MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Inpatient Management of Alcohol Withdrawal

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Psychiatry Consultation-Liaison Service

Burns/Trauma Psychiatry Service

Disclosures

"Neither I nor my spouse/partner has a relevant financial relationship with a commercial interest to disclose."

Goals & Agenda

1. Review AUD, AWS
2. Benzodiazepines for AWS
3. Phenobarbital for AWS
4. MGH Phenobarbital Protocol

Alcohol, Alcohol Use Disorder, Alcohol Withdrawal Syndromes - Demographics, Risk Factors, and Neurobiology

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The Numbers

- 200 million – Americans consume alcohol
- 8 million – meet criteria for AUD
- 75 million –world-wide prevalence of AUD
- 30-40% of hospitalized patients (medicine)
- 10% of ICU admissions
- 25-50% of trauma/surgical patients (all substances)

Stahre (2014), Magrudeh-Habuib (1991), Harwood (2000), Sacks (2015)

Alcohol Withdrawal Syndromes

Syndrome	Timeline	Characteristics
Initial Withdrawal Symptoms [1 3]	Begins 6–8 h after last drink	– Includes tachycardia, hypertension, increased body temperature, tremulousness, anxiety, nausea/vomiting, headache, diaphoresis, and palpitations
Alcohol hallucinations [10 11]	12–24 h after last drink	– 7–8% of patients with AWS – Tactile hallucinations common, visual less likely – Auditory hallucinations possible (sometimes persecutory) – May present with tremors and other withdrawal symptoms, though some do not – Normal sensorium
Withdrawal seizures [6 8 12]	12–48 h after last drink	– Generalized tonic-clonic, though often isolated, short in duration, short post-ictal period – 1/3 of patients with withdrawal seizures will progress to delirium tremens
Delirium tremens [5]	Begins 3 days after the appearance of withdrawal symptoms and lasts for 1 to 8 days	– Rapid-onset, fluctuating disturbance of attention and cognition plus alcohol withdrawal symptoms – Diagnosis requires autonomic instability

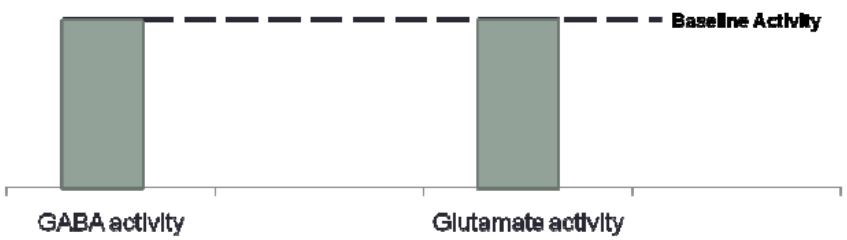
Risk Factors for Delirium Tremens

Factors associated with DT development
– History of previous DT
– Recent withdrawal seizures, specifically if left untreated
– Clinical Institute Withdrawal Assessment of Alcohol Scale, revised (CIWA-Ar) ≥ 15
– History of sustained drinking
– Patients with SBP > 150 mm Hg, or patients with HR > 100 beats/min
– Last alcohol intake > 2 days
– Age > 30 years
– Recent misuse of other depressants such as benzodiazepines
– Concurrent medical illness such as pneumonia or active ischemia

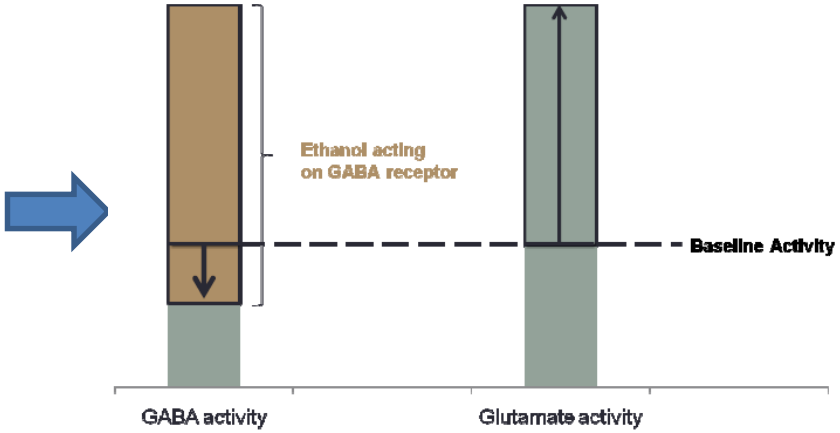
Alcohol Kills (L'Alcool Tue) Burnard 1920

Long (2017)

Basic Biology of Alcohol Use and Withdrawal



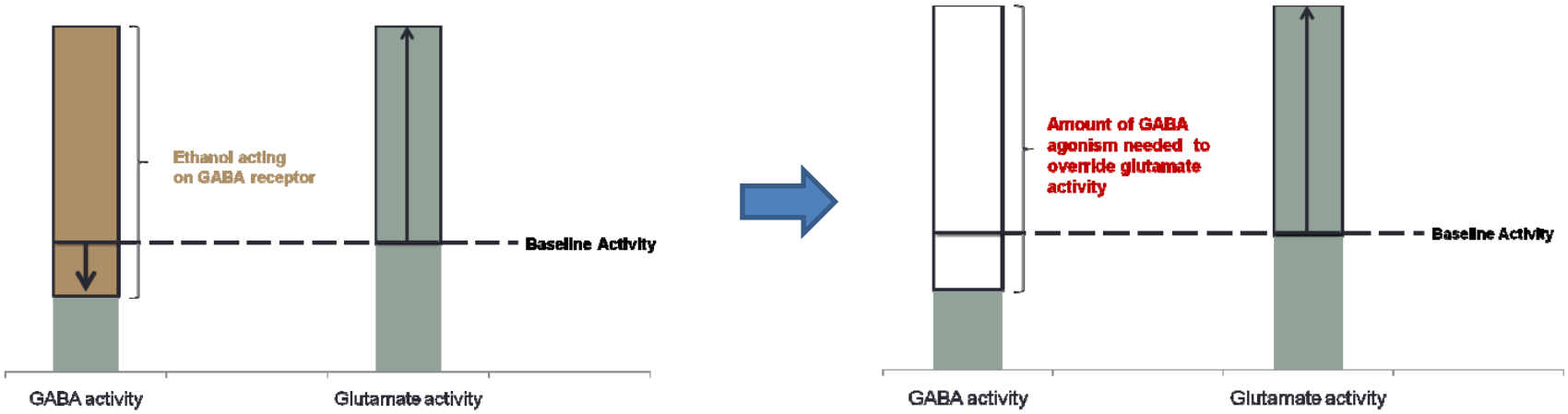
Baseline Homeostasis



With continous drinking, intrinsic GABA activity diminishes and intrinsic glutamate activity increases reaching new homeostasis

Nejad (2013)

Basic Biology of Alcohol Use and Withdrawal



Abrupt cessation or significant change in drinking (e.g. hospitalization) disrupts homeostasis leading to overall GABA/glutamate imbalance - withdrawal

Nejad (2013)

Treatment for AWS - Benzodiazepines

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Benzodiazepines for AWS

Mechanism of Action	•Bind GABA-A receptor and increase frequency of ion channel opening
Benefits	•Many drug options available •Variable routes of administration (including IV/IM) •Variable metabolic profiles •Familiar to providers and nursing in most clinical setitngs
Challenges	•Sedation/delirium •Misuse/diversion potential •Benzodiazepine resistance (>10mg lorazepam needed during 1h, or >40mg lorazepam needed during 4h)
Clinical Pathways	•Standard of care •Familiarity in clinical setting •CIWA (symptom triggered) vs. loading dose/taper

Saitz 1994, Jaeger 2001, Daeppen 2002

Benzodiazepines for AWS

- Symptom-Triggered vs. Fixed Dose Protocols
- Common treatment options:
  - Lorazepam
  - Diazepam
  - Chlordiazepoxide
- Specific treatment scenarios
  - Hepatic dysfunction – lorazepam, oxazepam, temazepar
  - Concurrent benzodiazepine misuse

Saitz 1994, Jaeger 2001, Daeppen 2002

CIWA-Ar Scale

- Nausea and vomiting (0-7)
- Paroxysmal sweats (0-7)
- Anxiety (0-7)
- Agitation (0-7)
- Tremor (0-7)
- Headache (0-7)
- Auditory hallucinations (0-7)
- Visual hallucinations (0-7)
- Tactile hallucinations (0-7)
- Orientation (0-4)

Score:

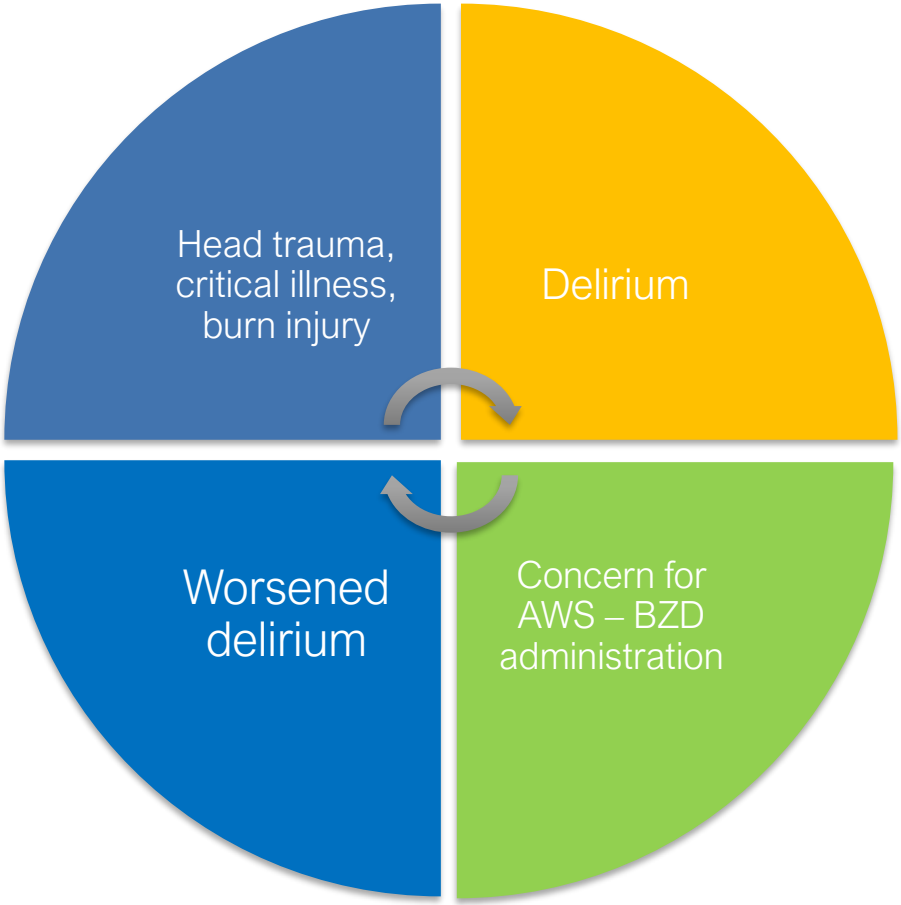
<15 mild withdrawal

15-20 moderate withdrawal

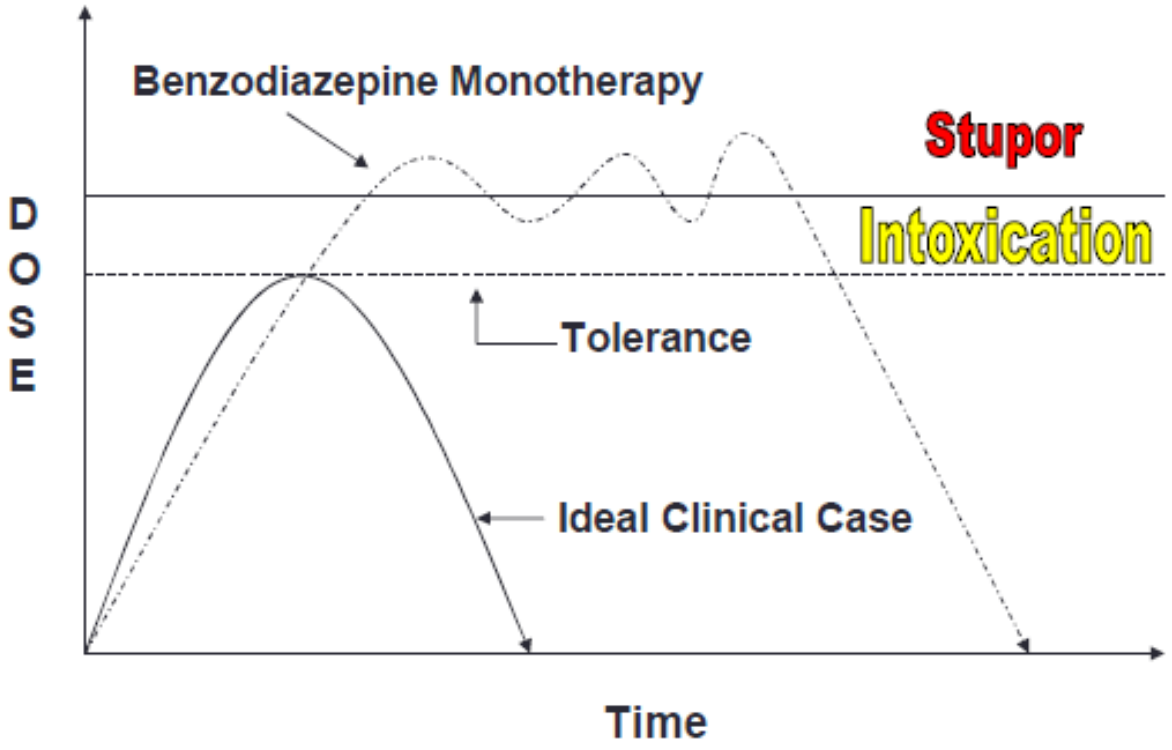
>20 severe withdrawal

Sullivan (1989)

Challenges


Head trauma, critical illness, burn injury
Delirium
Worsened delirium
Concern for AWS – BZD administration

Challenges



Nejad (2009)

Benzodiazepines are generally a safe choice, except when they are not …
What are our alternatives?

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Treatment of AWS - Phenobarbital

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Old Dog, New Tricks … or is it old tricks

Phenobarbital for AWS

Mechanism of Action	•Binds GABA-A receptor and increase duration of ion channel opening) •Acts directly on glutamate receptors
Benefits	•Very long half life •Dosing based on specific blood level •Variable routes of administration (including PO/IM) •Does NOT have a narrow therapeutic index
Challenges	•respiratory sedation, especially when co-administered with other sedatives •AMA risk •Concern for longer length of stay with fixed-dose protocol •Absolutely contraindicated if history of SJS, acute intermittent porphyria
Clinical Pathways	•Not a standard of care, accordingly only modest familiarity in clinical setting •Limited studies, with significant variability [phenobarbital alone, in conjunction w bzd, etc]

Nisavic (2019)

Phenobarbital for AWS

Reference	Study design	Interventions (population, N, treatment period, & duration of study)	Inclusion/exclusion criteria	Outcome measures	Assessments	Results
Kaim et al (1972) [23]	R, C, Partial DB, prospective	N = 46 chlordiazepoxide IM[b] + matching placebo X 10 D N = 46 perphenazine IM[b] + matching placebo X 10 D N = 41 pentobarbital IM[b] + matching placebo X 10 D N = 55 paraldehyde PO X 10 D	Inclusion criteria: DTs (disorientation, tremor, hallucination); male Exclusion criteria: frank schizophrenic reaction; chronic brain syndrome; serious medical or surgical Hx; DM; Dx of epilepsy (not associated with heavy drinking)	Efficacy: duration and severity of the episode from initiation of study drugs to delirium cessation (nurses' symptom record and physicians' judgments) Safety: mortality, complications	Goal of Tx: light somnolence or sleep	Mortality: 1 death (unrelated to Tx) Complications: 3 convulsions (1 each in chlordiazepoxide, paraldehyde, and perphenazine groups) Duration of episodes/severity of episodes (milder than average, average, worse than average, or very severe): no significant between- drug differences
Kramp et al (1978) [25]	DB, C, prospective	N = 44 (grade 1, N = 23; grade 2, N = 8; grade 3, N = 13) diazepam 20 mg IM (max 200 mg/d) + placebo PO N = 47 (grade 1, N = 19; grade 2, N = 11; grade 3, N = 17) barbital 500 mg PO (max 5 g/d) + placebo IM No psychoactive drugs were used Tx continued until psychotic symptoms, tremor, and sweat had disappeared	Inclusion criteria: acute AWS (tremor and intense perspiration) Exclusion criteria: intake of psychoactive drugs within 24 h before Tx; alcohol in blood at the time of Tx	Efficacy: (1) Course and duration of acute state (numbers of hours until last and last-but-one dose; total number of doses given; time to sleep, (2) Global assessment (satisfactory or nonsatisfactory) Safety: mortality, complications (seizures)	Grade 1: Tremor (no hallucination) Grade 2: Tremor + hallucination (no disorientation) Grade 3: Tremor + hallucination + disorientation	No pts died; no serious complications (one pt in each group developed a single convulsion) Course and duration of acute state: no marked differences are seen; in grade 2, pts treated with barbital fell asleep earlier than pts treated with diazepam ($P < .05$) Global assessment: in grade 1 and 2, the effects of Tx were not statistically significant; in grade 3, barbital significantly superior to diazepam ($P < .05$)
Gold et al (2007) [15]	Retrospective cohort	N = 41, Postguideline (100% diazepam, Avg total daily dose = 562 mg; 58% phenobarbital) N = 54 preguideline (100% diazepam, Avg total daily dose = 248 mg; 17% phenobarbital) Duration of data collection: preguideline (July 2000-June 2002); postguideline (July 2003-may 2005)	Inclusion criteria: pts admitted to medical ICU solely for Tx of severe AWS Exclusion criteria: presence of a serious medical or surgical diagnosis; evidence of use of other illicit substances Baseline characteristics: DTs (preguideline 98% vs postguideline 98%); AW seizures (preguideline 27% vs postguideline 38%)	Requirement of MV; incidence of nosocomial PNA, ICU LOS	Definition of AWS based on DSM-IV Guidelines: symptom-triggered therapy	Use of MV (postguideline 21.9% vs preguideline 47.3%, $P = .008$) Total ICU LOS (postguideline 3.8 ± 5.4 vs preguideline 4.5 ± 4.7 days, P not significant) Nosocomial complications (postguideline 19.5% vs preguideline 30.9%, $P = .1$)

Mo (2018)

Phenobarbital for AWS

Hendey et al (2011) [24]	Prospective, R, C, DB	N = 25 phenobarbital IV (260 mg initial dose, 130 mg subsequent doses, mean 509 mg); placebo PO at discharge N = 19 lorazepam IV (2 mg/dose, mean 4.2 mg); chlordiazepoxide PO at	Inclusion criteria: a known or suspected case of AW Exclusion criteria: severe symptoms or altered mental status; significant comorbid medical illness	Change in AW scores from ED baseline score to ED discharge and 48-hr reassessment; ED LOS; hospital admission rates	CIWA scores	Both drugs significantly decreased CIWA scores from baseline to ED discharge (phenobarbital 15.0-5.4, $P < .0001$ vs lorazepam 16.8-4.2, $P < .0001$); No differences between phenobarbital and lorazepam groups in baseline CIWA scores ($P = .3$), discharge scores ($P = .4$), ED LOS (267 min vs 256 min, $P = .8$), hospital admission rate (12% vs 16%, $P = .8$), and 48-hour follow-up CIWA scores ($P = .6$)
Michaelson et al (2010) [26]	Retrospective, cohort	(A) N = 53, phenobarbital Rigshospitalet (B) N = 53, phenobarbital Bispebjerg (C) N = 88, diazepam Bispebjerg Duration of data collection: 1998-2006[c]	Inclusion criteria: a hx of alcoholism and heavy alcohol intake within 96 h preceding admission; Two of the following symptoms: tremor, sweat, or psychomotor agitation; visual hallucinations; a disoriented state	Efficacy: LOS and DT duration Safety: respiratory and cardiac complications	Goal of Tx: sleep	A trend toward an increase in the frequency of DT per year in group C (A 5.9 ± 1.8 vs B 12.8 ± 4.1 vs C 17.0 ± [illegible]) No significant intergroup differences in mortality, DT duration, LOS, ICU admission rate, and complications 9% pts in Group C were resistant to large doses of diazepam
Rosenson et al (2013) [16]	Prospective, R, DB, PC,	N = 51, phenobarbital IV ×1 10 mg/kg N = 51, placebo All pts were placed on lorazepam-based AW protocol Duration of study: from January 2009 to March 2010	Inclusion criteria: ED admission; a primary admission diagnosis of AW Exclusion criteria: known severe hepatic impairment	Initial level of hospital admission; Use of continuous lorazepam infusion; ICU and hospital LOS; frequency of adverse events (intubation, seizure, mechanical restraints)	AWCA scores[d]	Baseline characteristics: male (phenobarbital 90% vs 88% placebo); median initial AWCA scores (phenobarbital 6 vs placebo 7) Phenobarbital resulted in a decrease in ICU admission (8% vs 25% [95% CI 4%-32%] and use of continuous lorazepam infusion (4% vs 31% [95% CI 7%-40]) No differences in ICU/hospital LOS, administration of other medications, and incidence of adverse outcomes
Duby et al (2014) [17]	Retrospective, cohort	N = 60 preintervention (PRE) group[e] N = 75 postintervention (POST) group[f] Duration of data collection: PRE (February 2008-February 2010); POST (February 2012-January 2013)	Inclusion criteria: ICU admission; a diagnosis of AWS Exclusion criteria: severe brain injury (GCS < 8)	ICU LOS; BZD/phenobarbital use; requirement of MV, duration of sedation; ventilator-free days	CIWA-Ar/RASS	Baseline characteristics (PRE vs POST): age (55.7 y vs 50.7, $P = .03$); SOFA score (6.1% vs 3.9%, $P = .0004$) Outcomes (PRE vs POST): ICU LOS (9.6 D vs 5.2 D, $P = .0004$); ventilator-free days (21.3 D vs 26.3 D, $P = .0004$); mean BZD use (319 mg vs 93 mg, $P = .002$); need for continuous sedation (55% vs 24%, $P < .001$); duration of sedation (10.8 D vs 3.5 D, $P < .001$); intubation due to AWS (22% vs 5%, $P < .001$); mean phenobarbital use (50 mg vs 90 mg, $P = .04$)

Phenobarbital for AWS

› Alcohol, 82, 23-27 2019 Jul 18[Online ahead of print]

Phenobarbital and Symptom-Triggered Lorazepam Versus Lorazepam Alone for Severe Alcohol Withdrawal in the Intensive Care Unit

Thu A Nguyen [1], Simon W Lam [2]

Phenobarbital for AWS

	Lorazepam (*n* = 36)	Phenobarbital-adjunct (*n* = 36)	*p*-value
Duration of treatment (days), *median (IQR)*	3.1 (1.6–4.8)	2.7 (1.7–6.4)	0.573
Change in CIWA-Ar at 24 h	6.5 ± 8.5	1.8 ± 9.0, *n* = 33	0.028
Length of ICU stay (days), *median (IQR)*	4.5 (2.8–6.1)	4.1 (2.4–8.4)	0.727
Adverse events (% yes)			
Mechanical ventilation	0 (0%)	3 (8.3%)	0.239
Hypotension	0 (0%)	0 (0%)	
Osmol gap >10	0 (0%)	0 (0%)	
Total dose of lorazepam given (mg), *mean ± SD*	48.2 ± 28.0	35.5 ± 48.8	0.183
Total dose of phenobarbital given (mg), *mean ± SD*		909.4 ± 785.4	

Ngyen (2019)

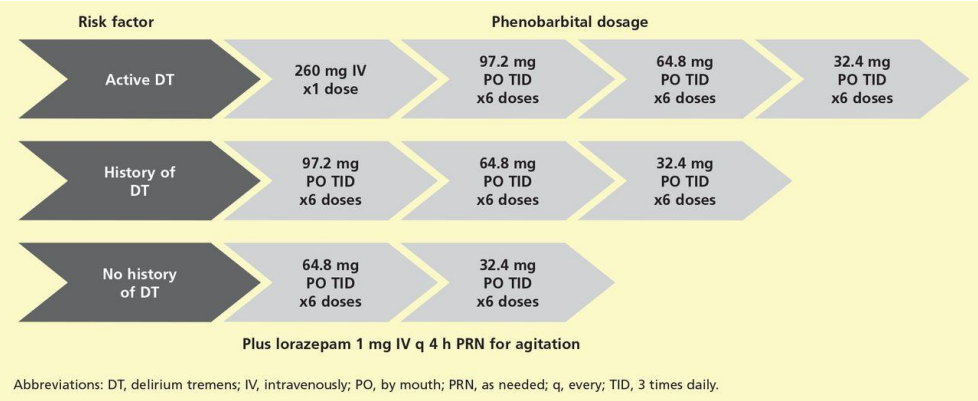
Phenobarbital for AWS

Am J Crit Care, 27 (6), 454-460 Nov 2018

Treatment of Alcohol Withdrawal Syndrome: Phenobarbital vs CIWA-Ar Protocol

William P Tidwell [1], Tonya L Thomas [2], Jonathon D Pouliot [2], Angelo E Canonico [2], Angus J Webber [2]

Phenobarbital for AWS



Abbreviations: DT, delirium tremens; IV, intravenously; PO, by mouth; PRN, as needed; q, every; TID, 3 times daily.

Initial or rising CIWA-Ar score	Stable or falling CIWA-Ar score
5-9: lorazepam 1 mg IV q 4 h	5-9: lorazepam 1 mg IV q 8 h
10-14: lorazepam 2 mg IV q 2 h	10-14: lorazepam 2 mg IV q 4 h
15-19: lorazepam 3 mg IV q 1 h	15-19: lorazepam 3 mg IV q 2 h
20-24: lorazepam 4 mg IV q 30 min	20-24: lorazepam 4 mg IV q 1 h
25-29: lorazepam 5 mg IV q 15 min	25-29: lorazepam 5 mg IV q 30 min
30-34: lorazepam 6 mg IV q 10 min	30-34: lorazepam 6 mg IV q 10 min

≥35: lorazepam 6 mg IV x 1 dose, lorazepam infusion at 4 mg/h, increase by 2 mg/h q 30 min until score stabilizes or falls

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; IV, intravenously; q, every.

Tidwell (2018)

Phenobarbital for AWS

Demographics	CIWA-Ar arm (n = 60)	Phenobarbital arm (n = 60)	P
Age, mean (SD), y	52 (15.5)	45 (11.4)	.003
Race, No. (%) of patients			>.99
White	57 (95)	57 (95)	
Black or African American	2 (3)	1 (2)	
Other	1 (2)	2 (3)	
Male sex, No. (%) of patients	43 (72)	44 (73)	.84
Left against medical advice, No. (%) of patients	1 (2)	3 (5)	
Comorbid conditions			
Psychiatric disorder	29	29	>.99
Polysubstance abuse	10	10	>.99
Seizure disorder	5	8	.41
Reactive airway disorder	8	6	.59
Liver disease	14	16	.68
Previous delirium tremens or withdrawal seizures	27	32	.92
Clinical presentation on admission			
Abnormal liver laboratory values	30	38	.17
Active alcohol withdrawal/delirium tremens	20	28	.46

Abbreviation: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised.

Outcome or clinical characteristic	CIWA-Ar arm (n = 60)	Phenobarbital arm (n = 60)	P
ICU stay (midnights), mean (SD)	4.4 (3.9)	2.4 (1.5)	<.001
Hospital stay (midnights), mean (SD)	6.9 (6.6)	4.3 (3.4)	.004
Total lorazepam equivalents, mean (SD), mg	35.2 (48.5)	11.3 (18)	<.001
Ventilator use, No. of patients	14	1	<.001
Dexmedetomidine use, No. of patients	17	4	.002
Olanzapine use, No. of patients	7	5	.54
Haloperidol use, No. of patients	10	4	.08
Quetiapine use, No. of patients	5	2	.24

Abbreviations: CIWA-Ar, Clinical Institute Withdrawal Assessment for Alcohol, revised; ICU, intensive care unit.

Tidwell (2018)

Take home point: Data remains limited given historical use and ongoing extent of use. Existing data indicative phenobarbital is safe and effective alternative to conventional benzodiazepines

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MGH Phenobarbital Protocol

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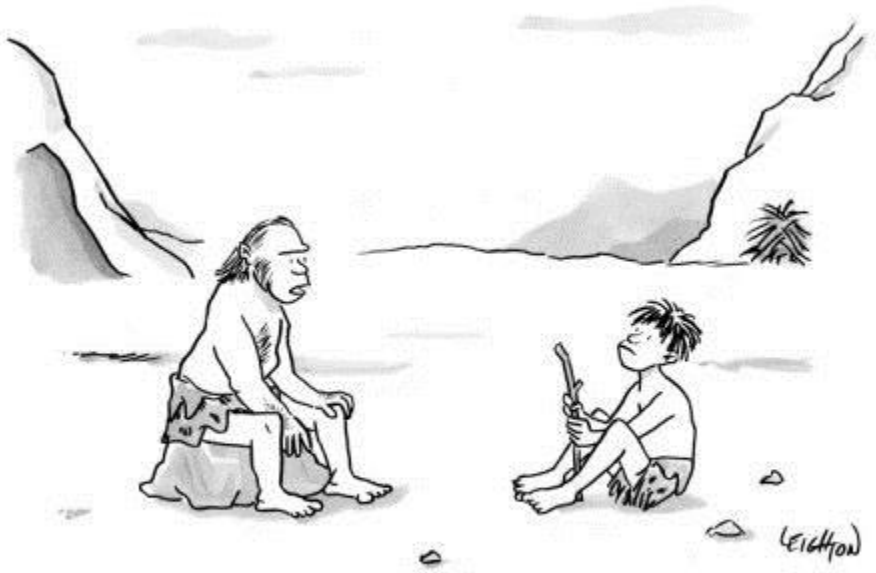
MGH Phenobarbital Protocol



"When I was your age, things were exactly the way they are now."

MGH Phenobarbital Protocol

Case Reports > South Med J, 84 (1), 18-21 Jan 1991

Pharmacokinetic Dosing of Phenobarbital in the Treatment of Alcohol Withdrawal Syndrome

T J Ives [1], A J Mooney 3rd, R E Gwyther

Admission Orders for Alcohol Withdrawal Syndrome

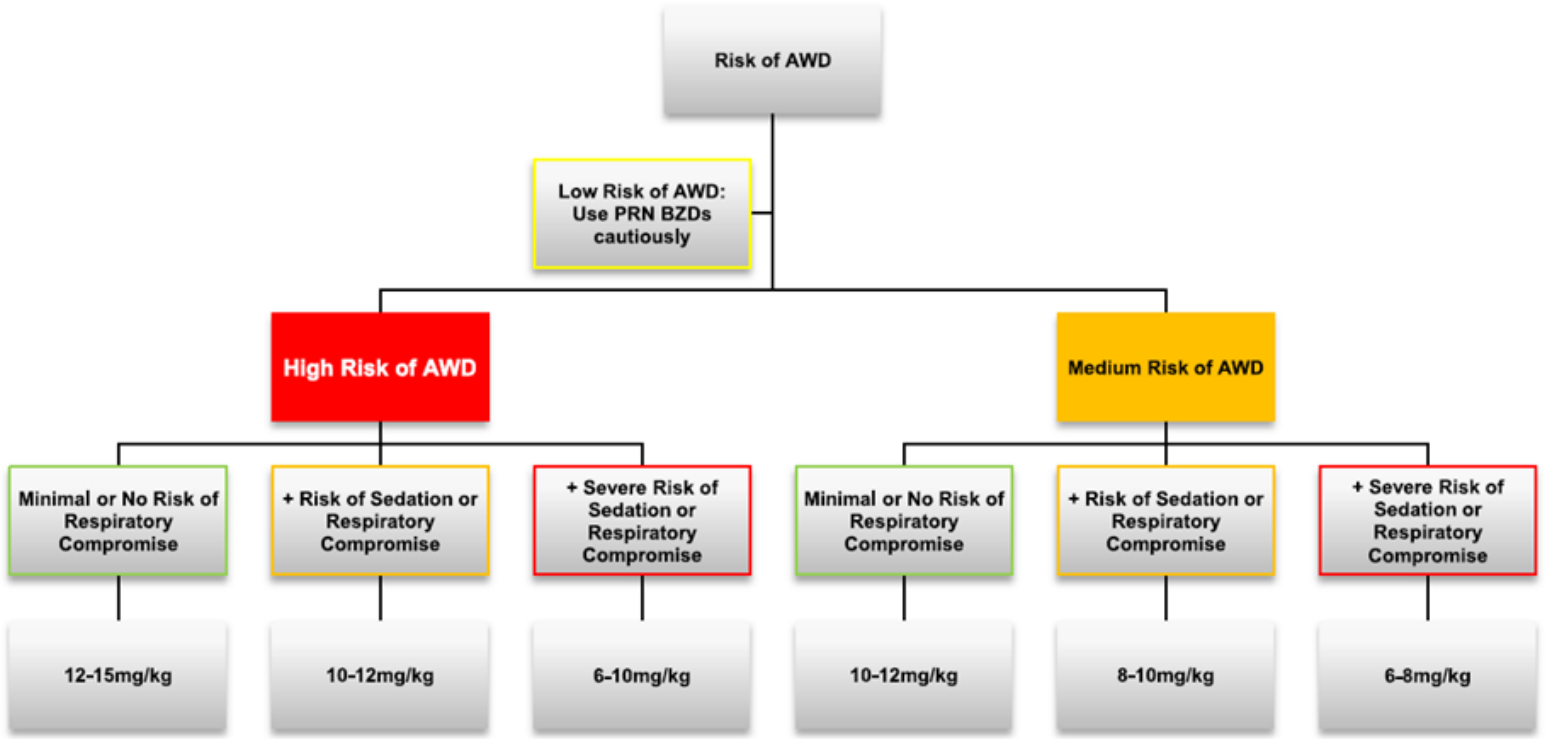
1. Admit to the Family Medicine Inpatient Service.
2. Diagnosis: _____
3. Condition: _____
4. Allergies: _____
5. Upon admission, obtain a weight and height to determine the Ideal Body Weight (IBWt):
   IBWt (men) = 50.0 kg + 2.3 kg/inch over 5 feet
   IBWt (women) = 45.5 kg + 2.3 kg/inch over 5 feet
   Weights are then obtained every other day.
6. Obtain temperature, blood pressure, pulse, and respiration every 4 hours for the first 48 hours, then every shift only if blood pressure ≤160/95 mm Hg or temperature ≤38.5°C (otherwise, continue every 4 hours).
7. Activity as tolerated.
8. Encourage oral fluids. Standard diet and fluids as tolerated, unless a special diet is ordered.
9. Admission laboratory values:
   Serum alcohol level, complete blood cell count with differential, sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, glucose, magnesium, amylase, liver function tests (ie, total bilirubin, aspartate aminotransferase, alanine aminotransferase), total protein, albumin, and urinalysis.
   Blood and/or urine sample for toxicologic screening (if not obtained before admission).
   Serum phenobarbital (trough) and serum alcohol levels on day 3.
10. Chest x-ray film and electrocardiogram, if none obtained within the last 6 months.
11. One injection of thiamine HCl 100 mg intramuscularly three times a day for 3 days.
12. $MgSO_4$ 50% 2 mL intramuscularly every 8 hours for 6 doses.
13. Multivitamin (with 1 mg of folate), one tablet by mouth every morning.
14. Upon admission:
    Loading dose (LD) of phenobarbital: 15 mg/kg of IBWt, given intramuscularly as follows: 40% of the LD is given stat, then 30% of the LD is given 3 hours later, and the final 30% in another 3 hours.
15. Maintenance dose (MD) of phenobarbital*:

$$MD = \frac{(Cl)\,(Cp_{ss})\,(T)}{(S)\,(F)} = \frac{(0.096\ L/day/kg \times IBWt\ [in\ kg])\,(20\ mg/L)\,(1\ day)}{(1.0)\,(1.0)}$$

$$= \_\_\_\_\_ \text{ mg of phenobarbital}$$

   a) The MD is to be given orally twice a day on days 2 and 3.
   b) The total daily dose is decreased by half on days 4 and 5.
   c) The daily dose is cut in half again on day 6 and again on day 7.
   d) Discontinue the MD on day 8.
16. For *excessive* agitation only, give lorazepam, 1 to 2 mg IM as needed. If agitation continues, notify the physician on call.
17. Do not give any benzodiazepines or any other barbiturates at *any* time!
18. Acetaminophen, 325 to 650 mg by mouth every 4 hours as needed for pain or headache (maximum = 2 g/day).
19. Aluminum hydroxide, magnesium hydroxide and simethicone (Mylanta II) 30 mL PO every 2 hours as needed for gastrointestinal discomfort.
20. Kaolin and pectin (Kaopectate) 60 mL PO after each loose stool as needed for diarrhea.
21. Milk of magnesia 30 mL PO daily as needed for constipation.
22. Notify the physician on call if:
    a) diastolic blood pressure (DBP) ≥110 or ≤50 mm Hg,
    b) systolic blood pressure (SBP) ≥160 or ≤100 mm Hg,
    c) pulse ≥120 or ≤55/minute,
    d) pulse increased by 20/minute over admission pulse,
    e) temperature ≥38.5°C,
    f) the patient demonstrates increasing signs or symptoms of withdrawal, or
    g) seizure activity.

Ives (1991)



MGH Phenobarbital-Based Alcohol Withdrawal Protocol

- High risk of alcohol withdrawal defined as either (A) Prior history of alcohol withdrawal, including history of alcohol withdrawal seizures and/or alcohol withdrawal delirium, and recent alcohol use (more than 2 weeks in duration), or (B) identification of early symptoms of alcohol withdrawal despite concurrent positive blood alcohol level.
- Medium risk of alcohol withdrawal defined as active alcohol use disorder plus two or more of the following: 2 or more days since last drink, positive blood alcohol level on admission, autonomic dysfunction with blood alcohol level >1000 mg/L, elevated MCV and/or AST: ALT ratio, prior history of significant alcohol use, age >35 years old, presence of burn-related injuries or long bone fractures.
- Risk of sedation: age > 65 years old, hepatic dysfunction, administration of opiate medication, acute head injury with the need for frequent neurologic examination, recent administration of benzodiazepines and/or current administration of other sedatives.
- Respiratory compromise: need for oxygen supplementation, pneumonia, rib fractures, chest tubes, pulmonary contusions, C-collar/brace.

Nisavic (2019), Nejad (2013)

MGH Phenobarbital Protocol

1) Calculate target loading dose with phenobarbital depending on alcohol use severity and comorbid medical illness based on criteria

Ideal Body Weight (IBW) x (6 to 15mg/kg) = total mg (of loading dose)

Where:

IBW for men is: 50 + 2.3kg/inch over 5 feet
IBW for women is 45.5 +2.3kg/inch over 5 feet

2) Give loading dose intramuscularly

- 40% of the loading dose given immediately
- 30% of the loading dose given 3 hours after first IM administration
- 30% of the loading dose given 3 hours after second IM administration
- Serum phenobarbital can be checked 5 hours after the last IM administration.

3) On day 2, initiate continuation dose taper based on following calculation:

Total CD = [(CL) x (CPss) x (T)] / [(S) x (F)

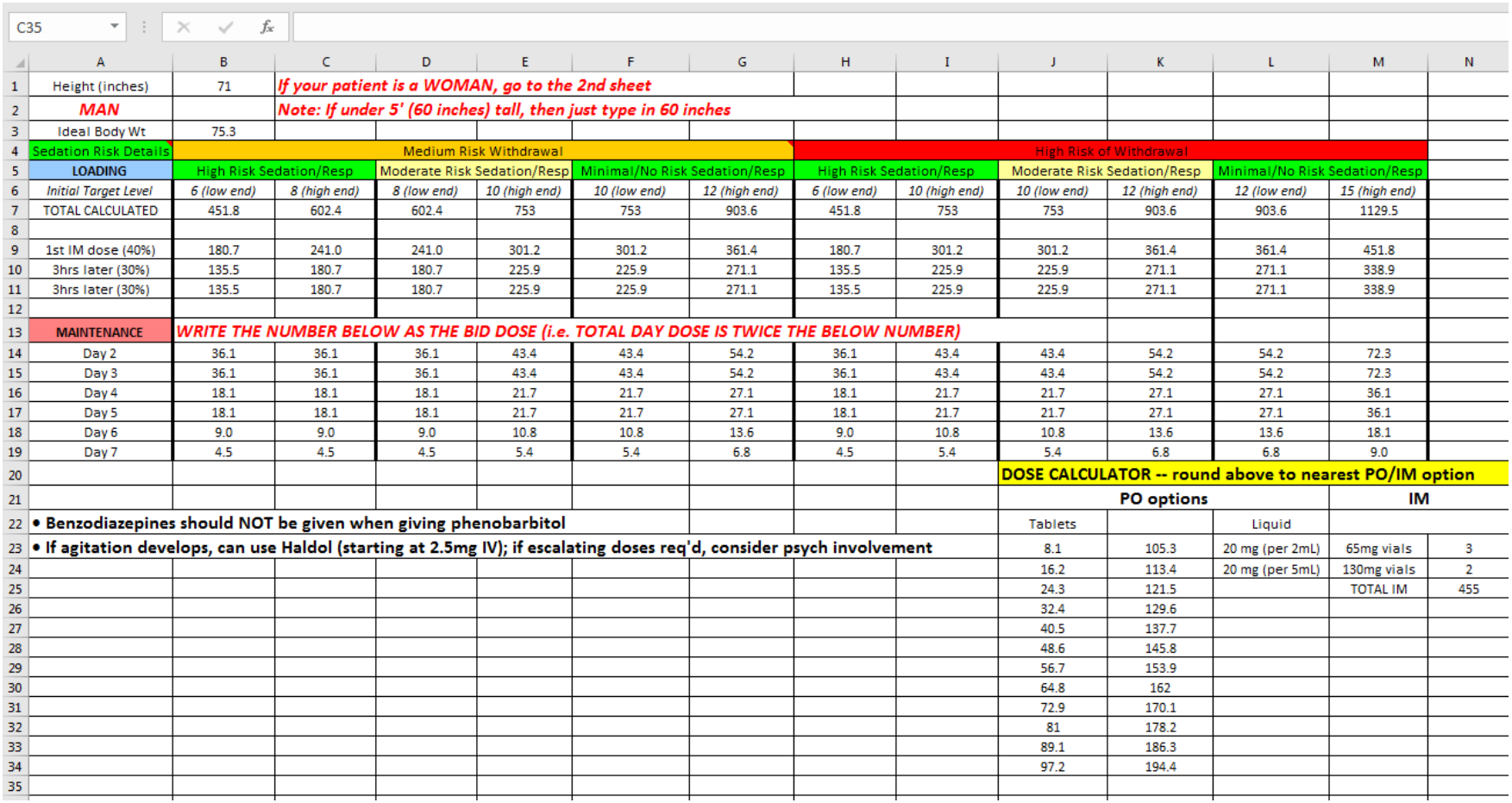
Where: CD – continuation dose, CL – rate of clearance (0.096 L/day/kg), CPss – desired steady state serum level (10-20ug/mL), S – fraction of the total molecular weight of active drug in salt form, F – bioavailability

Continuation dose is given orally (or intramuscularly) and split into BID dosing

- Day 3 is the same as day 2
- Day 4 the oral dose is decreased by 50%
- Day 5 it stays the same
- Day 6 decrease 50%
- Day 7 decrease 50%, then discontinue

Nisavic (2019), Nejad (2013)

MGH Phenobarbital Protocol



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	Height (inches)	71	*If your patient is a WOMAN, go to the 2nd sheet*											
2	*MAN*		*Note: If under 5' (60 inches) tall, then just type in 60 inches*											
3	Ideal Body Wt	75.3												
4	Sedation Risk Details	Medium Risk Withdrawal						High Risk of Withdrawal						
5	LOADING	High Risk Sedation/Resp		Moderate Risk Sedation/Resp		Minimal/No Risk Sedation/Resp		High Risk Sedation/Resp		Moderate Risk Sedation/Resp		Minimal/No Risk Sedation/Resp		
6	*Initial Target Level*	*6 (low end)*	*8 (high end)*	*8 (low end)*	*10 (high end)*	*10 (low end)*	*12 (high end)*	*6 (low end)*	*10 (high end)*	*10 (low end)*	*12 (high end)*	*12 (low end)*	*15 (high end)*	
7	TOTAL CALCULATED	451.8	602.4	602.4	753	753	903.6	451.8	753	753	903.6	903.6	1129.5	
8														
9	1st IM dose (40%)	180.7	241.0	241.0	301.2	301.2	361.4	180.7	301.2	301.2	361.4	361.4	451.8	
10	3hrs later (30%)	135.5	180.7	180.7	225.9	225.9	271.1	135.5	225.9	225.9	271.1	271.1	338.9	
11	3hrs later (30%)	135.5	180.7	180.7	225.9	225.9	271.1	135.5	225.9	225.9	271.1	271.1	338.9	
12														
13	MAINTENANCE	*WRITE THE NUMBER BELOW AS THE BID DOSE (i.e. TOTAL DAY DOSE IS TWICE THE BELOW NUMBER)*												
14	Day 2	36.1	36.1	36.1	43.4	43.4	54.2	36.1	43.4	43.4	54.2	54.2	72.3	
15	Day 3	36.1	36.1	36.1	43.4	43.4	54.2	36.1	43.4	43.4	54.2	54.2	72.3	
16	Day 4	18.1	18.1	18.1	21.7	21.7	27.1	18.1	21.7	21.7	27.1	27.1	36.1	
17	Day 5	18.1	18.1	18.1	21.7	21.7	27.1	18.1	21.7	21.7	27.1	27.1	36.1	
18	Day 6	9.0	9.0	9.0	10.8	10.8	13.6	9.0	10.8	10.8	13.6	13.6	18.1	
19	Day 7	4.5	4.5	4.5	5.4	5.4	6.8	4.5	5.4	5.4	6.8	6.8	9.0	
20										**DOSE CALCULATOR -- round above to nearest PO/IM option**				
21										**PO options**			**IM**	
22	• **Benzodiazepines should NOT be given when giving phenobarbitol**									Tablets		Liquid		
23	• **If agitation develops, can use Haldol (starting at 2.5mg IV); if escalating doses req'd, consider psych involvement**									8.1	105.3	20 mg (per 2mL)	65mg vials	3
24										16.2	113.4	20 mg (per 5mL)	130mg vials	2
25										24.3	121.5		TOTAL IM	455
26										32.4	129.6			
27										40.5	137.7			
28										48.6	145.8			
29										56.7	153.9			
30										64.8	162			
31										72.9	170.1			
32										81	178.2			
33										89.1	186.3			
34										97.2	194.4			
35														

Nisavic (2019), Nejad (2013)

Results So Far

MASSACHUSETTS GENERAL HOSPITAL

Use of Phenobarbital in Alcohol Withdrawal Management – A Retrospective Comparison Study of Phenobarbital and Benzodiazepines for Acute Alcohol Withdrawal Management in General Medical Patients

Mladen Nisavic, M.D., Shamim H. Nejad, M.D., Benjamin M. Isenberg, B.A., Ednan Khalid Bajwa, M.D., Paul Currier, M.D., Paul M. Wallace, B.A., George Velmahos, M.D., Timothy Wilens, M.D.

TABLE 1. Demographic and Alcohol-Related Laboratory Characteristics of Patients Treated With Benzodiazepines or Phenobarbital for Alcohol Withdrawal Symptoms

	Benzodiazepines ($N = 419$)	Phenobarbital ($N = 143$)	Test statistics, p value
	N (%)	N (%)	
Male	334 (80%)	122 (85%)	$\chi^2 = 2.19, p = 0.14$
Prior history of alcohol withdrawal syndrome	305 (73%)	130 (91%)	$\chi^2 = 20, p < 0.001$
Prior history of seizure	190 (45%)	105 (73%)	$\chi^2 = 33.7, p < 0.001$
Prior history of alcohol withdrawal delirium	110 (26%)	54 (38%)	$\chi^2 = 6.83, p < 0.01$
Seizure prior to admission/in ED	31 (7%)	20 (14%)	$\chi^2 = 5.61, p = 0.02$
	Mean ± SD	**Mean ± SD**	
Age (Years)	49.9 ± 10.9	48.1 ± 10	$t = -1.82, p = 0.07$
Blood alcohol level (mg per liter)	1577 ± 1497	1895 ± 1609	$t = 2.09^*, p = 0.03$
AST (Units per liter)	144 ± 791	112 ± 129	$t = -0.49, p = 0.63$
ALT (Units per liter)	79.4 ± 286	62.8 ± 53.5	$t = -0.68, p = 0.5$
AST/ALT (Units per liter)	1.82 ± 0.95	1.89 ± 1.07	$t = 0.69, p = 0.49$
MCV (Fl.)	93.9 ± 8.12	93.1 ± 6.96	$t = -0.99, p = 0.32$

Note: Benzodiazepine group includes those initially treated with benzodiazepines and then transitioned to phenobarbital and Phenobarbital group includes one patient initially treated with phenobarbital and transitioned to Benzodiazepines mid-taper.

Nisavic et al (2019)

TABLE 3. Medical Outcomes of Patients Treated With Benzodiazepines or Phenobarbital for Alcohol Withdrawal Symptoms

	Benzodiazepines ($N = 419$)	Phenobarbital ($N = 143$)	Test statistics, p value
Primary outcomes	N (%)	N (%)	
Seizures	4 (1%)	1 (1%)	NS
Hallucinations	10 (2%)	3 (2%)	NS
Delirium	28 (7%)	6 (4%)	$\chi^2 = 1.16, p = 0.28$
ICU admissions	48 (12%)	17 (12%)	$\chi^2 = 0.01, p = 0.89$
Secondary outcomes			
Left against medical advice	50 (12%)	9 (6%)	$\chi^2 = 3.61, p = 0.06$
Mortality	1 (0%)	0 (0%)	NS
	Mean ± SD	**Mean ± SD**	
Length of stay (days)	5.14 ± 5.54	5.31 ± 2.91	$t = 0.34, p = 0.73$
ICU length of stay (days)	3.56 ± 3.19	3 ± 2.89	$t = -0.64, p = 0.53$
Medication adverse events	N (%)	N (%)	
Pancytopenia	0 (0%)	1 (1%)	NS
Sedation	6 (1%)	0 (0%)	NS

The abbreviation "NS" denotes instances where insufficient data were available for statistical analysis.

Note: Benzodiazepine group includes those initially treated with benzodiazepines and then transitioned to phenobarbital and phenobarbital group includes one patient initially treated with phenobarbital and transitioned to benzodiazepines mid-taper.

Nisavic et al (2019)

TABLE 2. Demographic and Alcohol-Related Laboratory Characteristics of Patients Treated With Benzodiazepines for Alcohol Withdrawal Symptoms

	Benzodiazepines to phenobarbital ($N = 16$)	Benzodiazepines only ($N = 403$)	Test statistics, p value
	N (%)	N (%)	
Male	13 (81%)	321 (80%)	$\chi^2 = 0.02$, $p = 0.88$
Prior history of alcohol withdrawal syndrome	13 (81%)	292 (73%)	$\chi^2 = 0.60$, $p = 0.44$
Prior history of seizure	6 (38%)	184 (56%)	$\chi^2 = 0.41$, $p = 0.52$
Prior history of alcohol withdrawal delirium	2 (13%)	108 (27%)	$\chi^2 = 1.63$, $p = 0.20$
Seizure prior to admission / in ED	0 (0%)	31 (8%)	$\chi^2 = 1.33$, $p = 0.62$
	Mean ± SD	**Mean ± SD**	
Age (Years)	47.6 ± 10.8	50.1 ± 10.9	$t = 0.91$, $p = 0.37$
Blood alcohol level (mg per liter)	1031 ± 1703	1596 ± 1488	$t = 1.18$, $p = 0.26$
AST (Units per liter)	117.6 ± 110	146 ± 806	$t = 0.58$, $p = 0.56$
ALT (Units per liter)	49.6 ± 33.2	80.6 ± 291	$t = 1.85$, $p = 0.07$
AST/ALT (Units per liter)	2.21 ± .850	1.81 ± .951	$t = 1.84$, $p = 0.08$
MCV (Fl.)	95.4 ± 8.15	93.8 ± 8.13	$t = 0.74$, $p = 0.47$

Note: Patients in the Benzodiazepines to Phenobarbital group were initially treated with benzodiazepines and then transitioned to phenobarbital, and patients in the Benzodiazepines only group were treated exclusively with benzodiazepines.

Nisavic et al (2019)

TABLE 4. Outcomes of Patients Treated With Benzodiazepines Initially and Then Transitioned to Phenobarbital Compared to Patients Treated With Benzodiazepines Only for Alcohol Withdrawal Symptoms

	Benzodiazepines ($N = 419$)	Benzodiazepines to phenobarbital ($N = 16$)	Test statistics, p value
Primary outcomes	N (%)	N (%)	
Seizures	4 (1%)	0 (0%)	NS
Hallucinations	8 (2%)	2 (13%)	Fisher's exact $p = 0.051$
Delirium	23 (6%)	5 (31%)	Fisher's exact $p < 0.01$
ICU admissions			
	41 (11%)	7 (44%)	Fisher's exact $p = 0.001$
Secondary outcomes			
Left against medical advice	49 (12%)	1 (6%)	$\chi^2 = 0.51$, $p = 0.48$
Mortality	1 (0%)	0 (0%)	NS
	Mean ± SD	**Mean ± SD**	
Length of stay (days)	4.98 ± 5.42	9.31 ± 7.1	$t = -3.10$, $p < 0.01$
ICU length of stay (days)	3.32 ± 2.78	5.00 ± 5.03	$t = -1.3$, $p = 0.2$
Medication adverse events	N (%)	N (%)	
Pancytopenia	0 (0%)	0 (0%)	NS
Sedation	6 (2%)	0 (0%)	NS

The abbreviation "NS" denotes instances where insufficient data were available for statistical analysis.

Nisavic et al (2019)

Phenobarbital for Acute Alcohol Withdrawal Management in Surgical Trauma Patients – A Retrospective Comparison Study

Shamim Nejad, M.D., Mladen Nisavic, M.D. , Andreas Larentzakis, M.D. , Suzan Dijkink M.D., Yuchiao Chang, Ph.D, Alexander R. Levine, Pharm. D. , Marc de Moya, M.D. , George Velmahos, M.D.

Table 1.
Demographic and Alcohol-Related Laboratory Characteristics of Patients treated with Phenobarbital or Benzodiazepines for Alcohol Withdrawal Syndrome.

	Phenobarbital (N=33)	BZD (N=52)	*p* Value
Age (years)	52.5 ± 11	52.3 ± 11	0.94
Male gender	28 (84.8%)	42 (80.8%)	0.77
Service			
Trauma Surgery	21 (63.6%)	41 (78.8%)	
Acute Care Surgery	4 (12.1%)	1 (1.9%)	
Burn Surgery	8 (24.2%)	10 (19.2%)	
ISS	17.4 ± 8.6	17.5 ± 10.5	0.96
Head AIS	2.2 ± 1.9	1.4 ± 1.9	0.24
BAL (mg/L)	2151 ± 1147	2147 ± 1301	0.99
AST:ALT	1.8 ± 0.9	1.4 ± 0.5	0.034
MCV (fL)	95.7 ± 6.7	95.4 ± 5.8	0.86
Prior AWD	5 (15.2%)	6 (11.5%)	0.74
Prior AWS - Seizures	7 (21.2%)	9 (17.3%)	0.78

Note: BZD, benzodiazepines; ISS, injury severity score; AIS, abbreviated injury scale; BAL, blood alcohol level; AST, aspartate aminotransferase; ALT, alanine aminotransferase; MCV, mean corpuscular volume; AWD, alcohol withdrawal delirium; AWS, alcohol withdrawal syndrome.

Nejad (2020)

Table 2.
Primary and Secondary Clinical Outcomes of Patients Treated with Phenobarbital or Benzodiazepines for Alcohol Withdrawal Syndrome

	Phenobarbital (N=33)	BZD (N=52)	*p* Value
AWD	0	25 (48.21%)	0.0001
AWS - Seizures	0	0	
AWS - Hallucinosis	0	4 (7.7%)	0.29
AWS - Uncomplicated	0	38 (73.1%)	0.0001
Medication Adverse Events	0	10 (19.2%)	0.006
Mortality	0	2 (3.8%)	0.52
ICU admission for AWS	0	6 (11.5%)	
LOS (days)	12.5 ± 10.0	10.9 ± 9	0.46

Note: BZD, benzodiazepines; AWD, alcohol withdrawal delirium; AWS, alcohol withdrawal syndrome; ICU, intensive care unit; LOS, length of stay.

Phenobarbital mean dose - 854.7mg total (range 480mg-1645mg).

Average total lorazepam dose - 41.6mg (dose range of 1mg-287mg).

Use of other benzodiazepines (adjunct):

- diazepam (n=8 patients, total dose range 10mg-300mg)
- chlordiazepoxide (n=10 patients, total dose range 100mg-500mg)
- clonazepam (n=3 patients, total dose range 8.5mg-18mg).

Use of neuroleptics (adjunct):

- None in the phenobarbital group.
- Intravenous haloperidol (total dose range of 5mg-403mg) – 23 bzd-treated patients;
- Quetiapine (total dose range of 25mg-5800mg) – 12 bzd-treated patients;

Nejad (2020)

Challenges and Steps Ahead

1) **Prospective randomized study – our goal for 2020 and beyond!**

2) **Practical Observations:**
   - **Trainee/Nursing strongly prefer protocol once familiar – ease of implementation and reduced need for frequent monitoring**
   - **Safety – split dosing assists with sedation monitoring, therapeutic index wide; sedation relatively uncommon unless co-administration of other sedatives (e.g. benzodiazepines)**
   - **Reduced "bargaining" for medications**
   - **Patient education paramount – including AMA risk assessment and education re: long half-life**

3) **Streamline current protocol – our other goal for 2020 and beyond!**

   - **PO taper – does not appear necessary (? Consolidate dosing to a 4th IM dose)**
     - **Improve LOS parameters**
     - **Reduce barriers to implementation of protocol**

   - **Simplify dosing parameters – most patients will dose at 10-12mg/kg range**
     - **Reduce barriers to implementation of protocol**

Thank you!

Questions, comments, thoughts?

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