Alcohol Withdrawal Syndrome

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Background

Estimated 8-18 million Americans are Alcohol dependent

Alcohol Use Disorder (AUD) reported in 20-42% of hospitalized medical patients

Only 7% are identified by a physician

Higher in specialized populations:
- 40% presenting to Emergency Department
- 42% of hospitalized veterans
- 59-67% of trauma patients
- 44% of elderly inpatients admitted to acute geriatric units
- 60% of ICU patients

Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med 2003; 348:1786

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Background

500,000 episodes per year of Alcohol withdrawal requiring pharmacologic treatment

Associated mortality is 5%

Manwell LB, Fleming MF, Johnson K, Barry KL. Tobacco, alcohol, and drug use in a primary care sample: 90-day prevalence and associated factors. *J Addict Dis.* 1998;17:67-81.

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Pathophysiology

Two major types of neurotransmitter-receptor systems in CNS

>80% neurons use one or both

Gamma-aminobutyric acid (GABA) –inhibitory neurotransmitter
- Ethanol binds to GABA receptor complex
- Chronic use leads to GABA down-regulation

Glutamate- excitatory neurotransmitter
- Binds to N-methyl-D aspartate (NMDA) receptor
- Ethanol inhibits glutamate induced excitation
- Chronic use leads to increased sensitivity to glutamate to maintain arousal

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Pathophysiology

Increased GABA inhibition, decreased NMDA activity

Alterations in glutamate and GABA balance during AWS

Decreased synthesis of GABA and increased synthesis of glutamate in patients presenting with AWS

Stehman, C. R., & Mycyk, M. B. (2013). A rational approach to the treatment of alcohol withdrawal in the ED. *The American journal of emergency medicine*, *31*(4), 734-742.

Brousse, G., Arnaud, B., Vorspan, F., Richard, D., Dissard, A., Dubois, M., ... & Schmidt, J. (2012). Alteration of Glutamate/GABA Balance during Acute Alcohol Withdrawal in Emergency Department: A Prospective Analysis. *Alcohol and alcoholism*, *47*(5), 501-508

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Pathophysiology

Neurologic consequences:
- Neuronal damage 24hr after onset of AWS
- Breakdown of synapses
- Decreased selectivity of blood-brain barrier permeability to proteins
- Impaired cerebral auto-regulation
- Alcohol related brain damage
- Increases risk of cerebro-vascular disease

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Diagnosis

DSM-IV Criteria for Alcohol Withdrawal	
A.	Cessation of (or reduction in) alcohol use that has been heavy and prolonged.
B.	Two (or more) of the following, developing within several hours to a few days after criterion A:
1.	Autonomic hyperactivity
2.	Increased hand tremor
3.	Insomnia
4.	Nausea or vomiting
5.	Transient visual, tactile, or auditory hallucinations or illusions
6.	Psychomotor agitation
7.	Anxiety
8.	Grand mal seizures
C.	The symptoms in criterion B cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D.	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder.

ef #14: Adopted from: American Psychiatric Association: *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington, DC, American Psychiatric Publishing Inc; 2000.

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Diagnosis

Clinical Diagnosis

Thorough H&P

- Recent drinking, frequency, amount, time of last drink
- Past history of withdrawal, seizures, hallucinations, or Delirium Tremens (DTs)
- Prescribed medications and drug use
  - identify medications that are associated with withdrawal syndromes

History provided by patient and family may be of limited value depending on social dynamics

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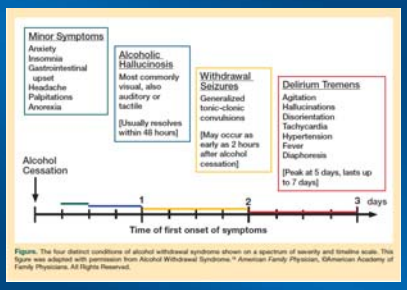
Alcohol Withdrawal Spectrum



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Delirium Tremens

Global clouding of sensorium, hallucinations, disorientation, diaphoresis, agitation, autonomic symptoms (hypertension/tachycardia/fever), hyperventilation resulting in respiratory alkalosis-subsequent reduction in cerebral blood flow

- 5-10% of patients with AWS develop DT's
- Onset: 48-96hrs
- Time course: 1-5 days
- Historical mortality of 37%, presently estimated to be 5%

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Delirium Tremens

Risk factors for development of DT's

- History of sustained drinking, previous DT's
- Age > 30
- Concurrent illness
- Presence of significant AWS in the presence of an elevated ETOH level

Risk factors for higher morbidity/mortality with DT's include:

- Elderly
- Lung disease
- Hyperthermia
- Significant hepatic dysfunction

CIWA-Ar

Clinical Institute Withdrawal Assessment for Alcohol scale- revised

Ten symptoms assessed, maximum score 67

Studied primarily in specialized alcohol treatment programs and medical detoxification facilities

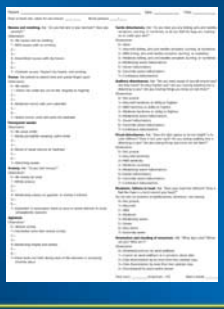
Has not been validated in the ED

Gray, S., Borgundvaag, B., Sirvastava, A., Randall, L., & Kahan, M. (2010). Feasibility and reliability of the SHOT: A short scale for measuring pretreatment severity of alcohol withdrawal in the emergency department. *Academic Emergency Medicine*, *17*(10), 1048-1054.

CIWA-Ar

1. Nausea/Vomiting
2. Tactile Disturbances
3. Tremor
4. Auditory Disturbances
5. Paroxysmal Sweats
6. Visual Disturbances
7. Anxiety
8. Headache
9. Agitation
10. Orientation

CIWA-Ar



CIWA-Ar

Pros:

- CIWA-Ar assesses whether AWS is present and quantifies severity
- CIWA-Ar is not intended to be a screening tool to determine who is most at risk
- Instead, detects withdrawal symptoms in those at known elevated risk and quantifies severity

Williams, K., & Mitchell, M. (2014). Inpatient Alcohol Withdrawal: Time to Prevent the Preventable?. *Journal of general internal medicine*, *29*(1), 7-9.

CIWA-Ar

Cons:

- Liberal use of CIWA-Ar protocols without ensuring proper diagnosis
- Leads to overuse of sedatives and complicates diagnosis and treatment of delirium from other causes
- Validated in only mild-moderate withdrawal
- Studies frequently exclude seizures (severe AWS, DT's)
- Does not predict which patients are at risk of withdrawal
- Once positive, patient already has AWS, opportunity for prophylaxis is lost

Management

Supporative Care

Appropriate fluid resuscitation

- Increased metabolic requirements and fluid losses due to hyperthermia, hyperventilation, diaphoresis, agitation

Glucose supplementation

- Increased metabolic requirements
- Lack of glycogen stores, nutritional deficiency
- Alcoholic ketoacidosis

Thiamine supplementation to prevent thiamine deficiency syndromes

- Wernicke's Encephalopathy Triad: encephalopathy, oculomotor dysfunction, gait ataxia
- Korsakoff's Syndrome: selective anterograde and retrograde amnesia

Magnesium, phosphorus, calcium replacement, folate

Stehman, C. R., & Mycyk, M. B. (2013). A rational approach to the treatment of alcohol withdrawal in the ED. *The American journal of emergency medicine*, *31*(4), 734-742.

Benzodiazepines

Current standard treatment for AWS

Most data available on older drugs

- Chlordiazepoxide
- Diazepam
- Lorazepam

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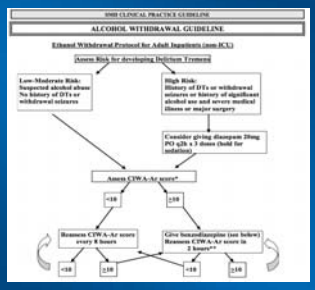
Benzodiazepines

Pros:

- Studies indicate using symptom triggered therapy for AWS versus fixed schedule result in shorter duration of therapy and decreased medication use
- Frequent monitoring using CIWA-Ar to determine dosing needs

Cons:

- Associated with unwanted side effects
- Addictive properties
- Relies on accurate assessment with CIWA-Ar



ALCOHOL WITHDRAWAL GUIDELINE

Ethanol Withdrawal Protocol for Adult Inpatients (non-ICU)

Assess Risk for developing Delirium Tremens

Low-Moderate Risk: Suspected alcohol abuse; No history of DTs or withdrawal seizures

High Risk: History of DTs or withdrawal seizures or history of significant alcohol use and severe medical illness or major surgery

Consider giving diazepam 20mg PO q2h x 3 doses (hold for sedation)

Assess CIWA-Ar score*

<10

≥10

Reassess CIWA-Ar score every 8 hours

Give benzodiazepine (see below) Reassess CIWA-Ar score in 2 hours**

<10

≥10

<10

≥10

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***Note that CIWA scores can be elevated for many reasons—it is NOT a diagnostic tool for alcohol withdrawal. This protocol should only be used for patients with known alcohol withdrawal. Administration of benzodiazepines to patients with elevated CIWA scores and/or delirium NOT caused by alcohol withdrawal may cause harm.**

****If CIWA-Ar score ≥ 10 for three consecutive assessments, page house officer for consideration of increase in dose (e.g., consider doubling dose if not responding to starting dose).**

Benzodiazepine Choice

Preferred agent: Diazepam (Valium) 20 mg PO.

If cirrhosis or liver synthetic dysfunction exists (PT > 14 without anticoagulation): consider starting with diazepam (Valium) 10 mg PO or using lorazepam (Ativan) 4 mg PO.

If older than 60 years: consider starting with 10 mg of diazepam (Valium) PO or using 2 mg lorazepam (Ativan) PO.

If unable to take PO: use diazepam (Valium) 10 mg IV at no faster than 5 mg/ minute through IV in a large vein (not hand or wrist) or lorazepam (Ativan) 4 mg IV if IV access is marginal.

If unable to take PO and no IV access: use lorazepam (Ativan) 4 mg IM

Delirium Tremens: Syndrome of delirium, tachycardia, hypertension, fever, agitation, and diaphoresis, usually 48-96 h after last drink. Treat with **Diazepam 10 mg IV q 15 minutes** until calm and **transfer to ICU**.

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Inappropriate use of symptom-triggered therapy in Hospitals

Fewer than half of randomly selected patients placed on CIWA-Ar met both inclusion criteria for CIWA-Ar tool (intact verbal communication and recent alcohol use)

Postoperative patients had higher percentage of inappropriate administration of benzodiazepines

Hecksel, K. A., Bostwick, J. M., Jaeger, T. M., & Cha, S. S. (2008, March). Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. In *Mayo Clinic Proceedings* (Vol. 83, No. 3, pp. 274-279). Elsevier.

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Adjunctive Therapies

Two types:

Manage autonomic dysfunction

- Beta-blockers, alpha agonists

Agitation control for symptoms refractory to benzodiazepines

- Barbiturates, neuroleptics, other GABA agonists

Used more frequently in severe cases

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Adjunctive Therapy:

Beta-Blockers
- Atenolol, Metoprolol, Labetalol

Alpha-Agonists
- Clonidine
- Dexmedetomidine (Precedex)

Anti-convulsants

Gabapentin
Dilantin
Carbamezapine

Barbiturates

Phenobarbital

Neuroleptics
- Haldol
- Olanzapine, Risperidone, other atypical antipsychotics

Baclofen

Ethyl Alcohol infusions

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Propofol

GABA-receptor agonist

NMDA receptor antagonist

Requires mechanical ventilation

Continuous infusion and IV boluses

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Phenobarbital

GABA-a receptor agonist (different mechanism than Benzo's)

Works synergistically with Benzodiazepines

Studies in ED settings for acute management in combination with benzodiazepines

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Phenobarbital

Prospective RCT compared phenobarbital versus lorazepam in ED and at 48 hrs

Used CIWA-Ar for screening, N=44

Similar effectiveness in treatment of mild-moderate alcohol withdrawal in the ED and at 48hrs

Hendey, G. W., Dery, R. A., Barnes, R. L., Snowden, B., & Mentler, P. (2011). A prospective, randomized, trial of phenobarbital versus benzodiazepines for acute alcohol withdrawal. *The American journal of emergency medicine*, *29*(4), 382-385.

Phenobarbital

Single dose IV phenobarbital combined with standard Lorazepam based AWS protocol

Prospective, double blind RCT (102 patients)

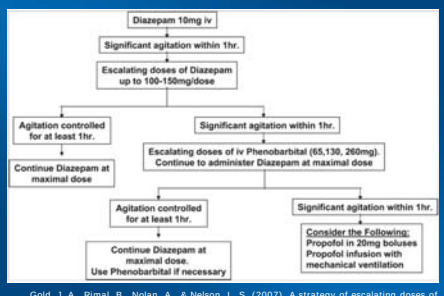
51 received phenobarbital, 51 placebo

Phenobarbital group had fewer ICU admissions (8% v 25%, 95% CI 4-32)

No differences in adverse events

Rosenson, J., Clements, C., Simon, B., Vieaux, J., Graffman, S., Vahidnia, F., ... & Alter, H. (2013). Phenobarbital for acute alcohol withdrawal: A prospective randomized double-blind placebo-controlled study. *The Journal of emergency medicine*, *44*(3), 592-598.

Phenobarbital in the ICU



Gold, J. A., Rimal, B., Nolan, A., & Nelson, L. S. (2007). A strategy of escalating doses of benzodiazepines and phenobarbital administration reduces the need for mechanical ventilation in delirium tremens. *Critical care medicine*, *35*(3), 724.

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Gabapentin

Inpatients with severe AWS (CIWA-Ar > 15)

Oral loading protocol 800mg initial dose, then

600mg QID (total of 3200mg in 24hr load)

600mg QID day 2

400mg TID day 3

400mg day 4

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Bonnet, U., Hamzavi-Abedi, R., Specka, M., Wilftang, J., Lieb, B., & Scherbaum, N. (2010). An open trial of gabapentin in acute alcohol withdrawal using an oral loading protocol. *Alcohol and alcoholism*, *45*(2), 143-145.

Gabapentin

A Double-Blind Trial of Gabapentin Versus Lorazepam in the Treatment of Alcohol Withdrawal

Hugh Myrick, Robert Malcolm, Patrick K. Randall, Elizabeth Boyle, Raymond F. Anton, Howard C. Becker, and Carrie L. Randall

Outpatient study, Gabapentin group had less craving, anxiety, sedation compared to lorazepam

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Dexmedetomidine (Precedex)

Adjunct treatment for AWS

Multiple studies for management of ICU delirium

Retrospective analysis of precedex in addition to benzodiazepenes

61% reduction in benzodiazepine use with Precedex (n=17, p<0.001)

21% reduction in alcohol withdrawal severity score (n=11, p=.015)

Rayner, S. G., Weinert, C. R., Peng, H., Jepsen, S., & Broccard, A. F. (2012). Dexmedetomidine as adjunct treatment for severe alcohol withdrawal in the ICU. *Annals of intensive care*, *2*(1), 1-6.

Baclofen

Mechanism: GABA-B agonist

Prospective double blind RCT using CIWA-Ar

Oral Baclofen 10mg TID and lorazepam PRN versus lorazepam PRN

Need for high dose lorazepam (>20mg over 72hrs) significantly reduced in Baclofen group (6% versus 53%, P=0.004)

Lyon, J. E., Khan, R. A., Gessert, C. E., Larson, P. M., & Repier, C. M. (2011). Treating alcohol withdrawal with oral baclofen: A randomized, double-blind, placebo-controlled trial. *Journal of Hospital Medicine*, *6*(8), 469-474.

Baclofen

Mechanism: GABA-B agonist

Alcohol dependence RCT

Groups: Placebo, 20mg TID, 10mg TID

10mg versus Placebo: 53% reduction in number of drinks per day (P<.0001)

20mg versus Placebo: 68% reduction in number of drinks per day (P<.0001)

Significant dose-effect relationship (P<.0214)

Addolorato, G., Leggio, L., Ferrulli, A., Cardone, S., Bedogni, G., Caputo, F., ... & Nicotra, N. (2011). Dose–response effect of baclofen in reducing daily alcohol intake in alcohol dependence: secondary analysis of a randomized, double-blind, placebo-controlled trial. *Alcohol and alcoholism*, *46*(3), 312-317.

Carbamazepine and Valproate

Retrospective Cohort

Carbamazepine n=374, Valproate n=453

Higher adverse reactions with Carbamazepine 7.6% versus 2%, P < 0.001

duration of pharmacologic treatment, need for ICU, length of stay all significantly longer in Carbamazepine group

Eyer, F., Schreckenberg, M., Hecht, D., Adorjan, K., Schuster, T., Felgenhauer, N., ... & Zilker, T. (2011). Carbamazepine and valproate as adjuncts in the treatment of alcohol withdrawal syndrome: a retrospective cohort study. *Alcohol and alcoholism*, *46*(2), 177-184.

IV Ethanol

Controversial, practiced sporadically

Pros:

- Administration prevents/reduces AWS severity
- Typically reserved for severe cases

Cons:

- Narrow margin of safety
- Short duration of action
- Potential toxicity, drug interactions
- Lack of RCT data

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Predictive Tools

None currently validated for ICU

None for prediction of severe AWS in hospitalized patients

Alcohol Use Disorders Identification Test (AUDIT)

SHOT

AUDIT-PC

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Gray, S., Borgundvaag, B., Sirvastava, A., Randall, I., & Kahan, M. (2010). Feasibility and reliability of the SHOT: A short scale for measuring pretreatment severity of alcohol withdrawal in the emergency department. *Academic Emergency Medicine, 17*(10), 1048-1054.

Screening Tools for Risk Stratification

Rationale:

- Most mild cases do not require pharmacologic treatment
- 5-20% of hospitalized patients with Alcohol dependence have AWS severe enough to require pharmacologic treatment

Unnecessary prophylaxis or treatment of patients with AWS can lead to:

- Excess sedation
- Falls
- Respiratory depression
- Propylene glycol toxicity (lorazepam)
- Delirium

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Screening Tools for Risk Stratification

Moderate-Severe AWS implications:

Increased morbidity/mortality

Increased hospital stay

Increased costs

Worsens cognitive function

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Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

Potential to predict moderate – severe AWS in hospitalized patients

CIWA-Ar quantifies severity of AWS, is not a predictive tool

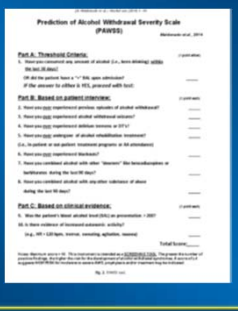
High sensitivity, specificity, positive and negative predictive values

10 items to assess risk of AWS

May be used to identify patients needing prophylaxis against AWS BEFORE severe AWS develops

Maldonado, J. R., Sher, Y., Ashouri, J. F., Hills-Evans, K., Swendsen, H., Lolak, S., & Miller, A. C. (2014). The "Prediction of Alcohol Withdrawal Severity Scale"(PAWSS): Systematic literature review and pilot study of a new scale for the prediction of complicated alcohol withdrawal syndrome. *Alcohol*.

Prediction of Alcohol Withdrawal Severity Scale (PAWSS)


Prediction of Alcohol Withdrawal Severity Scale (PAWSS)

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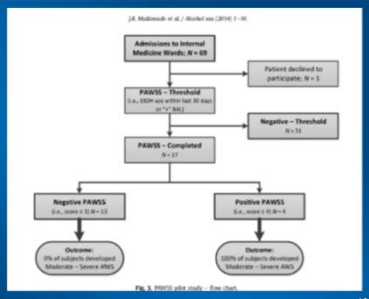
PAWSS

100% Sensitivity, Specificity

Limitations:

Self reporting could conceal alcohol use

Small N (69)



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Future Directions

More RCTs needed to determine risk stratification tools for AWS severity

Move toward earlier GABA replacement to complement current symptomatic treatment

Need for screening tools that incorporate patient history of currently prescribed GABA active drugs- associated risk of withdrawal

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