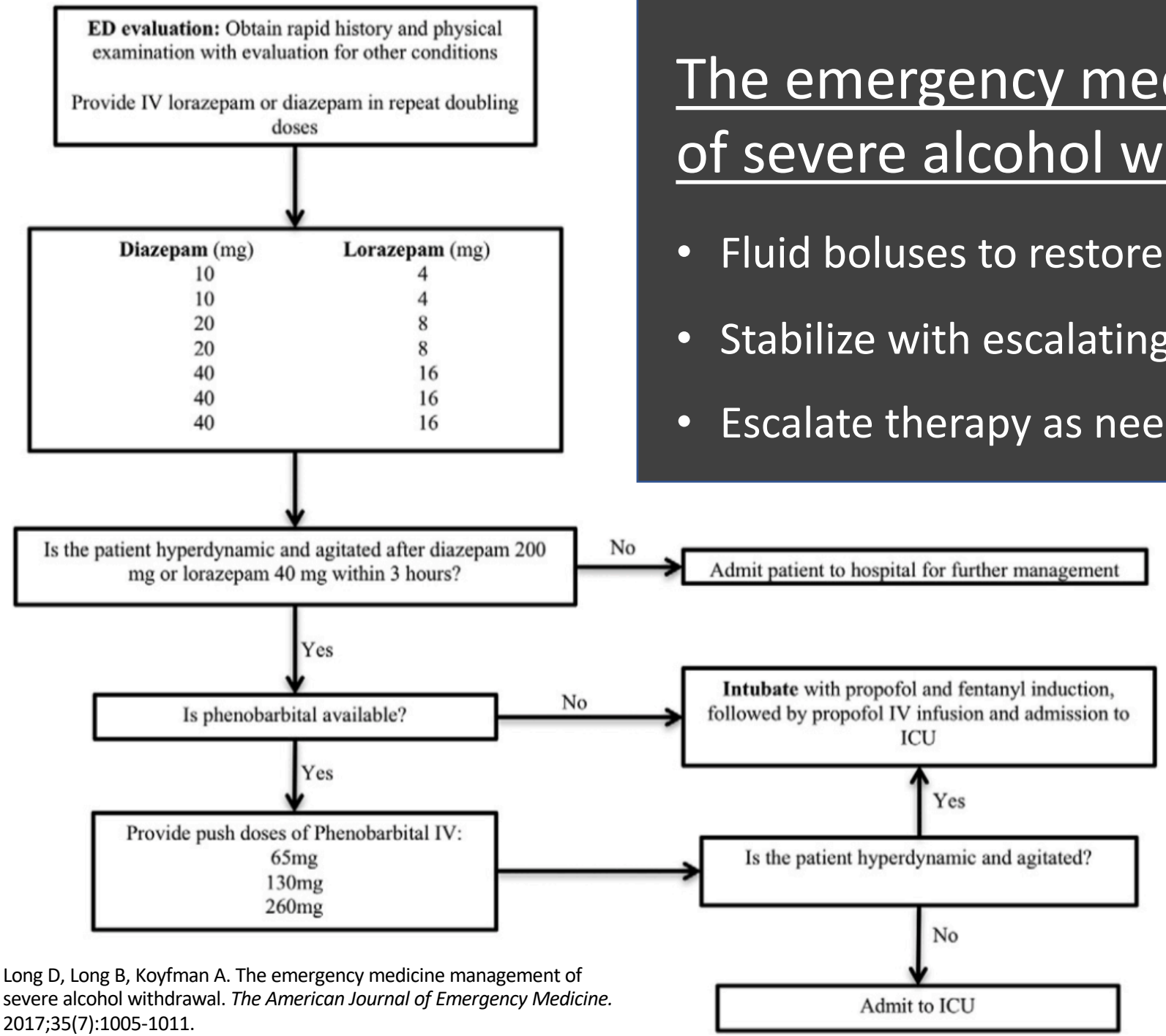


Fluid and Electrolyte Replacement

Adjunctive Therapies

The emergency medicine management of severe alcohol withdrawal.

- Fluid boluses to restore intravascular volume
- Stabilize with escalating doses of IV benzodiazepines
- Escalate therapy as needed to admit



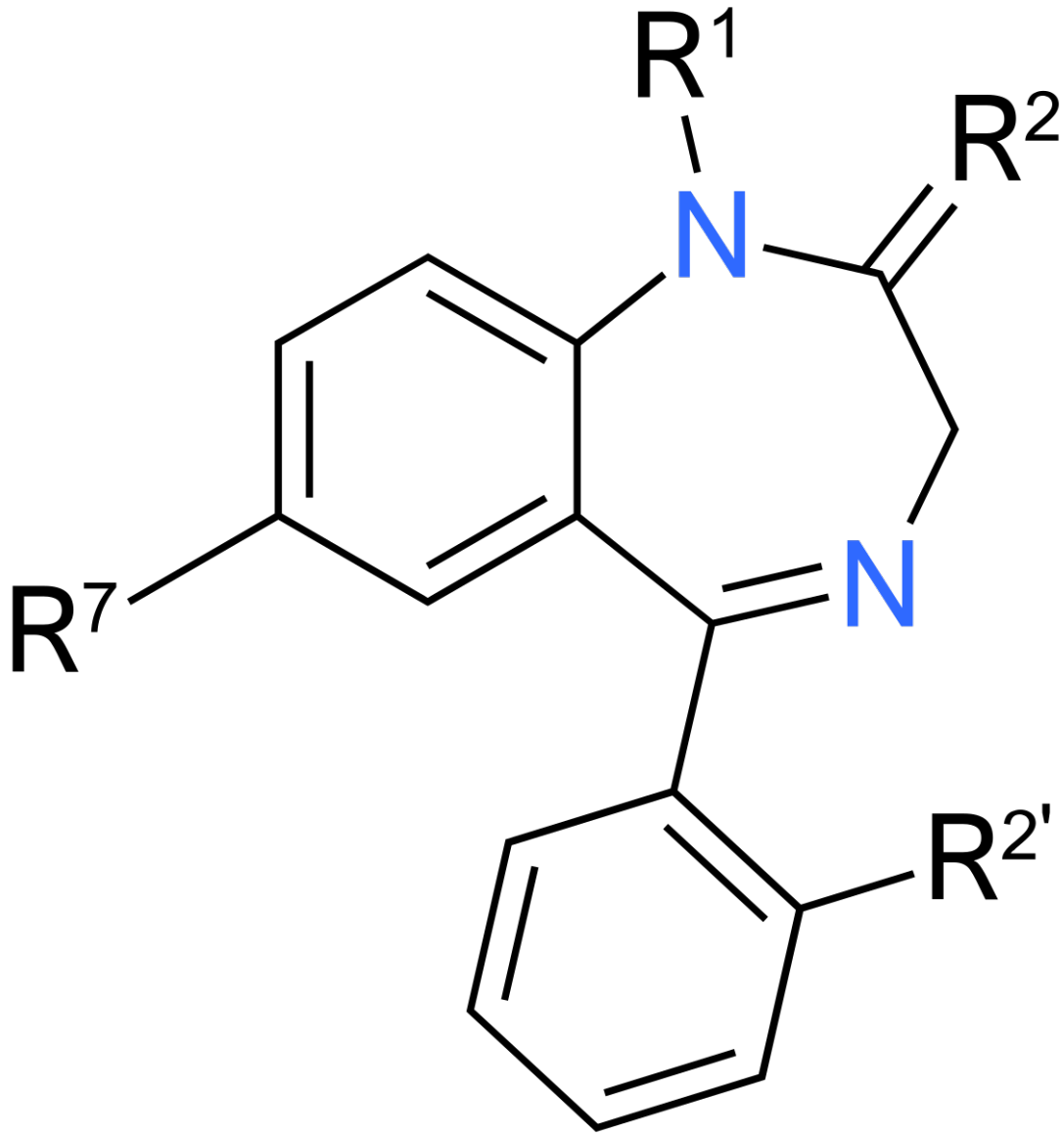
Long D, Long B, Koyfman A. The emergency medicine management of severe alcohol withdrawal. *The American Journal of Emergency Medicine.* 2017;35(7):1005-1011.

CIWA-Ar (Alcohol Withdrawal Assessment)		
Nausea and Vomiting		0-->no nausea and no vo...
Tremor		5
Paroxysmal Sweats		7-->drenching sweats
Anxiety		3
Agitation		5
Tactile Disturbances		0-->none
Auditory Disturbances		3-->moderate harshne...
Visual Disturbances		4-->moderately severe ha...
Headache, Fullness in Head		0-->not present
Orientation and Clouding of Sensorium		4-->disoriented for place ...
CIWA-Ar Score		31

Orientation and Clouding of Sensorium

	ED to Hosp-Admission (Discharged) from 9/23/2018 in BAPTIST HEALTH LOUISVILLE INTENSIVE CARE w...			
	9/23/18			9/24/18
	1700	1715	2000	0000
AUDIT-C (Alcohol Use Disorders ID Test)				
Alcohol Use In Past Year		4-->four or more times a ...		
Alcohol Amount Per Day In Past Year		4-->ten or more		
More Than 6 Drinks On One Occasion		4-->daily or almost daily		
Total AUDIT-C Score		12		

Benzodiazepines



Treatment of the acute alcohol withdrawal state: a comparison of four drugs.

Benzodiazepines vs Placebo

1. Reduce withdrawal severity
   (OR, 3.28; 95% CI, 1.30 to 8.28)

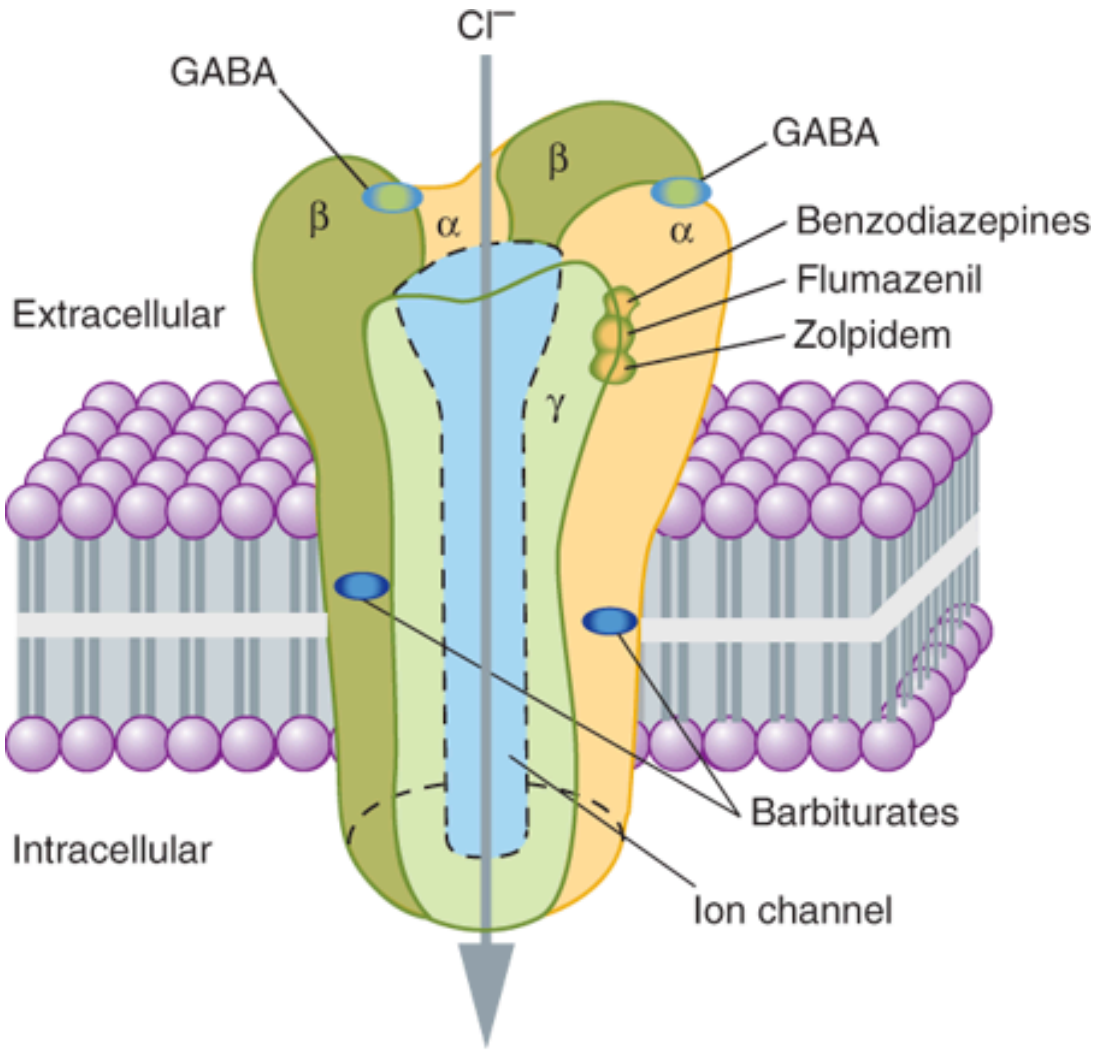
2. Reduce seizures
   (NNT 13; 95% CI, -12.0 to -3.5)

3. Reduce incidence of delirium
   (NNT 20; 95% CI, -9.0 to -0.7)

Mechanism of Action

Central $GABA_A$ Agonist

- Bind to the BZD binding site between the α and γ on $GABA_A$ receptor
  - Conformational changes allow endogenous GABA to more easily bind and open the ion channel
  - Cl^- more readily enters the cell, hyperpolarizing it



$GABA_A$ Receptor

Drug	Time to Onset	Active Metabolite	Half-life	Initial Dose
Diazepam	1-5 min IV	Yes	43 ± 13	10-20 mg IV/PO
Lorazepam	5-20 min IV	No	14 ± 5	2-4 mg IV/PO
Midazolam	2-5 min IM/IV	Yes	2 ± 1	2-4 mg IM/IV
Oxazepam	2-3 hours PO	No	8 ± 2	15-30 mg PO Q8H
Chlordiazepoxide	2-3 hours PO	Yes	10 ± 3	50-100 mg PO

> *No single agent is preferred for efficacy*

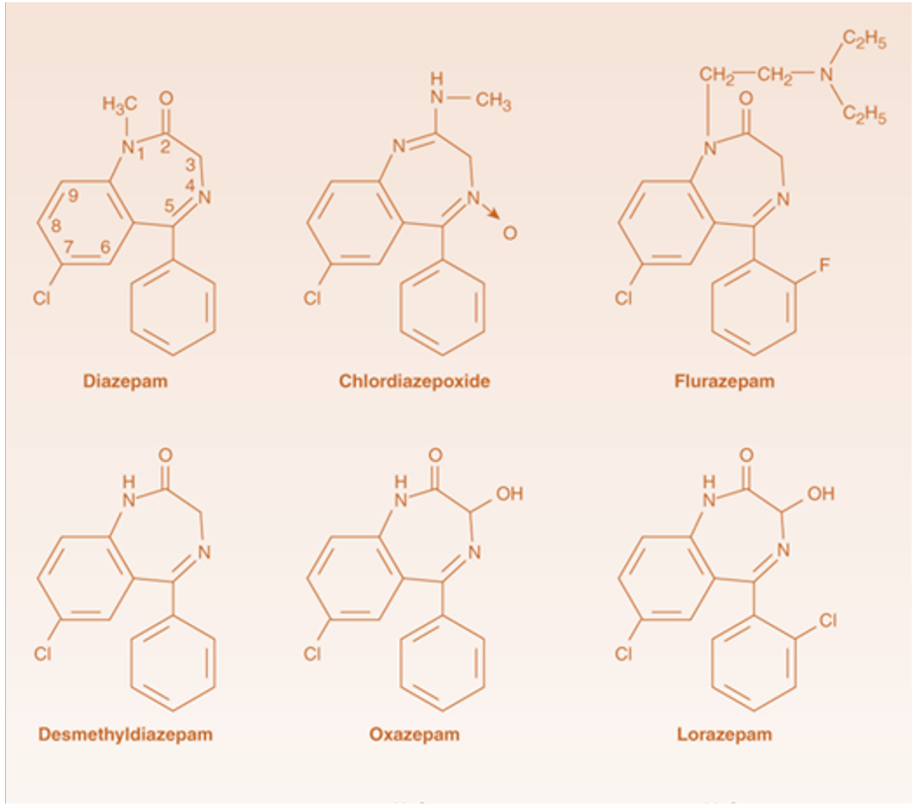
Choosing an Agent

Choice guided by:

- Duration of action
- Rapidity of onset
- Route of administration
- Co-morbidities
- Cost
- *Availability*

Decisions, Decisions

- Faster onset **Diazepam**
- Longer Half-Life **Diazepam**
- Hepatic Metabolism **Diazepam and Lorazepam**
- Active Metabolites **Diazepam**
  - Temazepam
  - Oxazepam
- Available?? **Lorazepam**



Drug	Diazepam	Lorazepam
Time to Onset	1-5 min IV	5-20 min IV
Active Metabolite	Yes	No
Half-life	43 ± 13	14 ±

Benzodiazepine Dosing Strategies

Fixed-Dose	Set amount of BZD given at regular intervals; then taper	Less monitoring Low risk, asymptomatic Not best practice
Loading-Dose	Big dose of a long-acting BZD is given to provide sedation	Easy to administer Avoidance of breakthrough symptoms Over-sedation
Symptom-Triggered	Based on CIWA score, BZD given. Doses are adjusted based on severity of symptoms	Less BZD exposure Shorter treatment required

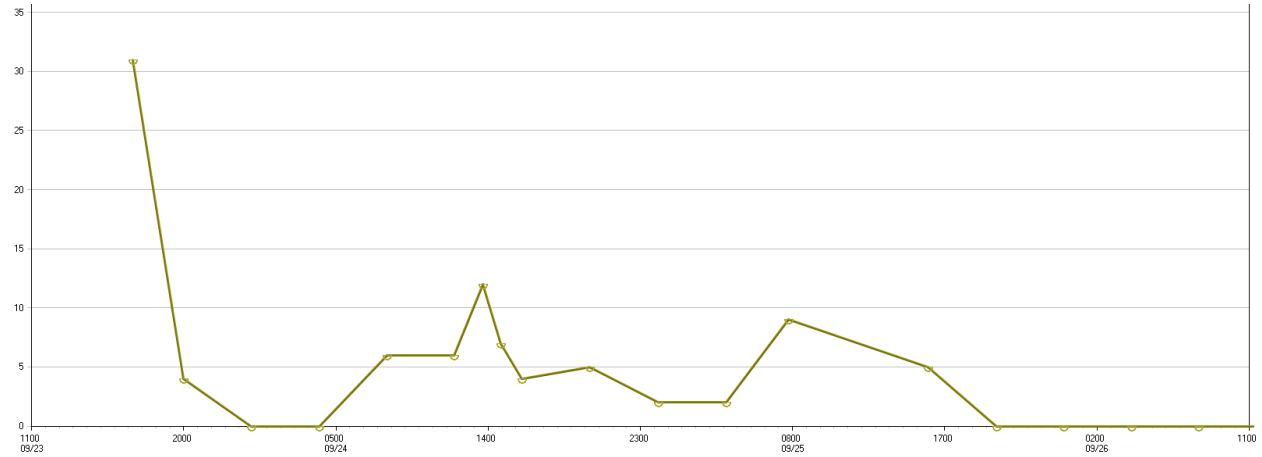
PRN Lorazepam – Symptom Triggered Dosing

CIWA-Ar	Reassess CIWA-Ar	Low Dose (>65 years or <50 kg)	Standard Dose
< 8	Every 1 hour until CIWA-Ar is less than 8 for 3 consecutive assessments, then every 4 hrs.	No Lorazepam	No Lorazepam
8-10	Every 2 hours	Lorazepam 0.5mg oral or IV	Lorazepam 1mg oral or IV
11-15	Every 1 hour	Lorazepam 1mg oral or IV	Lorazepam 2mg oral or IV
> 15	Every 15 minutes x 2. If CIWA-Ar not decreasing contact physician for transfer to higher level of care.	Lorazepam 1mg IV/IM, May Repeat in 15 minutes if CIWA-Ar is not decreasing. (Use IV first, if unable to use IV, give IM)	Lorazepam 2mg IV/IM, May Repeat in 15 minutes if CIWA-Ar is not decreasing. (Use IV first, if unable to use IV, give IM)
>15 and in Critical Care Unit	******** Every 15 minutes x 2 THEN Every 1 hour	******** Lorazepam 1mg IV/IM, May Repeat in 15 minutes if CIWA-Ar is not decreasing. (Use IV first, if unable to use IV, give IM) Lorazepam 2mg oral or IV	******* Lorazepam 2mg IV/IM, May Repeat in 15 minutes if CIWA-Ar is not decreasing. (Use IV first, if unable to use IV, give IM) Lorazepam 4mg oral or IV

Scheduled Lorazepam – Fixed Dosing

CIWA-Ar	Low Dose (>65 years or <50 kg)	Standard Dose
< 8	No Lorazepam	No Lorazepam
8-15	Lorazepam 0.5mg PO/IV q6h x4 doses, then 0.5mg q8h x 3 doses. Then STOP. (Use oral first, if unable to take orally, use IV)	Lorazepam 1mg q6h PO/IV x4 doses, then 1mg q8h x 3 doses. Then STOP. (Use oral first, if unable to take orally, use IV)
> 15	Contact physician	Contact physician

Administered Lorazepam in the ICU



Date	Time	Lorazepam Dose	Frequency	Comments
09/23	1654	2 mg IV	Once	-
	1851	1 mg IV	Q6H	Scheduled
	2302	4 mg IV	Q1H PRN	For CIWA-Ar > 15
09/24	0117	1 mg IV	Q6H	Scheduled
	0526	1 mg IV	Q6H	Scheduled
	1241	1 mg IV	Q6H	Scheduled
	1354	2 mg IV	Q1H PRN	For CIWA-Ar 11-15
	1813	1 mg IV	Q8H	Scheduled
09/25	0217	1 mg IV	Q8H	Scheduled
	0941	1 mg IV	Q8H	Scheduled

Fluid and Electrolyte Replacement

Volume replacement with isotonic fluids

Electrolytes

- Potassium
- Magnesium
- Phosphate

Vitamins

- Thiamine
- Folate
- MVI

Volume replacement with isotonic fluids

NS

D5W

LR

- Patients lost lots of fluid to diaphoresis, hyperthermia, vomiting/GI loss, tachypnea

- Although NS is more advantageous than D5W in patients requiring intravascular volume resuscitation, some patients with an extensive, chronic AUD may present in a starved state

Flannery AH, Adkins DA, Cook AM. Unpeeling the Evidence for the Banana Bag: Evidence-Based Recommendations for the Management of Alcohol-Associated Vitamin and Electrolyte Deficiencies in the ICU. *Critical care medicine.* 2016;44(8):1545-1552.

Electrolytes

K^+

Hypokalemia

- Dysrhythmias

Mg^{2+}

Hypomagnesemia

- Dysrhythmias, Seizures, tremors
- Magnesium Sulfate 64 mg/kg on day 1, followed by 32 mg/kg on days 2–4

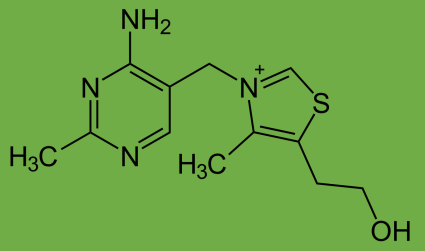
P

Hypophosphatemia

- May contribute to cardiac failure or rhabdomyolysis, muscle weakness

Flannery AH, Adkins DA, Cook AM. Unpeeling the Evidence for the Banana Bag: Evidence-Based Recommendations for the Management of Alcohol-Associated Vitamin and Electrolyte Deficiencies in the ICU. *Critical care medicine.* 2016;44(8):1545-1552.

Vitamins



B_1

Thiamine

- Prevent Wernicke's encephalopathy
- Give IV followed by PO before Glucose
- 200–500 mg IV every 8 hr

Fo

Folate

- Anemia, confusion, sleep disturbances, seizures
- 400–1,000 µg IV daily

MVI

Multivitamin

- No published data exist investigating the efficacy or safety of acute use of multivitamin injection in patients with possible alcohol withdrawal.

Flannery AH, Adkins DA, Cook AM. Unpeeling the Evidence for the Banana Bag: Evidence-Based Recommendations for the Management of Alcohol-Associated Vitamin and Electrolyte Deficiencies in the ICU. *Critical care medicine.* 2016;44(8):1545-1552.

Baptist Health Louisville Alcohol Withdrawal Vitamin and Nutrition Orders

Meds:

1. Thiamine 100 mg IV or PO Now (Use IV first. If unable to give IV, give PO)
2. Follow with one of the following DAILY x 3 Days

ORAL (use first)		IV (use if cannot take ORALLY)
Thiamine 100mg qday x3		Thiamine 100mg
Adult Multi-vitamin qday x3		MVI 10mL
Folic Acid 1mg qday x3		Folic Acid 1mg
	OR	Magnesium 2Gm
		1000 mL Normal Saline
		Give 100mL/hr once daily for 3 days.

Al Coholic's Inpatient Meds

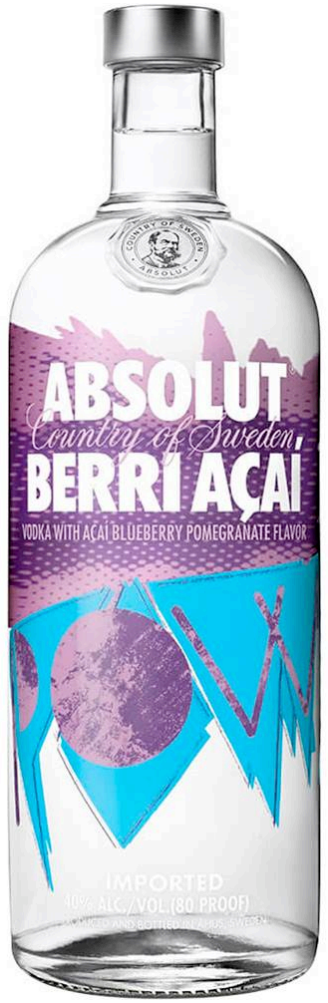
- Lorazepam Alcohol Withdrawal Protocol
- Dexmedetomidine 0.2-1.5 mcg/kg/hr
- Ketamine 5 mcg/kg/hr
- Lactated Ringers 100 mL/hr
- Clonidine 0.3 mg/24 hour patch
- D5W and LR with 20 mEq K+, 10 mL MVI, Thiamine 100 mg, Folic Acid 1 mg daily

Adjunctive and Alternative Therapies

Ethanol

- The most logical of all
- Doesn’t prevent seizures or DT
- Known toxicities…
- Short half-life

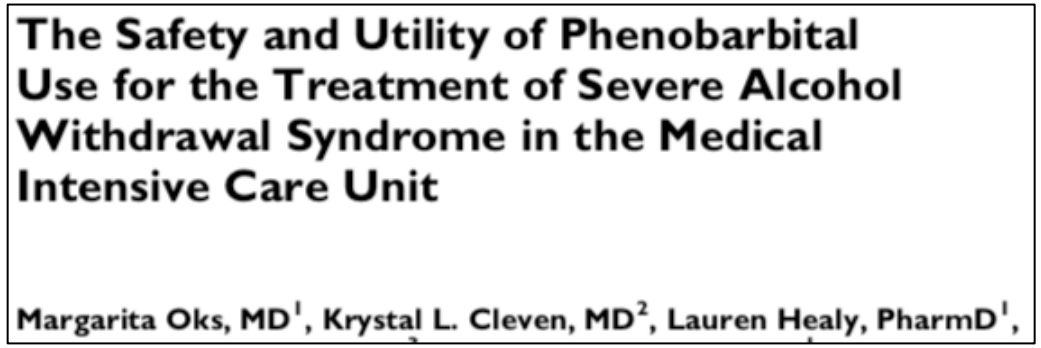
Bottom Line – Skip it. It doesn’t work.



Phenobarbital

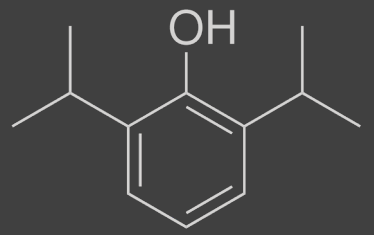
- Long-acting barbiturate
- Targets underlying pathophysiology of DT
  - Decreased anxiety and autonomic hyperactivity
- Requires intubation – unlike BZD
- Not first line
  - Small therapeutic index
  - Over-sedation
  - Hemodynamic instability
- Study of single 10 mg/kg IV dose in ED reduced ICU admissions and reduced BZD use

Bottom Line: Use for severe withdrawal resistant to BZD


The Safety and Utility of Phenobarbital Use for the Treatment of Severe Alcohol Withdrawal Syndrome in the Medical Intensive Care Unit

Margarita Oks, MD[1], Krystal L. Cleven, MD[2], Lauren Healy, PharmD[1],

Propofol



- $GABA_A$ agonist + NMDA receptor antagonist
  - Increases inhibitory CNS effects and decreases excitatory effects
  - Decreased anxiety and autonomic hyperactivity
- Increases seizure threshold
- Lipid Effects
- Hypotension and bradycardia
- Requires intubation

Refractory delirium tremens treated with propofol: A case series

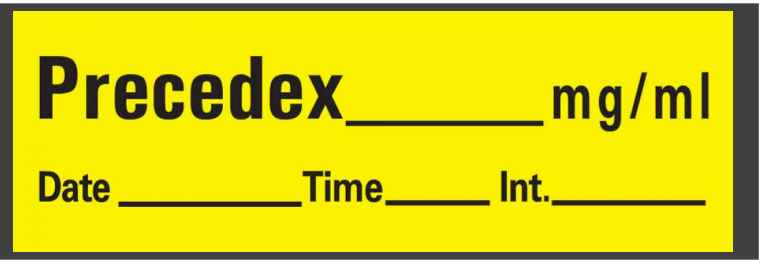
Christy McCowan, MD; Paul Marik, MD, FCCM

Delirium tremens, the most serious manifestation of alcohol withdrawal, occurs in ~5% of hospitalized alcoholics and has a mortality rate approaching 15%. Patients with delirium tremens are usually treated in an intensive care unit in which benzodiazepines form the cornerstone of therapy. In this report, we describe four patients who proved refractory to high doses of benzodiazepines and were successfully treated with a propofol infusion.
(Crit Care Med 2000; 28:1781–1784)

KEY WORDS: alcohol withdrawal; delirium tremens; propofol; benzodiazepines; lorazepam; γ-aminobutyric acid; *N*-methyl-D-aspartate

Bottom Line: Consider in patients with severe delirium tremens, poorly controlled with high doses of BZDs

Dexmedetomidine



- α_2-agonist that reduces SNS output
- Doesn't affect airway
- Bradycardia; Hypotension
- Doesn't affect underlying pathophysiology of DT
- When added to BZDs for treatment of DT, cumulative BZD dose has been shown to decrease

Bottom Line: consider for patients requiring additional symptomatic control


RESEARCH Open Access

Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU

Samuel G Rayner[1*], Craig R Weinert[2], Helen Peng[3], Stacy Jepsen[3], Alain F Broccard[4] and Study Institution[5]

Sympatholytics

Dexmedetomidine to Clonidine Conversion/Taper	
Initiate Clonidine	
Dexmedetomidine Dose	**Clonidine Starting Dose (enteral or oral)**
> 0.7 mcg/kg/hr, wt>100kg or age<50 yo	*0.3 mg* PO/NG q6h. Hold for SBP<120 or MAP<65.
</= 0.7 mcg/kg/hr, wt<100kg or age>50 yo	*0.2 mg* PO/NG q6h. Hold for SBP<120 or MAP<65.

β-Blockers

- Symptomatic management
- No effect on seizures or DT
- Manage BP and HR

α_2-agonists (clonidine)

- Stimulates peripheral α adrenergic receptors resulting in vasodilation
- Does not target underlying pathophysiology of DT

Bottom Line: Symptomatic management of withdrawal

Ketamine

- NMDA antagonist
- Logic: EtOH use results in upregulation of NMDA receptors
- Can reduce cumulative BZD administration
  - Ketamine 0.20 mg/kg/h infusion reduced benzodiazepine use from 40 mg to 13.3 mg

Adjunctive Use of Ketamine for Benzodiazepine-Resistant Severe Alcohol Withdrawal: a Retrospective Evaluation

Poorvi Shah[1] · Marc McDowell[1] · Reika Ebisu[2] · Tabassum Hanif[3] · Theodore Toerne[4]

Adjunct Ketamine Use in the Management of Severe Ethanol Withdrawal

Anthony F. Pizon, MD, FACMT[1]; Michael J. Lynch, MD[1]; Neal J. Benedict, PharmD[2]; Joseph H. Yanta, MD[1]; Adam Frisch, MD[3]; Nathan B. Menke, MD, PhD[4]; Greg S. Swartzentruber, MD[5]; Andrew M. King, MD[6]; Michael G. Abesamis, MD, MS[1]; Sandra L. Kane-Gill, PharmD, MS, FCCM, FCCP[2]

Haloperidol

- First generation anti-psychotic
- Non-selectively blocks postsynaptic dopaminergic D_2 receptors in the brain
- Decreases psychiatric symptoms of DT
- QTc prolonging
  - Arrhythmias
- Risk of extrapyramidal effects; NMS
- Lowers seizure threshold
- The usual dose is 2 to 20 mg IV every 1 hour PRN until the patient is calm
- Utility if patient has underlying psychiatric condition

Anticonvulsants

- Carbamazepine
  - May reduce seizures, not extensively studied
  - No studies for use in DT
  - Nausea and ataxia at high doses
- Valproic Acid
  - It appears that VPA may be a more effective and safer adjunct than CBZ
  - Evidence very limited
- **Bottom Line** – Not recommended for treatment of DT

Summary

- Assessing for potential withdrawal from chronic alcohol use is imperative for patients presenting with AWS symptoms in the ED
- IV Benzodiazepins are the gold-standard for treatment
- Patients will require IVF to replete intravascular volume, supplementation with thiamine and folate, and should received electrolyte protocol orders for electrolyte abnormalities (K, Mg, Phos)
- Adjunct agents may provide benefits of their own, but should not be used as monotherapy

Questions?

Benzodiazepine Shortages

10/3/2018

Lorazepam Injection

Products Affected - Description

- Ativan injection, Hikma, 2 mg/mL, 10 mL vial, 10 count, NDC 00641-6000-10
- Ativan injection, Hikma, 4 mg/mL, 10 mL vial, 10 count, NDC 00641-6002-10
- Lorazepam injection, Hikma, 4 mg/mL, 10 mL vial, 10 count, NDC 00641-6047-10
- Lorazepam injection, Pfizer, 2 mg/mL, 1 mL Carpuject syringe, 10 count, NDC 00409-1985-30
- Lorazepam injection, Pfizer, 2 mg/mL, 10 mL vial, 10 count, NDC 00409-6780-02
- Lorazepam injection, Pfizer, 4 mg/mL, 1 mL Carpuject syringe, 10 count, NDC 00409-1539-31
- Lorazepam injection, Pfizer, 4 mg/mL, 10 mL vial, 10 count, NDC 00409-6781-02

FDA Drug Shortages

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Start Over | Back to Previous Screen

Diazepam Injection, USP
Status: Currently in Shortage
»**Date first posted:** 09/22/2017
»**Therapeutic Categories:** Neurology

Expand all

Hospira, Inc. *(Reverified 09/28/2018)*

Company Contact Information:
844-646-4398

Presentation	Availability and Estimated Shortage Duration	Related Information	Shortage Reason (per FDASIA)
10 mg/2 mL (5 mg/mL); Carpuject Luer Lock Glass Syringe (NDC 00409-1273-32)	Next Delivery: October 2018; Estimated Recovery: March 2019	Shortage per Manufacturer: Manufacturing Delay Dear Customer Letter	Other
50 mg/10 mL (5 mg/mL); Multiple Dose Glass Fliptop Vial (NDC 00409-3213-12)	Available		Other

Transition from dexmedetomidine to enteral clonidine for ICU sedation: an observational pilot study.

- Single-center prospective observational pilot study
- Fifteen (75%) were successfully transitioned from dexmedetomidine within 48 hours of starting clonidine.
- Lower fentanyl requirements
- No differences in safety or efficacy
- The potential drug acquisition cost avoidance was $819-$2338 per patient during the 3-month study.
- https://www.ncbi.nlm.nih.gov/pubmed/25809176

Dexmedetomidine to Clonidine Conversion/Taper	
Initiate Clonidine	
Dexmedetomidine Dose	**Clonidine Starting Dose (enteral or oral)**
> 0.7 mcg/kg/hr, wt>100kg or age<50 yo	*0.3 mg* PO/NG q6h. Hold for SBP<120 or MAP<65.
</= 0.7 mcg/kg/hr, wt<100kg or age>50 yo	*0.2 mg* PO/NG q6h. Hold for SBP<120 or MAP<65.
Establish effective clonidine dose and taper off of Dexmedetomidine	
Decrease dexmedetomidine dose by *25%* 3-4 hrs after each clonidine dose.	If patient is agitated (RASS>1), has significant pain (CPOT≥3), or requires PRN medication to treat agitation, increase clonidine dose by 0.1 mg at the next regular dosing interval or decrease the interval by 1 "step" (i.e., q8 to q6), as allowed by BP.
Continue decreasing dexmedetomidine dose as tolerated.	If patient develops hypotension (SBP<90 or MAP<65), investigate other medications that could be adjusted temporarily and contact physician.
Begin tapering off Clonidine	
Once completely off of dexmedetomidine for 24 hrs, begin to taper off of clonidine.	Decrease clonidine interval by one step in dosing *interval* every 24-48 hrs (i.e., q6 to q8 to q12 to q24). If agitation (RASS>1 or PRN medication use), pain, withdrawal symptoms, or hyperactive delirium occurs or worsens, change clonidine to previous dosing regimen for 24-48 hrs and then resume tapering off.

Implementation of an ICU-Specific Alcohol Withdrawal Syndrome Management Protocol Reduces the Need for Mechanical Ventilation

Jason J. Heavner,[1,*] Kathleen M. Akgün,[2] Mojdeh S. Heavner,[3] Claire C. Eng,[4] Matthew Drew,[5] Peter Jackson,[6] David Pritchard IX,[7] and Shyoko Honiden[8]

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