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Medication Controversies in Alcohol Withdrawal

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6.6.19

Disclosure Statement

Lisa Sagardia, PharmD declares no conflicts of interest, real or apparent, and no financial interests in any company, product, or service mentioned in this program, including grants, employment, gifts, stock holdings, and honoraria.

Objectives

1. Compare and contrast current treatment strategies for alcohol withdrawal
2. Review novel therapy approaches for treatment refractory withdrawal
3. Given a patient at risk for alcohol-induced withdrawal symptoms, develop an appropriate treatment regimen

Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of nausea and vomiting

His vitals taken in triage are as follows: Temp: 100.8, BP: 184/88, HR: 130's

On physical examination, you find that he is diaphoretic with beads of sweat on his forehead, anxious, and has tremors

His social history includes 2 six-packs of beer/day. His last drink was 3 days ago

Questions to think about:

1. What are the signs and symptoms of alcohol withdrawal in this patient?
2. What screening tool can we use for this patient to monitor his symptoms?
3. Is this patient at risk for developing Delirium Tremens or seizures?

Classifying Withdrawal

- Epidemiology
  - 16-31% have a history of alcohol use disorder
- Healthcare Impact
  - Longer ICU length of stay (LOS)
  - Prolonged mechanical ventilation
  - Increased mortality
- Complications
  - Respiratory Failure
  - Seizures
  - Delirium Tremens
  - Wernicke's Encephalopathy/Wernicke-Korsakoff Syndrome

Ann Pharmacother. 2016;50(5):389-401

Delirium Tremens (DT) – DSM-5 Criteria

- Altered attention from baseline with fluctuating severity
- Visual, auditory, memory, orientation, or language disturbances
- Exclusion of Coma
- Diminished attention & awareness
- Alcoholic disease history

N Engl J Med. 2014;371(22):2109-13

Wernicke-Korsakoff Syndrome

Thiamine (Vitamin B1) Deficiency (chronic syndrome from alcohol consumption)

Characterized by a triad of symptoms including neurologic, ocular, and gait abnormalities

90% of diagnoses are missed as symptoms are nonspecific and symptoms overlap with DT

Treatment with high dose thiamine 500mg IV x 3-5 days for suspicion and preemptive supplementation for alcohol withdrawal

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Ind Psychiatry J. 2013;22(2):100-8

Onset of Symptoms

Timing	Signs and Symptoms
6-24 hours	• Tremors • Nausea & Vomiting • Autonomic abnormalities
7-48 hours	• Autonomic instability • Hallucinations • Seizures
49-96 hours	• Delirium Tremens • Severe autonomic instability

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Ann Pharmacother. 2016;50(5):389-401
Ind Psychiatry J. 2013;22(2):100-8

Screening Tools

- Identify Patient's at Risk
  - CAGE Questionnaire
  - Alcohol Use Disorders Identification Test
  - Short Michigan Alcoholism Screening test
- Severity of Withdrawal
  - Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-AR)
  - Riker Sedation Agitation Scale (SAS) or Richmond Agitation Sedation Scale (RASS)

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Am Fam Physician. 2013;88(9):589-595

CIWA-Ar Scoring: The Non-Intubated Patient

Autonomic	Disturbances	Orientation	Scoring
• Nausea/Vomiting • Tremors • Sweating • Anxiety • Agitation • Headache	• Auditory • Visual • Tactile	• Orientated to time and place	• Mild ≤ 8 • Moderate 9 – 15 • Severe > 15

- **Clinical Pearls**
  - Each quality above is rated 1-7 with higher scores representing higher severity
  - Requires communication by patient for full assessment
  - Scores < 8 typically do not need medical treatment and patients can be treated in the outpatient setting
  - CIWA-Ar scores should be taken at least every 2 hours

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British Journal of Addiction 84:1353-1357, 1989

SAS and RASS Scoring: The Intubated Patient

Score	SAS Description
7	Severely Agitated/Dangerous
6	Very Agitated
5	Agitated
4	**Calm/Cooperative**
3	**Sedated**
2	Very sedated
1	Unarousable

Score	RASS Description
+4	Combative
+3	Very Agitated
+2	Agitated
+1	Restless
0	**Alert/Calm**
-1	**Drowsy**
-2	Light Sedation
-3	Moderate Sedation
-4	Deep Sedation
-5	Unarousable

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J Trauma Acute Care Surg 2014;77:938–43
Crit Care Med 2007;35:724–30

Consideration of ICU Admission

- Hemodynamic instability
- High dose sedative requirements
  - CIWA-AR and benzodiazepine (BZD) requirements vary per institution for ICU admission
    - Study out of Advocate Christ Medical Center from 2012-2014 criteria for ICU admission: CIWA-AR ≥ 20 and > 12 mg BZD within 2 hours
  - Initiation of continuous infusion drips
- Worsening respiratory status
- Hyperthermia
- End-organ dysfunction
- Elderly patients
- History of cardiac disease

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J Crit Illness 1998; 13:311
J Med Toxicol. 2018;14(3):229-236

Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of **nausea and vomiting**

His vitals taken in triage are as follows: **Temp: 100.8,** BP: **184/88, HR: 130's**

On physical examination, you find that he is **diaphoretic** with beads of sweat on his forehead, **anxious**, and has **tremors**

He has a social history that includes 2 six-packs of beer/day and it has been about **3 days** since their last drink

Questions

1. What are the signs and symptoms this patient has of alcohol withdrawal?
   - **Nausea, vomiting, and diaphoresis**
   - **Hypertensive, tachycardic, and febrile**
2. What screening tool can we use for this patient to monitor his symptoms?
   - **CIWA-Ar**
3. Is this patient at risk for developing Delirium Tremens or seizures? **Yes**
   - **Seizure onset typically > 7 hours**
   - **Delirium Tremens > 48 hours**

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Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of nausea and vomiting

This patient is not intubated, so you choose the CIWA-Ar screening tool for scoring symptoms and his score comes back as **22**

Questions

4. Does DS have mild, moderate, severe, or refractory withdrawal?
5. What is the recommended medication for this patient with a CIWA-Ar Score of 22?
6. How frequently should we monitor CIWA-Ar scores?

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Management: Practices Vary Widely

Category	Medications
Antipsychotics	Haloperidol Atypicals
BZD	Alprazolam Chlordiazepoxide Clonazepam **Diazepam** **Lorazepam** Midazolam Oxazepam
Adjunctive Therapies	Clonidine **Ethanol** **Ketamine** **Phenobarbital** **Propofol** **Dexmedetomidine**

- In the treatment of refractory withdrawal, 3 hospital systems had very different practices:
  - 16 medications
  - 74 medication combinations
  - 1 patient received 7 medications

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J Crit Care. 2015;30(2):405-9

General Management of Withdrawal

	Mild	Moderate	Severe	Refractory
CIWA-Ar	< 8	8-15	> 15	> 15
First Line Therapy	Non-BZD monotherapy	Treatment with **oral/IV** BZD's	Treatment with **intravenous** BZD's	
Adjunctive Therapy	BZD's	Non-BZD	Intravenous sedatives	
Service	Outpatient	Inpatient	ICU	

- All patients should receive supportive care
- Non-BZD: valproic acid, topiramate, carbamazepine gabapentin, baclofen
- Oral benzodiazepines: diazepam, chlordiazepoxide, lorazepam, oxazepam
- BZD's can be given in symptom triggered or fixed dose approach
- Intravenous sedatives include: Dexmedetomidine, phenobarbital, propofol, and ketamine

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Drugs. 2015;75(4):353-65

Refractory Withdrawal

No Standard Definition Exists

> 10 mg lorazepam (~75mg diazepam) in 1 hour or > 40 mg lorazepam in 4 hours

> 27 mg lorazepam (200mg diazepam) within 3 hours + hemodynamic instability

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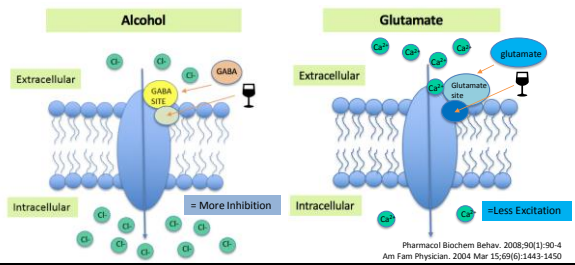
J Med Toxicol 2006;2(2):55–60
Ind Psychiatry J. 2013;22(2):100-8

Mechanism of Action of Alcohol



Pharmacol Biochem Behav. 2008;90(1):90-4
Am Fam Physician. 2004 Mar 15;69(6):1443-1450

Neurotransmitter changes with Chronic Alcohol Intake

Glutamate receptors upregulate in response to decreased glutamate signaling

GABA receptors down regulate in response to enhanced chloride activation

Abrupt Cessation of Alcohol Leads to:

- **Glutamate overactivity** (these receptors have become more sensitive over time)
- **Unopposed GABA** inhibition due to downregulation of receptors

Pharmacol Biochem Behav. 2008;90(1):90-4
Am Fam Physician. 2004 Mar 15;69(6):1443-1450

Drug Targets in Alcohol Withdrawal

Reduce glutamate over excitability

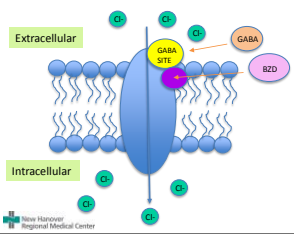
Increase GABA signaling

Pharmacol Biochem Behav. 2008;90(1):90-4
Am Fam Physician. 2004 Mar 15;69(6):1443-1450

Moderate-Severe Withdrawal: Parenteral Therapy

- Benzodiazepines
- Dexmedetomidine
- Propofol
- Phenobarbital
- Ketamine

Benzodiazepines: Mechanism of Action



- BZD binds to a similar area of the GABA site to promote GABA activity and enhance signaling
- Dependent on GABA receptors that are present

Ind Psychiatry J. 2013;22(2):100-8

First Line Treatment – Benzodiazepines

Classification	Drug	Dosage Forms	Dosing	Onset
Short acting	Lorazepam	Oral, IV	• **Symptom: Triggered**: 2-4 mg q1hr • **Fix Dose**: 2 mg IV q6hrs x 4 doses, followed by 1 mg IV q6hrs x 8 doses	IV: 10 min Oral: Within 60 min
	Oxazepam	Oral	15-30 mg 3-4 times daily	Oral: 1-4 hrs
	Midazolam	IV, IM	0.5-2 mg IV q5min	IM: 15 min IV: 5 min
Long	Diazepam	Oral, IV, IM	IV, IM: 5-10 mg q3-4 hours Oral: 10 mg 3-4 times daily PRN	IV: 1-3 min IM: 60 min Oral: 15 min – 2.5 hrs

Common conversions:
Diazepam 10 mg = lorazepam 1.5 mg = midazolam 1 mg = phenobarbital 3.3 mg

Anesth Prog. 2007;54(3):118-28.
Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. 2019

Benzodiazepine Approach

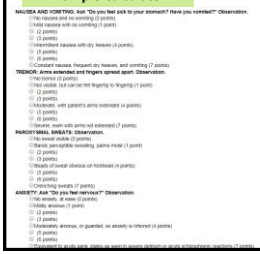
Symptom Triggered
- Utilizes a symptom scale (CIWA-Ar) and frequent evaluations to assess need for medication administration

Fixed-Dosed
- Scheduled BZD Regimen

Ann Pharmacother. 2016;50(5):389-401

Example Symptom Triggered Protocol

Example Calculator



Reference Scores and BZD Dose To Give

CIWA Score	Lorazepam
CIWA 0	Hold
CIWA 1-7	1mg PO/IV
CIWA 8-9	2 mg PO/IV
CIWA 10-11	3 mg PO/IV
CIWA ≥ 12	4 mg PO/IV
If CIWA < 8 x 48 hours	Discontinue Protocol
Re-evaluate	Every Hour

UpToDate Calculator, 2019
New Hanover Regional Medical Center Alcohol Withdrawal ICU Protocol

Study Protocol: Symptom-Triggered vs. Fixed Dose

Prospective, Randomized, Double Blind Trial (N=117)

Symptom Triggered	Fixed Dose
Placebo PO q6hrs x 4 doses	Oxazepam 30 mg PO q6hrs x 4 doses
Assessment 30 minutes after Placebo CIWA 8-15: Oxazepam 15 mg x 1 CIWA > 15: Oxazepam 30 mg x 1	**Assessment 30 minutes after Drug** CIWA 8-15: Oxazepam 15 mg x 1 CIWA > 15: Oxazepam 30 mg x 1
Placebo PO q6hrs x 8 doses	Oxazepam 15 mg PO q6hrs x 8 doses

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Arch Intern Med. 2002;162(10):1117-21

Study Results

Outcomes	Symptom Triggered, n=56	Fixed Dose, n=61	Statistics
No. (%) who received oxazepam	**22 (39.3)**	61 (100)	P < 0.001
PRN Oxazepam, mg (range)	37.5 ± 81.7 (0-375)	**6.9 ± 20.4 (0-135)**	P < 0.05
Total Oxazepam, mg (range)	**37.5 ± 81.7 (0-375)**	231.4 + 29.4 (180-375)	P < 0.001
Treatment Duration (hours)	**20 + 20.5**	62.7 + 5.4	P < 0.001

- Takeaways
  - Decreased BZD use and duration of treatment with symptom-triggered approach
  - Trends towards **less BZD use** in the 19 patients classified as having severe alcohol withdrawal with statistically significant **shortened treatment times** with symptom-triggered approach

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Arch Intern Med. 2002;162(10):1117-21

Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of nausea and vomiting

This patient is not intubated, so you choose the CIWA-Ar screening tool for scoring symptoms and his score comes back as **22**

Questions

4. Does DS have mild, moderate, severe, or refractory withdrawal?
   - **Severe (CIWA-Ar > 15)**
5. What is the recommended medication for this patient with a CIWA-Ar Score of 22?
   - **IV BZD such as lorazepam 4mg IV**
6. How frequently should we monitor CIWA-Ar scores?
   - **At least every 2 hours; most protocols are hourly monitoring**

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Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of nausea and vomiting

DS receives 4 mg IV x 1 dose. Despite hourly dosing of BZD's, the patient requires frequent PRN boluses to stay calm

Over the next 4 hours, DS receives 50mg of lorazepam. He is starting to develop respiratory depression

The patient has had a marked change in disposition and is now aggressive and combative with the nursing staff

Questions

7. Does this patient need to be transferred to the ICU?

8. Does he need to be intubated?

9. What are adjunctive therapies we can consider for this patient?

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Moderate-Severe Withdrawal: Parenteral Therapy

- Benzodiazepines
- Phenobarbital
- Ketamine
- Propofol
- Dexmedetomidine

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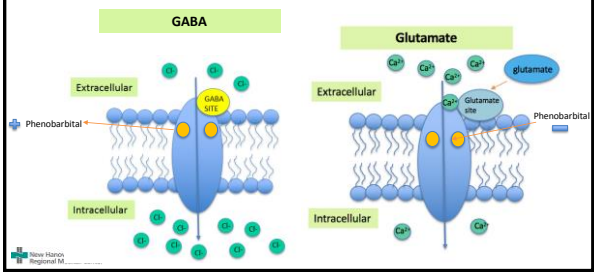
Phenobarbital Mechanism



Phenobarbital Dosing

Drug	Phenobarbital
Dosing (Adult)	• 260 mg bolus followed by 130 mg based in CIWA-Ar scoring • 10 mg/kg (IBW)
Adverse Events	• Bradycardia/Hypotension • CNS depression • Respiratory Depression
Pharmacokinetics	• Onset: 5 minutes • Peak: ~15 minutes • T ½ life: 79 hours (53-118 hours)

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. 2019

Phenobarbital vs. Benzodiazepines

Trial	Study population	Intervention	Results
Multicenter, retrospective cohort study (N=209)	Non-intubated patients in the Emergency Department	Phenobarbital IV + BZD vs. BZD monotherapy	• 260 mg (218-650 mg) was the total median dose and range used • 14% phenobarbital vs. 11% BZD admitted to ICU (p=0.529) • No difference in complications or ED LOS • Less lorazepam use in the phenobarbital group (14 vs. 22 mg)
Retrospective Cohort Study	Patients admitted to the ICU	Monotherapy Phenobarbital 130 mg IV q15min (symptom triggered) with goal of achieving RASS 0 to -1	• Patients received 23 mg lorazepam prior to transfer to ICU on average • Mean phenobarbital dose was 1978 mg (28 mg/kg) • 80% of ICU patients not intubated

Am J Emerg Med. 2018 Oct 11
J Intensive Care Med. 2018

Study Takeaways

- Emergency department study:
  - Utilized lower dosing of phenobarbital that previous studies
  - They did lack a defined study protocol
  - Differences in ICU admission criteria
  - Phenobarbital's role as adjunctive therapy should not be discounted based on this study
- ICU Study:
  - **Less intubations with the use of phenobarbital monotherapy**
  - Phenobarbital doses require compounding; q15min dosing could be difficult to achieve realistically
  - If used appropriately, phenobarbital is a safe alternative for the management of management

Am J Emerg Med. 2018 Oct 11
J Intensive Care Med. 2018

Benefits of Phenobarbital in Withdrawal

- More Predictable Response
  Blood level: 12-25 mcg/ml for 10-20 mg/kg dose)
- Ideal Kinetics
  Quick onset and long ½ life
- Multimodal mechanism for withdrawal
  Agonizes GABA; antagonizes glutamate
- Does not require intubation for use
- Safety shown in multiple studies if used appropriately
- Multiple formulations

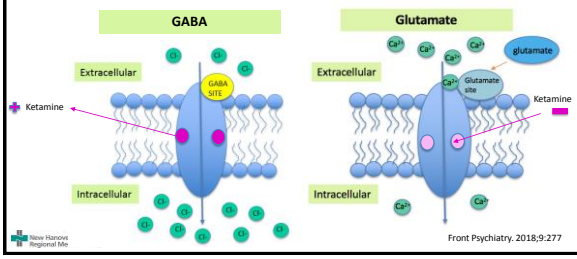
Concerns of Phenobarbital in Withdrawal

- Slower onset compared to BZD
- Accidental rapid administration
- Compounding and delays in delivery
- Not ideal for acute aggressive episodes
- Risks for adverse events in hepatic impairment

Moderate-Severe Withdrawal: Parenteral Therapy

- Benzodiazepines
- Phenobarbital
- Ketamine
- Propofol
- Dexmedetomidine

Ketamine Mechanism



Front Psychiatry. 2018;9:277

Ketamine Dosing

Drug	Ketamine (IV)
Dosing	• Analgesic Dose: < 1 mg/kg (sub-dissociative) • Study Dose: 0.3 mg/kg bolus followed by 0.15-0.3 mg/kg/hr
Adverse Events	• Dizziness • Nausea/vomiting • Enhanced pressor response (rapid administration) • Mild neuropsychological reaction
Pharmacokinetics	• Onset: 5-10 min • Peak: 10-15 min • T ½ life: 2.5 hr • Duration : 15-30 min

Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. 2019

Ketamine Evidence: Trial I

Observational, Retrospective cohort study (N=63)	
*Intervention	• **Pre-Guideline: Symptom triggered BZD's (January 2008-March 2011) • Post Guideline Symptom triggered BZD's + Ketamine 0.15-0.3 mg/kg/hr (April 2011-January 2015)
Outcomes	• ICU and HLOS • BZD, propofol, and dexmedetomidine use • Intubations
Inclusion Criteria	• Diagnosis of Delirium Tremens (DT) per DSMV criteria

*A ketamine bolus of 0.3 mg/kg could be given under discretion of provider
**All BZD were converted to diazepam equivalents using the following conversion: Diazepam 10mg = lorazepam 1.5 mg = midazolam 1mg = phenobarbital 3.3 mg

Crit Care Med. 2018;46(8):e768-e771

Ketamine Results

Outcomes

- **Shorter ICU and HLOS** *(11.2 vs. 5.7 ICU days, 16.6 vs. 12.5 inpatient days)*
- **Less BZD use** (2,525 mg vs. 1508 mg, P = 0.02)
- **Less Intubations** (22 vs. 10, P < 0.001)
- **Shorter Duration on Propofol** (4.57 vs. 2.4 days, p=0.03)

Safety

- One event of oversedation

Crit Care Med. 2018;46(8):e768-e771

Study Evaluation

- Limitations
  - Nonrandomized, bias
  - Long study duration – standard of care may have improved
- Reflection
  - Prior to the initiation of ketamine, average BZD use was Diazepam 333mg = 50mg of lorazepam
  - Average duration of use was 47 hours

Crit Care Med. 2018;46(8):e768-e771

Ketamine Evidence: Trial II

Observational, Retrospective cohort study (N=40)	
Intervention	• Ketamine 0.5 mg/kg/hr – 4.5 mg/kg/hr added if lorazepam infusion
Outcomes	• Time to symptom control • Lorazepam requirements • Ketamine initial and max dosing rates • Adverse events
Inclusion Criteria	• Severe alcohol withdrawal (CIWA-Ar > 20) • Continuous infusion of lorazepam • Received ketamine > 1 hour
Exclusion	• Concomitant use of propofol or dexmedetomidine

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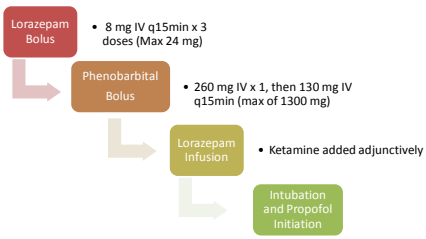
J Med Toxicol. 2018;14(3):229-236

Study Algorithm: Trial II



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J Med Toxicol. 2018;14(3):229-236

Study Comparison Analysis : Trial II and II

	Crit Care Med, 2018	J Med Toxicol, 2018
Population	• 53 years of age, 96% male	• 46 years of age, 82% male • 73% intubated prior to ketamine initiation • 87% received phenobarbital prior to ketamine
Refractory Definition	• DSMV Criteria	• Used adjunctively with lorazepam infusion after failure of lorazepam (24mg) and phenobarbital dosing (1300mg)
Prior BZD Use	• 50 mg of lorazepam	• 105.8 mg of lorazepam
Ketamine Dose	• Median dose: 0.19 mg/kg/hr	• Median dose: 0.75 mg/kg/hr • Max dose: 1.6 mg/kg/hr
Duration	• 47 hours	• 53.7 hours
Safety	• 1 occurrence of over sedation	• < 10% overall; no reports of CNS
Utility	• Improved HLOS and ICU LOS • Less intubations	• Symptom control within 1 hour

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Crit Care Med. 2018;46(8):e768-e771
J Med Toxicol. 2018;14(3):229-236

Ketamine

Benefits	Concerns	Future Research
• Improved ICU and HLOS • Rapid symptom control • Less intubations	• True instance of adverse events • Optimal titrations	• Ideal dosing strategy • Ketamine vs. phenobarbital adjunctively for withdrawal

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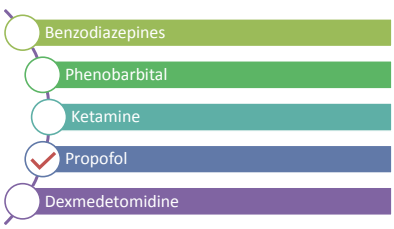
Moderate-Severe Withdrawal: Parenteral Therapy



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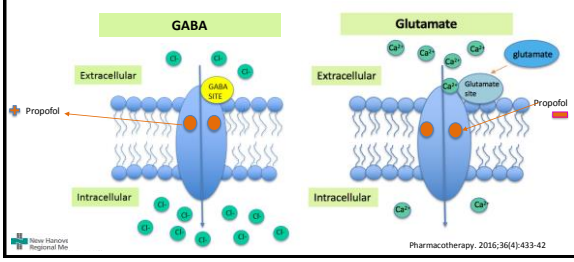
Propofol Mechanism



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Pharmacotherapy. 2016;36(4):433-42

Propofol Kinetics

Drug	Ketamine (IV)
Dosing	• 5-80 mcg/kg/min; titrate by 5 mcg/kg/min q5min
Adverse Events	• Hypotension/Bradycardia • Hypertriglyceridemia • Propofol Related Infusion Syndrome (PRIS) • Respiratory depression
Pharmacokinetics	• Onset: 30 seconds • Duration 3-10 minutes • Distribution: highly lipophilic • ½ life: Biphasic: 40 minutes (initial), 4-7 hours (terminal)

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Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. 2019

Trial	BZD prior to intervention	Intervention	Results

Single Center, Retrospective, (N=64), 2014	56mg lorazepam equivalents	Propofol containing regimens vs. midazolam	• Withdrawal resolution within 8 days with propofol
			• No differences in the following:
			  • Time to resolution of withdrawal symptoms
			  • Number of BZD boluses
			  • Duration of time of infusions
			  • HLOS, ICU, MV, mortality, or re-intubation
			  • Adverse events

Single Center, Retrospective (N=41), 2014	17.4 mg lorazepam equivalents	Propofol vs. Dexmedetomidine	• Both regimens with comparable reductions in haloperidol and benzodiazepine • MV was longer with propofol • No differences in ICU LOS
Single Center, Retrospective, (N=66), 2015	6 mg lorazepam equivalents within 1 hour	Benzodiazepines vs. Propofol	• Short term reductions in BZD use initially • No differences in BZD use within 7 days • No difference in withdrawal complications • MV was longer with propofol • ICU and HLOS longer with Propofol

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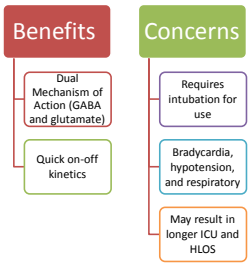
Ann Pharmacother. 2014;48(4):456-61
Clin Pharmacol. 2014;6:171-7
Drug Alcohol Depend. 2015;154:296-9

Propofol



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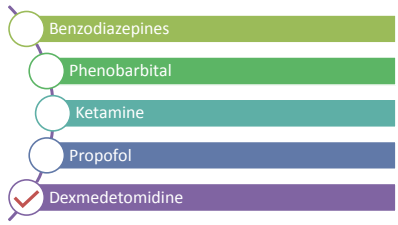
Pharmacotherapy. 2016;36(4):433-42

Moderate-Severe Withdrawal: Parenteral Therapy



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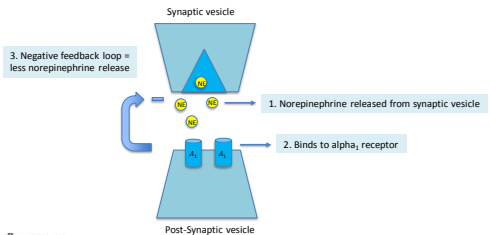
Mechanism of Action: Alpha 2 Agonists



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Anesth Prog. 2015;62(1):31-9

Drug Profile

Drug	Dexmedetomidine
Dosing (Adult)	• Bolus: 1 mcg/kg over 10 minutes • Infusion 0.2 – 0.7 mcg/kg/hr • Max dose: 1.4 mcg/kg/hr
Adverse Events	• Bradycardia • Hypotension
Pharmacokinetics	• Onset: 5-10 minutes • Peak: 15-60 minutes • T ½ life: 3 hours

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Pharmacotherapy. 2017;37(10):1309-21

Dexmedetomidine in Refractory Withdrawal

Prospective, Randomized, Double-Blind, Placebo Controlled Single Center Study (N=24)	
Intervention	• *Dexmedetomidine 1.2 mcg/kg/hr **vs**. 0.4 mcg/kg/hr **vs**. placebo
Outcomes	• Change in lorazepam requirements before and after study drug initiation • Total lorazepam dose required over 7 days
Inclusion Criteria	• Severe alcohol withdrawal **AND** ≥ 16mg lorazepam within 4 hours
Exclusion Criteria	• Pediatric and Elderly patients • Use of BZD for seizures or other indications • Comorbid neurologic conditions • Child-Pugh C liver disease • Underlying known bradyarrhythmia

*Both high and low dose dexmedetomidine were combined in the analysis of the the primary endpoint vs. placebo

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Crit Care Med. 2014;42(5):1131-9

Results

Primary Endpoint: BZD Use
- **Pre-post**: 56.4 mg (IQR, 16.8-84.5) vs. 8 mg (IQR 31.3-76.2), P=0.037
- **24 hr post-randomization:** 22.3 mg (IQR, 9.3-53.3) vs. placebo: 77.1 mg (IQR, 10.3-182), p=0.33
- **7 days**: 180.6 mg vs. 159.1 mg, p=0.58

Secondary Endpoints
- No differences in antipsychotic use, CIWA/Riker scores between the groups, or phenobarbital use

Adverse Events
- Decrease in heart > 20 bpm in dexmedetomidine group
- No differences in hypotension

*Both high and low dose dexmedetomidine were combined in the analysis of the the primary endpoint vs. placebo

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Crit Care Med. 2014;42(5):1131-9

Study Evaluation

- Limitations
  - Small sample size
  - 24 hours of BZD use prior to randomization
  - Impact on clinically significant outcomes
- Reflection
  - Does lower BZD dose correlate to improvement in alcohol withdrawal syndrome?
  - Can we do harm in masking the symptoms of alcohol withdrawal?

CIWA Criteria: Autonomic
- Nausea/Vomiting
- Tremors
- Sweating
- **Anxiety**
- **Agitation**
- Headache

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Benefits and Concerns of Dexmedetomidine

Pros
- Can reduce agitation and promote sedation
- Does not induce respiratory depression

Cons
- Lack of activity towards receptors primarily involved with withdrawal
- Lack of clinically meaningful outcome data

Role
- Adjunctive use to standard BZD therapy
- Consider addition of fixed-dosing BZD to treat withdrawal

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Medication Summary

	Benzodiazepine	Phenobarbital	Ketamine	Propofol	Dexmedetomidine
Pros	-Extensively studied -Symptom-triggered approach with established protocols	-Predictable response -Multimodal mechanism -Ideal kinetics -Multiple formulations -No intubation needed for use	-Improved ICU and HLOS-Rapid symptom control -Less intubations	-Quick on/off kinetics -Targets similar withdrawal receptors	-Reduce agitation and delirium symptoms -Does not induce respiratory depression
Cons	-Respiratory depression -Unpredictable kinetics -No effect on excitability	-Slower onset compared to BZD -Accidental rapid administration -Compounding delays -Risks in hepatic impairment	-True instance of adverse events -Optimal titrations	-Hypotension -Respiratory Depression -Triglyceride elevations -PRIS	-Lack of clinically meaningful outcome data -Lack of activity against critical receptors
Role in Therapy	First Line	Alternative First Line	Adjunctive, may prevent need for intubation	Adjunctive, only for intubated patients	Adjunctive, sedation

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Enteral Alcohol: why not treat fire with fire?

Pros
- Less respiratory depression
- Less need for adjunctive medications
- Less complications

Cons
- Limited data to drive its use and dosing
- Ethical dilemma
- Worsening hyponatremia
- Complications with comorbid conditions

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Enteral Alcohol Studies

Trial	Intervention	Endpoints	Results
Single Center, Retrospective Chart Review, Neurocritical care patients; 2016 (N=50)	Enteral ethanol vs. BZD	• 24-hr Change in CIWA • 5-day maximum and minimum CIWA scores • Glasgow Coma Scale (GCS) • LOS	• Severity of illness scores were lower and GCS was higher in the ethanol group • No superiority in terms of changes in CIWA scores • Higher treatment cross over (ethanol failure?) • Shorter ICU and HLOS • No differences in phenobarbital use or hyponatremia management
Prospective, Randomized, Controlled Pilot Study (AWARE), 2015 (N=57)	Lorazepam 2mg IV q6hrs and PRN BZD **vs.** lorazepam 2mg IV q12 hours and oral ethanol q4-6 hrs	• Composite outcomes (DT development, self-extubation, arrhythmias, retrained, re-infarction) • Hospital and ICU LOS	• No difference in composite outcomes, hospital and ICU LOS • Adjunctive use of ethanol resulted in less agitation and less feeding tube dislodgement • Safe adjunctive measure in critically ill cardiac patients

J Clin Neurosci. 2016;31:88-91
Am J Crit Care. 2013;22(5):398-406

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Patient Case

DS is a 31 yoM who presents to the emergency department with a chief complaint of nausea and vomiting.

DS receives 4 mg IV x 1 dose. Despite hourly dosing of BZD's, the patient requires frequent PRN boluses to stay calm.

Over the next 4 hours, DS receives 50mg of lorazepam. He is starting to develop respiratory depression.

The patient has had a marked change in disposition and is now aggressive and combative with the nursing staff

Questions

7. Does this patient need to be transferred to the ICU?
   - Yes, based on his BZD requirement, changes in disposition, worsening respiratory status

8. Does he need to be intubated?
   - If IV continuous infusions need to be started **and** respiratory status is worsening, then yes

9. What are adjunctive therapies we can consider for this patient?
   - Phenobarbital, ketamine, propofol

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Patient Case

After receiving 50mg of lorazepam, DS was transferred to the ICU and intubated on arrival. Propofol was started adjunctively.

DS was successfully managed on PRN lorazepam and propofol. 8 days was extubated and transferred to the floor.

Further evaluation of his substance abuse disorder occurred starting with CAGE questionnaire

DS is now seeking help for his substance abuse disorder

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Patient Case: Alternate Routes to the Same Outcome

- Initial Management
  - BZD symptom triggered monotherapy vs. BZD + Phenobarbital
- ICU Management (in the non-intubated patient)
  - Phenobarbital monotherapy with q15-30 min re-dosing based on monitoring protocols
  - Ketamine initiation
- ICU Management (intubated patient)
  - Propofol
  - Phenobarbital
  - Ketamine

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Summary

- A symptom-triggered approach with BZD is considered first line for initial management
- Phenobarbital has the benefit of multi-modal withdrawal treatment and predictable kinetics that may reduce the number of intubations
- Ketamine is an attractive alternative to other continuous infusions as it is respiratory-sparring and also has shown a reduction in intubations
- For the intubated patient, propofol is a reasonable adjunctive medication but carriers the risk of hypotension and bradycardia
- Dexmedetomidine may have a more limited role in withdrawal as it does not target the ideal receptors for management

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Leading Our Community to Outstanding Health

Medication Controversies in Alcohol Withdrawal

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6.6.19