UTAH SOCIETY OF HEALTH-SYSTEM PHARMACISTS

Bryn Lindley, PharmD
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1

1

Let's CIWAt We Know About Withdrawal: Alcohol Withdrawal Management Updates

Bryn Lindley, PharmD
PGY2 Internal Medicine Pharmacy Resident
University of Utah Health

2

2

Disclosures

Relevant Financial Conflicts of Interest
- CE Presenter: Bryn Lindley
  - No conflict of interest
- CE mentors: Jennifer Babin, Ashley Crosby, Heather Nyman
  - No conflict of interest

Off-Label Uses of Medications
- Gabapentin, lorazepam, phenobarbital, topiramate

3

3

Abbreviations

- AUD – alcohol use disorder
- CIWA-Ar – Clinical Institute Withdrawal Assessment for Alcohol, Revised
- CrCl – creatinine clearance
- GABA – gamma-aminobutyric acid
- PAWSS – Prediction of Alcohol Withdrawal Severity Scale

4

4

Pharmacist Learning Objectives

- Differentiate between the four stages of acute alcohol withdrawal
- Interpret CIWA-Ar and PAWSS scores for a patient with acute alcohol withdrawal
- Explain the mechanism of action for the medications used to treat alcohol withdrawal and AUD
- Design an appropriate drug regimen for the treatment of alcohol withdrawal and AUD based on patient specific factors

5

5

Technician Learning Objectives

- Apply appropriate storage and handling of common medications used for the treatment of alcohol withdrawal
- Identify medications used for alcohol withdrawal on a patient's medication list
- Recognize common dosing instructions for medications used for the treatment of alcohol withdrawal

6

6

Let's Get to Know Each Other…

7

7

What is your job title?

A. Pharmacy Technician
B. Pharmacist
C. Pharmacy Student

8

8

What is the setting in which you practice?

A. Acute Care Pharmacy
B. Ambulatory Care Pharmacy
C. Community Pharmacy
D. Other

9

9

How often do you encounter patients experiencing alcohol withdrawal?

A. Weekly
B. Monthly
C. Yearly
D. Never

10

10

How comfortable do you feel treating a patient with alcohol withdrawal (inpatient or outpatient)?

A. Very comfortable
B. Moderately comfortable
C. Not comfortable at all

11

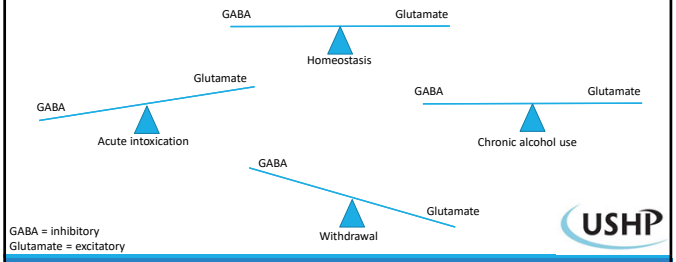
11

Alcohol Withdrawal

12

12

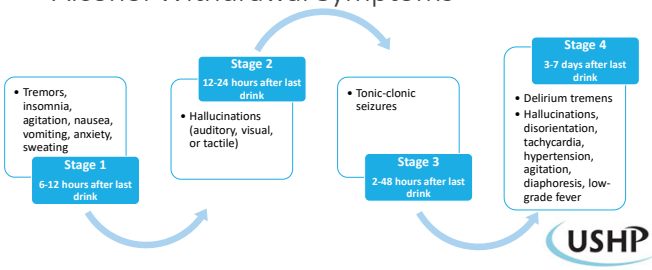
Alcohol Withdrawal Pathophysiology



GABA = inhibitory
Glutamate = excitatory

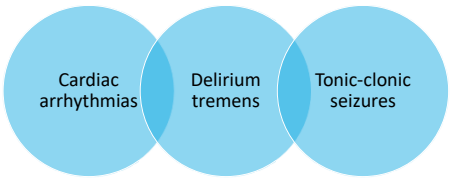
13

Alcohol Withdrawal Symptoms



14

Alcohol Withdrawal Complications



15

Knowledge Check

16

When is a patient in acute alcohol withdrawal at the highest risk for seizures?

A. Never
B. 2-48 hours after last drink
C. 3-7 days after last drink
D. 14 days after last drink

17

Which of the following are complications of alcohol withdrawal?

A. Cardiac arrhythmias
B. Delirium tremens
C. Tonic-clonic seizures
D. All of the above

18

Acute Alcohol Withdrawal Management

19

Acute Alcohol Withdrawal - Diagnosis

As described in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)

≥2 must be present within a few hours to days after alcohol reduction/cessation
Autonomic hyperactivity (eg. Sweating, tachycardia)
Increased hand tremor
Insomnia
Nausea or vomiting
Transient hallucinations or illusions
Psychomotor agitation
Anxiety
Generalized tonic-clonic seizures

Alcohol Withdrawal Syndrome. *DynaMed* [database online]. EBSCO Information Services
American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.).

20

Acute Alcohol Withdrawal - Severity

As described in the American Society of Addiction Medicine's (ASAM) Clinical Practice Guideline on Alcohol Withdrawal Management

Common Assessment Scales

- Prediction of Alcohol Withdrawal Severity Scale (PAWSS)
- Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA-Ar)

The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management.

21

PAWSS

PAWSS Risk Stratification

- Low risk: < 4
- High risk: ≥ 4

Assessment Questions	Point Value
Have you been recently intoxicated within the last 30 days?	1
Have you ever experienced previous episodes of alcohol withdrawal?	1
Have you ever experienced alcohol withdrawal seizures?	1
Have you ever experienced delirium tremens?	1
Have you ever undergone AUD rehabilitation treatment or treatment for alcoholism?	1
Have you ever experienced blackouts?	1
Have you combined alcohol with other downers (eg benzodiazepine, barbiturates) in the last 90 days?	1
Have you combined alcohol with any other substance of abuse during the last 90 days?	1
Clinical Findings	**Point Value**
Blood alcohol ≥ 200 on presentation?	1
Evidence of increased autonomic activity?	1

Alcohol Withdrawal Syndrome. *DynaMed* [database online].
The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management.

22

CIWA-Ar

CIWA-Ar Severity

- Mild: < 10
- Moderate: 10-18
- Severe: ≥ 19
- Complicated: ≥ 19 + delirium or hallucinations

Clinical Dimension	Point Value
Nausea and vomiting	0-7
Tremor	0-7
Paroxysmal sweats	0-7
Anxiety	0-7
Agitation	0-7
Tactile disturbances	0-7
Auditory disturbances	0-7
Visual disturbances	0-7
Headache	0-7
Orientation	0-4

Alcohol Withdrawal Syndrome. *DynaMed* [database online]. EBSCO Information Services
The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management.

23

Knowledge Check

24

A 50 year old female is admitted to the Internal Medicine service with acute alcohol withdrawal. Based on her CIWA-Ar Score, how would you classify her withdrawal severity?

A. Mild
B. Moderate
C. Severe
D. Complicated

Clinical Dimension	Point Value
Nausea and vomiting	2
Tremor	1
Paroxysmal sweats	0
Anxiety	3
Agitation	1
Tactile disturbances	0
Auditory disturbances	0
Visual disturbances	0
Headache	2
Orientation	0

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25

25

Inpatient Management Overview

Supportive Care

- Standard delirium precautions
- Thiamine IV or IM x 5 days
- Folate replacement
- Electrolyte replacement

Pharmacologic

- Benzodiazepine
- Phenobarbital
- Gabapentin

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26

Benzodiazepines

Mechanism of action: binds highly to GABA-benzodiazepine receptor complex without displacing GABA

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Lorazepam (IV/PO)	2-4 mg PRN OR 6-8 mg/d + 4 d taper	IV: ~10 min PO: 2 hr	12-14 hr (N/A)	Hepatic
Diazepam (IV/PO)	5-20 mg PRN OR 10 mg q6h x 1 d, then 5 mg q6h x 2 d	IV: ~10 min PO: 1 hr	33-48 hr (desmethyldiazepam: 87-100 hr)	Hepatic
Chlordiazepoxide (PO)	25-100 mg PRN OR 50 mg q6h x 1 d, then 25 mg q6h x 2 d	30 min-2 hr	24-48 hr (Demoxepam: 14-95 hr)	Hepatic

Pearls: Lorazepam IV solution should be stored at 2° C and 8° C (36° and 46° F)

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27

Benzodiazepine Dosing Regimens

Symptom-Triggered

- Monitored through the use of an assessment scale (e.g. CIWA-Ar)
- Medication given if symptoms cross a threshold of severity

Fixed Dosing

- Medication given at fixed intervals
- Doses usually taper gradually over several days
- Can provide additional doses for break through symptoms

Front Loading

- Use of long-acting benzodiazepine given frequently at the onset of treatment
- Can be driven by symptom assessment or fixed dosing schedule

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28

Phenobarbital

Mechanism of action: exhibits GABA-like effects similar to benzodiazepines and reversibly depresses activity of all excitable tissue

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Phenobarbital (IV/PO)	IV: 260 mg x 1, then 130 mg PRN PO: 60 mg q6h x 1 d, then 3 d taper	IV: 5-15 min PO: 30 min	79 hr (N/A)	Hepatic

Pearls:

- Narrow therapeutic index → therapeutic drug monitoring suggested
- Can be used in place of OR as adjunct to benzodiazepines with close observation

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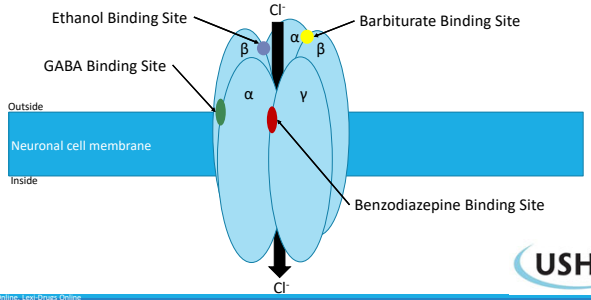
The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management. 29

29

Mechanism of Phenobarbital and Benzodiazepines



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30

Gabapentin

Mechanism of action: mechanism is unknown; it is structurally similar to GABA, but does not bind to GABA receptors.

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Gabapentin (PO)	300 mg TID x 3 d, then 300 mg BID x 1 d	2-4 hr	5-7 hr (N/A)	N/A

Pearls:

- For patients with low risk of severe withdrawal
- Could also be used as adjunct therapy with benzodiazepine
- May provide an effective bridge therapy for long term alcohol use disorder (AUD) treatment
- Dose reduce in renal dysfunction (CrCl <30 mL/min)

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The ASAM Clinical Practice Guideline on Alcohol Withdrawal Management

31

31

Considerations in Special Populations

- Short acting benzodiazepine (e.g. lorazepam) or phenobarbital preferred

- Short acting benzodiazepine (e.g. lorazepam) or dose reduced benzodiazepine preferred

- Benzodiazepine or reduced gabapentin dose preferred

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32

32

Knowledge Check

33

33

A 28 year old female who is 8 weeks pregnant presents to the emergency department for suspected alcohol withdrawal (PAWSS 3). After observation, her CIWA-Ar is 8. Which medication would be the most appropriate treatment for this patient?

A. Lorazepam
B. Gabapentin
C. Lorazepam with phenobarbital
D. Gabapentin with phenobarbital

34

34

Which of the following best describes the mechanism of action of benzodiazepines?

A. Binds to the NMDA receptors
B. Binds to the GABA-benzodiazepine receptors
C. Binds to the opiate receptors
D. Unknown mechanism of action

35

35

Which of the following best describes the storage requirements for lorazepam IV solution?

A. Store between 20° C and 25° C
B. Store between 2° C and 8° C
C. Store between 30° C and 40° C

36

36

Which medication on the following patient's medication list would you expect to be treating alcohol withdrawal?

A. Chlordiazepoxide
B. Amlodipine
C. Oxycodone
D. Lisinopril

Amlodipine 5 mg PO daily
Chlordiazepoxide PO 50 mg q6h x 1 d, then 25 mg q6h x 2 d
Folic acid 1 mg PO daily
Lisinopril 10 mg PO daily
Multivitamin PO daily
Oxycodone 2.5-5 mg PO q6h PRN pain
Thiamine IV 400 mg x 5 days

37

37

Alcohol Use Disorder

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38

38

Alcohol Use Disorder (AUD) - Diagnosis

- Drinking in excess
- Impact on physical safety
- Impact on social interactions

Severity
- Mild = 2-3 criteria
- Moderate = 4-5 criteria
- Severe = ≥6 criteria

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Alcohol Use Disorder. *DynaMed* [database online]. EBSCO Information Services
American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.).

39

39

Why Should We Care about AUD?

- The aggregate cost for all hospital stays with an alcohol-related diagnosis in 2015 was $32.5 billion
- ~ 14.8 million people aged ≥ 12 years had an AUD diagnosis in 2018
- 10,497 people died in alcohol-impaired driving crashes in 2016 (~28% of all traffic-related deaths in the U.S.)

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Alcohol, Tobacco, and Other Drugs. SAMHSA. U.S. Department of Health and Human Services.
Trends in Alcohol-Related Morbidity among Community Hospital Discharges. National Institute on Alcohol Abuse and Alcoholism.
"Impaired Driving: Get the Facts." Centers for Disease Control and Prevention.

40

40

Chronic AUD Management

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41

41

Chronic AUD Management

As described in the American Psychiatric Association (APA) Practice Guideline for the Pharmacologic Treatment of Patients with Alcohol Use Disorder

Mild AUD
- Naltrexone
- Acamprosate

Moderate to Severe AUD
- Naltrexone
- Acamprosate
- Disulfiram
- Gabapentin
- Topiramate

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The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder . American Journal of Psychiatry.

42

42

Naltrexone

Mechanism of action: pure opioid antagonist and modifies the hypothalamic-pituitary-adrenal axis to suppress alcohol consumption

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Naltrexone (PO/IM)	PO: 50 mg daily May titrate up to max 100 mg per day IM: 380 mg q4weeks	PO: 60 min IM: 2 hr	PO: 4 hr (6-beta-naltrexol: 13 hr) IM: 5-10 d	Hepatic

Monitoring: liver function, pregnancy test, depression, and suicidal thoughts

Pearls:
- Could be beneficial in patient with concomitant opioid use disorder
- Avoid in liver disease
- IM formulation requires REMS registration due to injection site reactions

43

Acamprosate

Mechanism of action: structurally similar to GABA, so increases activity of GABA and decreases activity of glutamate

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Acamprosate (PO)	666 mg TID	PO: 3-8 hr	20-33 hr (N/A)	N/A

Monitoring: renal function and suicidal thoughts

Pearls:
- Contraindicated in patients with CrCl ≤30 mL/min

44

Disulfiram

Mechanism of action: blocks the oxidation of alcohol at the acetaldehyde stage

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Disulfiram (PO)	125 mg daily, may titrate every 1-2 weeks (max 500 mg per day)	PO: 2 hr	12 hr (Diethyldithiocarbamate: 15 hr)	Hepatic

Monitoring: liver function and alcohol cessation

Pearls:
- Avoid if patient cannot commit to complete alcohol cessation
- On ASHP Drug Shortage list (updated 10/1/2020)

45

Topiramate

Mechanism of action: blocks voltage-dependent sodium channels, enhances GABA activity, antagonizes glutamate, inhibits carbonic anhydrase

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Topiramate (PO)	25 mg daily, may titrate weekly (max 300 mg per day)	PO: 2 hr	19-23 hr (N/A)	Hepatic (minor)

Monitoring: suicidal thoughts, weight, and sedation

Pearls:
- Could be considered in patients with concomitant obesity
- Can use if patients have contraindication to naltrexone and acamprosate

46

Gabapentin

Mechanism of action: mechanism is unknown; it is structurally similar to GABA, but does not bind to GABA receptors.

Drug (route)	Dose	Onset	Half-life (active metabolite)	Metabolism
Gabapentin (PO)	300 mg daily, may titrate every 2 days (max 1800 mg per day)	2-4 hr	5-7 hr (N/A)	N/A

Monitoring: renal function and suicidal thoughts

Pearls:
- Dose reduce in renal dysfunction (CrCl <30 mL/min)
- Can use if patients have contraindication to naltrexone and acamprosate

47

Efficacy of Gabapentin for the Treatment of Alcohol Use Disorder in Patients with Alcohol Withdrawal Symptoms	
Study design	Double blind, placebo controlled, randomized clinical trial
Objective	Is gabapentin useful in the treatment of alcohol use disorder (per DSM V) especially in patients with the most alcohol withdrawal symptoms?
Population	Patients with AUD per DSM-V and abstinent ≥3 days prior to randomization Patients had a mean of 4.5 criteria for alcohol withdrawal (DSM-V)
Intervention	Gabapentin titration up to 1200 mg/d (N=44)
Comparison	Placebo (N=46)
Outcome	Primary: Percentage of patients with no heavy drinking days Secondary: Percentage of patients with no drinking days
Results	Primary: Gabapentin group had 18.6% more patients with no heavy drinking days Secondary: Gabapentin group had 13.8% more patients who were abstinent

48

Considerations in Special Populations

- Avoid pharmacologic treatment

- Avoid naltrexone

- Avoid acamprosate
- Dose reduce gabapentin

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The American Psychiatric Association Practice Guideline for the Pharmacological Treatment of Patients With Alcohol Use Disorder . American Journal of Psychiatry

49

Knowledge Check

50

A 55 year old male with a history of decompensated alcoholic cirrhosis presents to his primary care provider seeking treatment for AUD. The primary care provider comes to you for a recommendation. Which of the following medications should be avoided in this patient?

A. Acamprosate
B. Disulfiram
C. Gabapentin
D. Naltrexone

51

Which of the following best describes the mechanism of action for naltrexone?

A. Increases activity of GABA and decreases activity of glutamate
B. Pure opioid antagonist and modifies the hypothalamic-pituitary-adrenal axis
C. Pure NMDA antagonist and modifies the hypothalamic-pituitary-adrenal axis
D. Blocks the oxidation of alcohol

52

Summary

- Alcohol withdrawal has several complications and is important to treat
- PAWSS and CIWA-Ar are two assessment scales that can be used to assess the severity of alcohol withdrawal
- There is variation in the treatment of alcohol withdrawal and is often institution specific
- There are several agents that can be used to treat AUD in the outpatient setting and the choice of agent will depend on patient specific factors

53

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54

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Bryn Lindley, PharmD
PGY2 Internal Medicine Pharmacy Resident
University of Utah Health

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55

55