Acute Withdrawal in the Hospitalized Patient

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Disclosures

No relevant commercial relationships to disclose

Learning Objectives

- At the conclusion of this session, participants should be able to:
- List the agents that can cause life-threatening acute withdrawal syndrome
- Anticipate and recognize the signs of acute withdrawal from GABA-agonists
- Discuss the pathophysiology of acute withdrawal and benzo-resistant withdrawal
- Describe the treatment of acute withdrawal syndrome and list the drugs that should be avoided

What drugs can your patient withdrawal from if abruptly or inadvertently stopped?

- Best Practice is making sure we know what drugs can produce a characteristic and expected withdrawal syndrome

Agents or Class of Agents that can result in withdrawal:

Agents that can result in Withdrawal

- GABA-A agonists
  - Ethanol, Benzos, Barbs, carisoprodol
- GABA-B agonists
  - Baclofen, GHB, phenibut
- Gabapentin/Pregabalin
- α_2-agonists
- Opioids
- Nicotine
- Caffeine
- SSRIs/SNRIs*
- Cannabis*

Agents that can result in Life-Threatening Withdrawal

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Case #1

- 48 year old man presents with complaints of nausea, vomiting, and abdominal pain
- Exam reveals an ill-appearing, thin male who appears older than his chronological age
- Initial work-up is significant for an elevated lipase

Case #1

- Admitted for pancreatitis
- Overnight you are called because the patient has become diaphoretic, febrile (T 100.6^{o} F), and tachycardic
- You order acetaminophen for the fever and pan culture the patient and tell the RN you will stop by as soon as you can
- When you arrive to the bedside you find the patient is agitated, tremulous, and diaphoretic
- Vitals: HR 138 RR 22 BP 162/94 T 100.9^{o}
- What do you think is going on?

Additional History

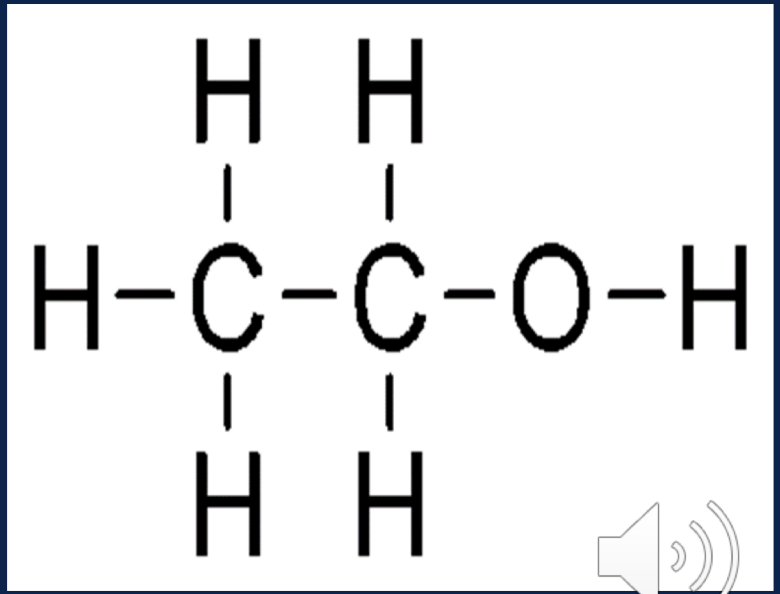
- You discover that the patient drinks 4-6 40 oz. a day
- His last drink was >36 hours ago due to vomiting and abdominal pain

Ethanol Related Illness

- Most abused drug in the world
- In the U.S. 17 million with alcohol use disorder
- 200,000 deaths each year are attributed to alcoholism
- $185 billion in estimated U.S. healthcare costs annually
- Estimated 3-fold increased risk of mortality in trauma and post-surgical patients with AWS

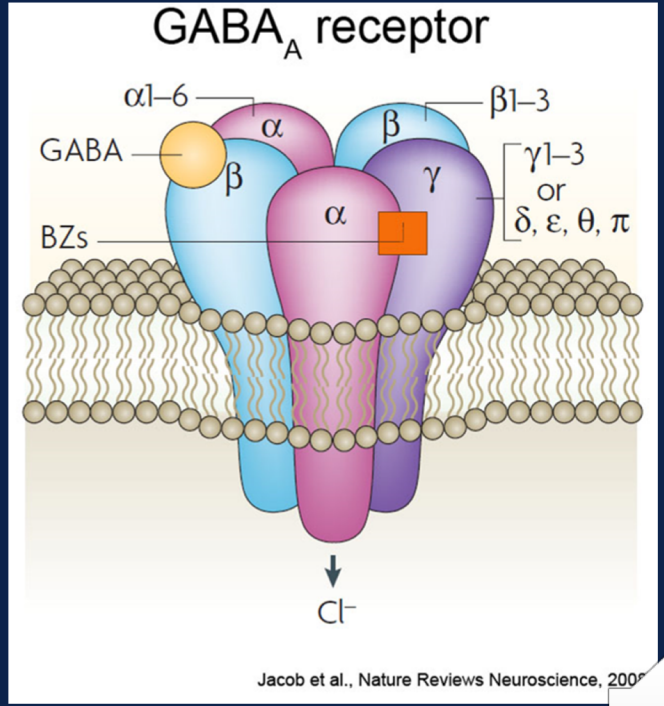
Ethanol

- Agonist at the γ-aminobutyric acid receptor (GABA)
- Antagonist at the N-methyl-D-aspartate (NMDA) receptor
  - A subtype of the main excitatory neurotransmitter glutamate

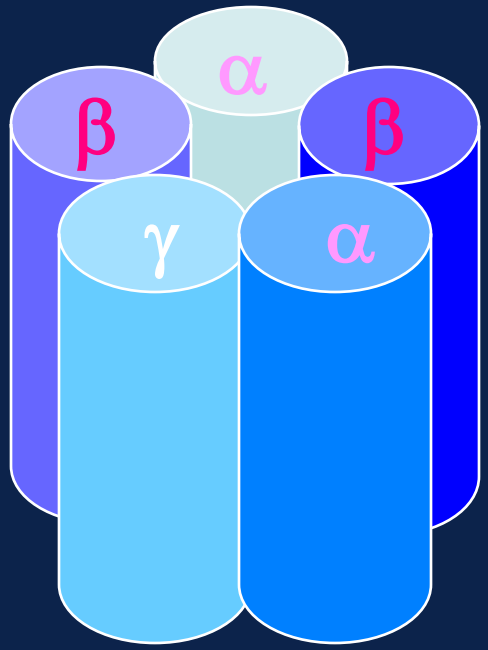


GABA A Neurotransmission

- Inhibitory neurotransmitter
- Receptor is a ligand gated ion channel
- It is a pentameric receptor when activated results in hyperpolarization of the postsynaptic neuron from inward Cl^- influx



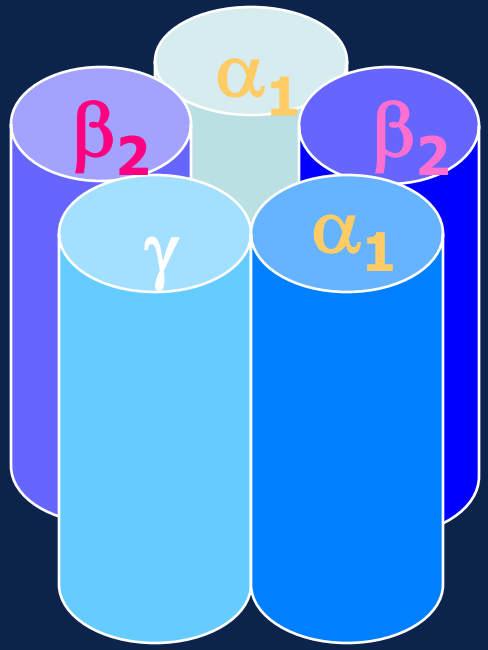
$GABA_A$ Receptor



Each receptor composed of 5 subunits
19 identified

$\alpha_{1\text{-}6}$ **forms**
$\beta_{1\text{-}3}$ **forms**
$\gamma_{1\text{-}3}$ **forms**
δ, ε, π, θ, $\rho_{1\text{-}3}$

$GABA_A$ Receptor



Most CNS receptors contain 2 α and 2 β subunits, with a γ or δ

Usually $\alpha_1\beta_2\gamma_2$

Ethanol Withdrawal

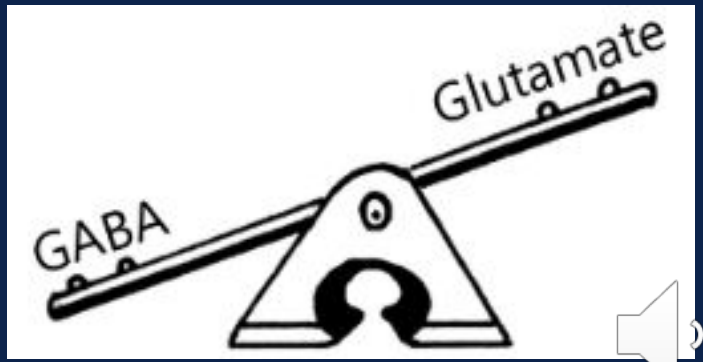
- Persistent stimulation of the inhibitory GABA receptor leads to downregulation of the GABA receptor-chloride channel complex
  - The exact adaptive change is complex and involves subunit substitution
- Simultaneous up-regulation of the excitatory NMDA receptors is also occurring
- Increased excitation and loss of inhibition results in autonomic excitability and psychomotor agitation

Ethanol Withdrawal

- Onset likely varies with degree of tolerance
- Can begin a few to 48 hours after cessation of drinking
- Patients may still have a measurable blood alcohol concentration

Early Uncomplicated Withdrawal

- Tremor
- Tachycardia
- Hypertension
- Psychomotor agitation
- Diaphoresis
- Insomnia
- Anxiety



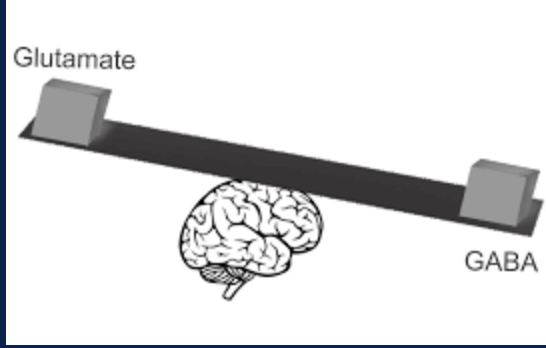
Alcohol Withdrawal Seizures

- Typically a short brief generalized seizure with a short post-ictal period occurring in 10% of patients with AWS
- Status epilepticus occurs in < 3%
- May be the first manifestation of AWS
- May occur in absence of other signs or symptoms of AWS

Alcoholic Hallucinosis

- 25% of patients will develop hallucinations typically visual or tactile (formication)
- A subset of these patients develop persistent hallucinations
- Differs from delirium tremens (DTs) in that patients have a clear sensorium
- Does not predict development of DTs

Delirium Tremens



- Most serious manifestation of AWS
- Generally begins 2-4 days after cessation and can last up to 2 weeks
- Symptoms may be similar to early uncomplicated WD only more severe and with altered sensorium

Delirium Tremens

- Tremors
- Autonomic instability
  - -Hypertension
  - -Tachycardia
  - -Diaphoresis
  - -Hyperthermia
- Psychomotor agitation
- Disturbance of consciousness or change in cognitio

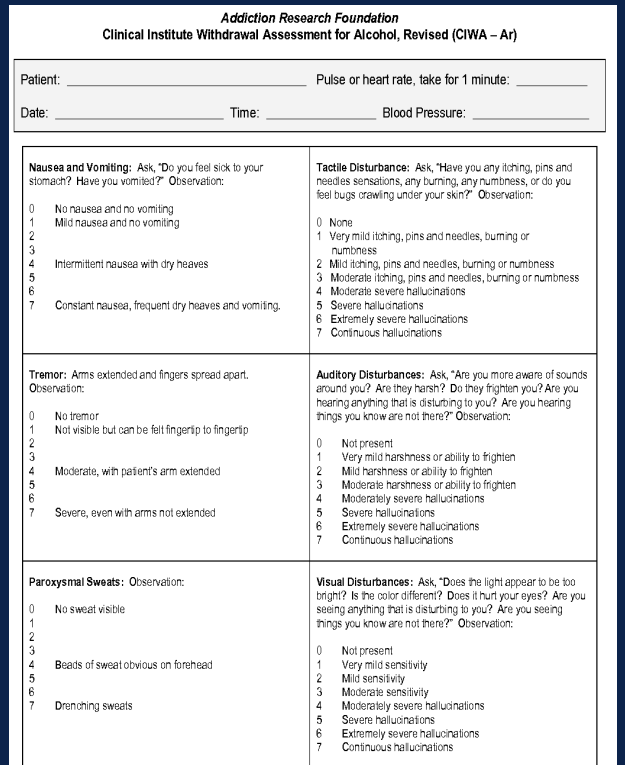
Diagnosis of AWS

- Prior history of AWS is the strongest predictor for development
- Numerous attempts to develop biochemical predictors for the presence or severity have been made without success

  -ALT, GGT, homocysteine, Mg, ETOH level
- The CIWA-Ar scale has been used as a clinical tool in assessing AWS

Clinical Institute Withdrawal Assessment of Alcohol Scale, revised

- Scoring system based on 10 clinical categories and requires < 5min. to complete
- Often completed by RN for hospital based protocols



Addiction Research Foundation
Clinical Institute Withdrawal Assessment for Alcohol, Revised (CIWA – Ar)

Patient: _____ Pulse or heart rate, take for 1 minute: _____

Date: _____ Time: _____ Blood Pressure: _____

Nausea and Vomiting: Ask, "Do you feel sick to your stomach? Have you vomited?" Observation:

0 No nausea and no vomiting
1 Mild nausea and no vomiting
2
3
4 Intermittent nausea with dry heaves
5
6
7 Constant nausea, frequent dry heaves and vomiting.

Tactile Disturbance: Ask, "Have you any itching, pins and needles sensations, any burning, any numbness, or do you feel bugs crawling under your skin?" Observation:

0 None
1 Very mild itching, pins and needles, burning or numbness
2 Mild itching, pins and needles, burning or numbness
3 Moderate itching, pins and needles, burning or numbness
4 Moderate severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Tremor: Arms extended and fingers spread apart. Observation:

0 No tremor
1 Not visible but can be felt fingertip to fingertip
2
3
4 Moderate, with patient's arm extended
5
6
7 Severe, even with arms not extended

Auditory Disturbances: Ask, "Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?" Observation:

0 Not present
1 Very mild harshness or ability to frighten
2 Mild harshness or ability to frighten
3 Moderate harshness or ability to frighten
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Paroxysmal Sweats: Observation:

0 No sweat visible
1
2
3
4 Beads of sweat obvious on forehead
5
6
7 Drenching sweats

Visual Disturbances: Ask, "Does the light appear to be too bright? Is the color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?" Observation:

0 Not present
1 Very mild sensitivity
2 Mild sensitivity
3 Moderate sensitivity
4 Moderately severe hallucinations
5 Severe hallucinations
6 Extremely severe hallucinations
7 Continuous hallucinations

Which of the following is the best initial approach to managing acute withdrawal?

- A. Begin fixed-dose/scheduled chlordiazepoxide
- B. Use symptom-triggered titration of single benzodiazepine
- C. Give a “banana bag” and order beer with meals
- D. Expedite discharge before signs worsen +/- benzo taper

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Treatment

- Starts with bedside evaluation by the physician
- Fever and altered mental status always warrant an infectious work-up
- Supportive care with supplementation to correct vitamin and nutritional deficiencies

  -MVI, folate, thiamine, glucose
- IV fluids for adequate volume resuscitation

Treatment

- Benzodiazepines are first-line therapy for AWS
  - -Oral dosing may be used in early or mild AWS
  - -IV allows for rapid control and accurate titration
- Diazepam has the most rapid time to peak effect and an active metabolite
- Goal is to achieve sedation with airway protection, spontaneous breathing, and normal vital signs

Fixed Scheduled Dosing vs Symptom Triggered Titration

Benzodiazepine loading versus symptom-triggered treatment of alcohol withdrawal: a prospective, randomized clinical trial☆

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Symptom-Triggered vs Fixed-Schedule Doses of Benzodiazepine for Alcohol Withdrawal

A Randomized Treatment Trial

Jean-Bernard Daeppen, MD; Pascal Gache, MD; Ulrika Landry, BA; Eva Sekera, MD; Verena Schweizer, MD; Stéphane Gloor, PhD; Bertrand Yersin, MD

Research for Practice

Symptom-Triggered vs. Fixed-Dosi Management of Alcohol Withdraw Syndron

Reagan T. Sk

Alcohol abuse and dependence are a significant public health problem, with alcohol being the most commonly abused substance in the United States and worldwide (National Council on Alcoholism and Drug Dependence, Inc. [NCADD], 2014). Alcohol abuse has many associated

A literature review was conducted with the o ctive of creating dence-based recommendations for use tom-triggered t apy (STT) or fixed-schedule dosing in t alcohol withdra syndrome in inpatients. Use of STT reduced ration of therap well as the number of patients requiring treatment or medicat potentially reducing costs and risk of adverse medication reacti

Oral Dosing Equivalents

Agent	Equivalence to Diazepam 5 mg
Diazepam	5 mg
Alprazolam	0.5 mg
Lorazepam	1 mg
Clonazepam	0.25 mg
Chlordiazepoxide	10 mg
Oxazepam	15 mg
Midazolam (IV)	2 mg

The key is to pick one and stick with it

CASE #2

- A 40 yo man with alcohol dependence is admitted for sedation following polypharmacy ingestion
- He awakens and feels anxious, HR=110
- You give valium 10 mg IV but symptoms worsen HR=120
- You give another 20 mg valium IV, he becomes more agitated with HTN and HR = 130
- You give 40 mg valium IV, then 80 mg valium IV without effect

CASE #2

- He receives 150 mg IV valium in 2 hours and his withdrawal is uncontrolled
- You know that benzos should work and prefer valium due to its active metabolite
- Over the next several hours you administer another 200 mg IV valium
- Now diaphoretic, tachycardic, tachypneic, hypertensive and agitated

What is going on?

- IV has infiltrated and he is not getting IV benzos but subQ depot
- Nurse is anxious and is self-medicating because he needs it more than the patient
- Due to budgetary constraints Banner has made an automatic substitution to saline

Benzo-Resistant Alcohol Withdrawal

- Literature defines as uncontrolled withdrawal despite > 40 mg of diazepam in 1 hour*
- Associated with higher incidence of
  - Mechanical Ventilation
  - Nosocomial Pneumonia
- Longer ICU stays

Benzo-Resistant Alcohol Withdrawal

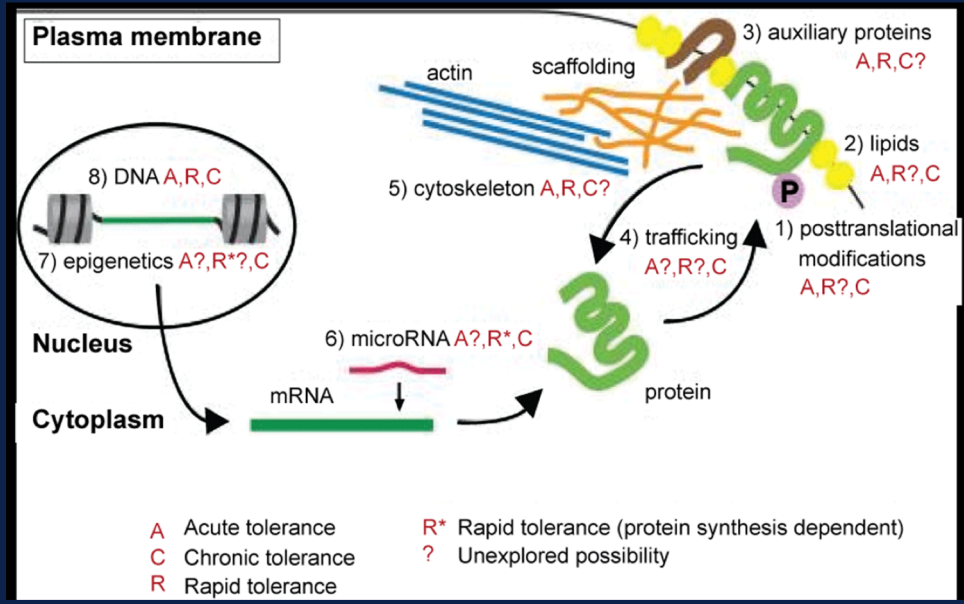
- One study of 184 patients with RAW
- 16 unique medications used; 74 unique combinations
  - Greatest # of meds used in a single patient = 7
- 96% admitted to ICU; 82% mech. ventilation
- Median LOS 9 (ICU) & 12.7 days (hospital); 7% died
- Propofol, antipsychotics and dexmedetomidine

Benzo-Resistant Withdrawal

- Why does it happen?
- How does it happen?
- What am I supposed to do about it?

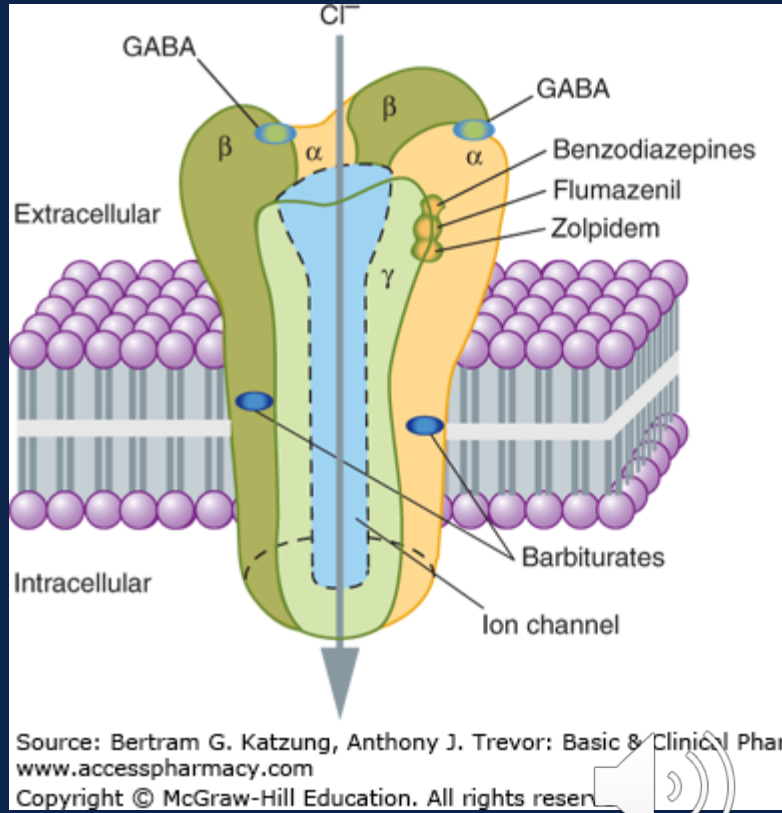
Mechanisms of AWS

- Altered $GABA_A$ receptor gene expression
- Second messenger effects
- Subcellular localization
- Changes in sensitivity and affinity for agonists
- Changes in intracellular signaling
- Neurosteroidal modulation of GABA receptor



$GABA_A$ Receptor

- Not all $GABA_A$ receptors are the same
  -Heterogeneous, non-uniformity
- Plasticity- change in response to stimuli
- All agonists do not bind to all receptors
- Affinity of agonists for receptor varies depending on specific $GABA_A$ receptor subtype
- Receptor subtype is determined by its 5 subunit components



Source: Bertram G. Katzung, Anthony J. Trevor: Basic & Clinical Phar
www.accesspharmacy.com

ETOH Tolerance & Dependence

- Alters expression of $GABA_AR$ subunits $\Rightarrow$ *changes* the subtype of $GABA_AR$ which changes affinity for agonists
- Very complex and not fully understood
- Receptor subunit changes appear to occur in response to all $GABA_A$ modulators
  - Specific changes in response to acute or chronic stimulation may differ in different regions of brain

Chronic Ethanol

- Alpha subunit
  - decreased α_1
  - increased α_4
  - increased α_6

γ_2: altered expression
$\beta_2\beta_3$: increased in cortex
δ: tolerance?

Receptor Changes with Ethanol Withdrawal

- Instead of reversal of these changes with withdrawal of stimulus, further changes occur:
  - Most notably $\Uparrow\Uparrow \alpha_4$ subunit

“Kindling” Phenomenon

- Subsequent episodes of WD become increasingly more severe and are more resistant to treatment with benzodiazepines
- May be secondary to permanent dysregulation in GABA receptors

I know what your thinking…
This is fascinating (tell me more)!

- Why do I care?
- What do I do about it?

Benzos Don't Bind!

- Benzos bind α 1, 2, 3, 5 - containing receptors
- Require gamma subunit
  - Bind at the $\alpha\gamma_2$ interface
- About 75% of $GABA_A$Rs have benzo binding site
- Do not bind α 4 or 6 containing receptors at all
  - Less alpha 1: fewer receptors responsive to benzos
  - More alpha 4 and 6: more receptors resistant to benzos

What about barbiturates?

- Act at different site on $GABA_AR$ than benzos
  - Many effects mediated through beta subunit binding
  - Affinity and pharmacologic effect independent of specific alpha subunit
- Some barbs also directly open the chloride channel
  - Don’t need GABA present

How About Propofol?

- Low concentrations potentiate GABA at the $GABA_AR$
- High concentrations directly activate $GABA_AR$
- Effects mediated through binding to β_2 subunits
  - β_2 increases with ETOH
  - binding unaffected by α changes
- Also inhibits the NMDA receptor
- Limitation: short duration of action; resp depression, negative ionotropic effects

Dexmedetomidine

- Alpha-2 agonist
- Case reports, case series, retrospective reviews
- Most authors state benzo sparing effect
- Data not compelling
- Anecdotally our service has not found it useful
- Better studies needed

Ketamine

- PCP analog with 10% the potency
- Dissociative anesthetic with NMDA antagonism
- Catecholamine reuptake inhibition results in sympathomimetic effects
- 2 retrospective reviews addressing use of ketamine in benzo-resistant withdrawal

Evaluation of Adjunctive Ketamine to Benzodiazepines for Management of Alcohol Withdrawal Syndrome

Annals of Pharmacotherapy
2015, Vol. 49(1) 14–19

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aop.sagepub.com
SAGE

Adrian Wong, PharmD[1], Neal J. Benedict, PharmD[1,2], Michael J. Armahizer, PharmD[1], and Sandra L. Kane-Gill, PharmD[1,2]

Abstract

Background: Adjunctive medications to manage alcohol withdrawal syndrome (AWS) in patients not adequately responding to escalating doses of benzodiazepines (BZDs) are limited. The use of the *N*-methyl-D-aspartate antagonist ketamine, may serve as an effective adjunct agent; however, no published data currently exist for this practice. **Objective:** To determine the safety and efficacy of adjunct ketamine for management of AWS. **Methods:** The study was a retrospective review of adult patients from April 2011 to March 2014 who were administered ketamine specifically for management of AWS. Outcomes included changes in BZD requirements and ketamine-related adverse reactions. **Results:** Of 235 patients screened, 23 patients met study eligibility. Ketamine was initiated primarily with toxicology consultation for significant BZD requirements or delirium tremens. The mean time to initiation of ketamine from first treatment of AWS, and total duration of therapy were 33.6 and 55.8 hours, respectively. Mean initial infusion dose and median total infusion rate during therapy were 0.21 and 0.20 mg/kg/h, respectively. There was no change in sedation or alcohol withdrawal scores in patients within 6 hours of ketamine initiation. The median change in BZD requirements at 12 and 24 hours post–ketamine initiation were −40.0 and −13.3 mg, respectively. The mean time to AWS resolution was 5.6 days. There was one documented adverse reaction of oversedation, requiring dose reduction. **Conclusions:** Ketamine appears to reduce BZD requirements and is well tolerated at low doses. Prospective dose range evaluations in the management of AWS would be helpful in determining its place as an adjunctive agent.

Other Agents

- Anti-psychotics
  - Lower seizure threshold, alter thermal regulation
- Ethanol
  - One RCT showed no advantage over diazepam
  - Ethical concerns, side-effect profile
- Adrenergic antagonists
  - Do not address underlying pathophysiology
  - Masks clinical effects making titration of benzos difficult

Which of the following represents the best approach to managing benzo-resistant alcohol withdrawal?

- A. Move to ICU and aggressively titrate haloperidol
- B. Give beta blockers and consider dexmedetomidine infusion
- C. Recognize inadequate response to benzos and titrate Phenobarbital
- D. Transfer to progressive care unit and start ketamine infusion

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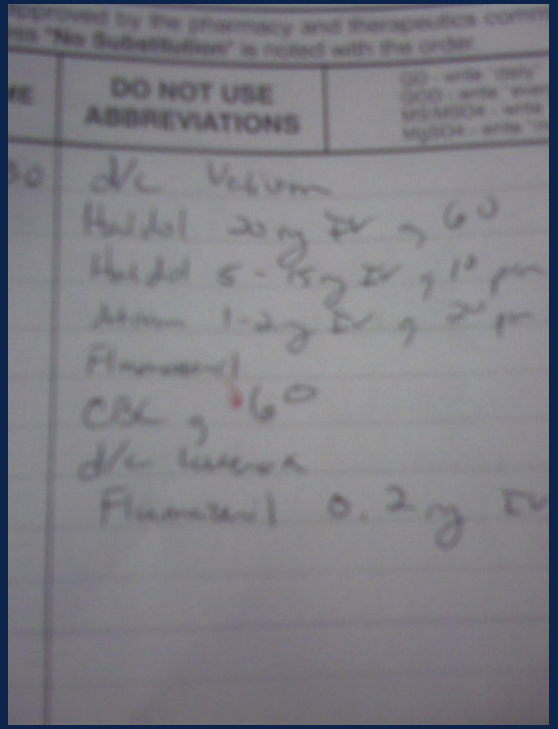
How NOT to treat ethanol withdrawal!

- d/c valium
- Haldol 20 mg IV q 6
- Haldol 5-15 mg IV q1 prn
- Ativan 1-2 mg IV q 2 prn
- Flumazenil
- CBC q 6
- d/c lovenox
- Flumazenil 0.2 mg IV



Mortality from Withdrawal

- Mortality expected to approach zero unless insufficient treatment
- Still occurs when syndrome is mistaken for alternative diagnosis
  - Infectious process, encephalopathy
- Or when the underlying condition that forced abstinence is not identified and treated
  - Pancreatitis, pneumonia, trauma, PUD etc.

Take Home Points

- Prior history of AWS is the best predictor of AWS
- Early recognition and symptom-triggered titration of Benzos is first line therapy
- Recognize benzo-resistant withdrawal and move to phenobarbital
- In the absence of hyperadrenergic signs and agitation, fever should not be attributed to AWS
- Patients should be informed that subsequent and worsening episodes of AWS can be expected

Please email questions to

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