Alcohol & Sedative Withdrawal Management

Kapila Marambage, MD
Assistant Professor - UTSW
Addiction Psychiatry Service - Parkland Hospital

Withdrawal

Characteristic group of signs & symptoms that typically develop after rapid, marked decrease or discontinuation of a substance of dependence, which may or may not be clinically significantly or life threatening.

Detoxification

Interventions aimed at managing acute intoxication & withdrawal in order to clear the substance from body & minimize physical harm.

The acute medical management of related medical problems is NOT included within the term detoxification.

Detox does NOT constitute substance use disorder treatment but is only one part of a continuum of care for substance use disorders.

Pathophysiology of EtOH Withdrawal

GABA - Major inhibitory neurotransmitter

Chronic EtOH exposure decrease in GABA A alpha 1 receptor activity

NMDA (N-methyl-D-aspartate) - Major excitatory neurotransmitter

Chronic EtOH exposure increase in NMDA receptor concentration neuron hyperexcitability.

ASAM Criteria for treatment setting

Level I-D: Ambulatory Detoxification Without Extended Onsite Monitoring

Level II-D: Ambulatory Detoxification With Extended Onsite Monitoring

Level II.2-D: Clinically Managed Residential Detoxification

Level III.7-D: Medically Monitored Inpatient Detoxification (hospital ward)

Level IV-D: Medically Managed Intensive Inpatient Detoxification (ICU)

Delirium Tremens

Begins 3 to 5 days after last drink. Occurs in less than 5% of withdrawal patients

Risk factors - Acute concurrent medical illness, History of seizures or delirium tremens, Heavier & longer EtOH history, Age > 60, Elevated BAL on admission (greater than 300 mg/dl)

Symptoms & signs - Confusion & disorientation, Hallucinations, Hyper-responsiveness, Hypertension, Tachycardia, Fever

Mortality - without treatment = 20%

Temperature > 104 ~ 45% mortality; Seizures ~ 24% mortality

Cause of death - Pneumonia, Liver disease, Hypotension, Trauma

Indications for Admission

Hx of complicated withdrawals, withdrawal seizures or delirium tremens

Hx of heavy prolonged EtOH use with a high degree of tolerance.

Abuse of multiple substances

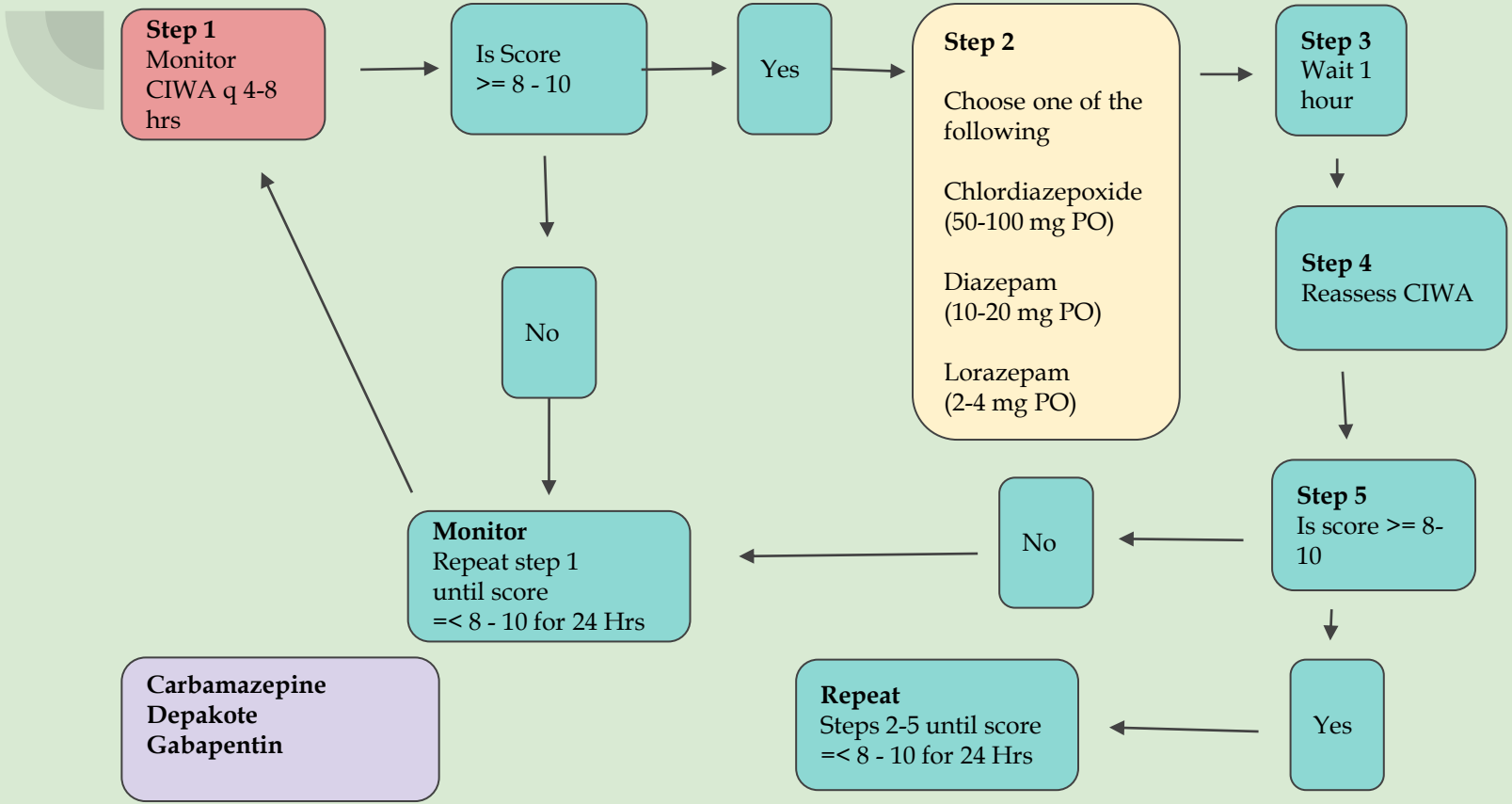
Concomitant psychiatric or medical illness

Pregnancy

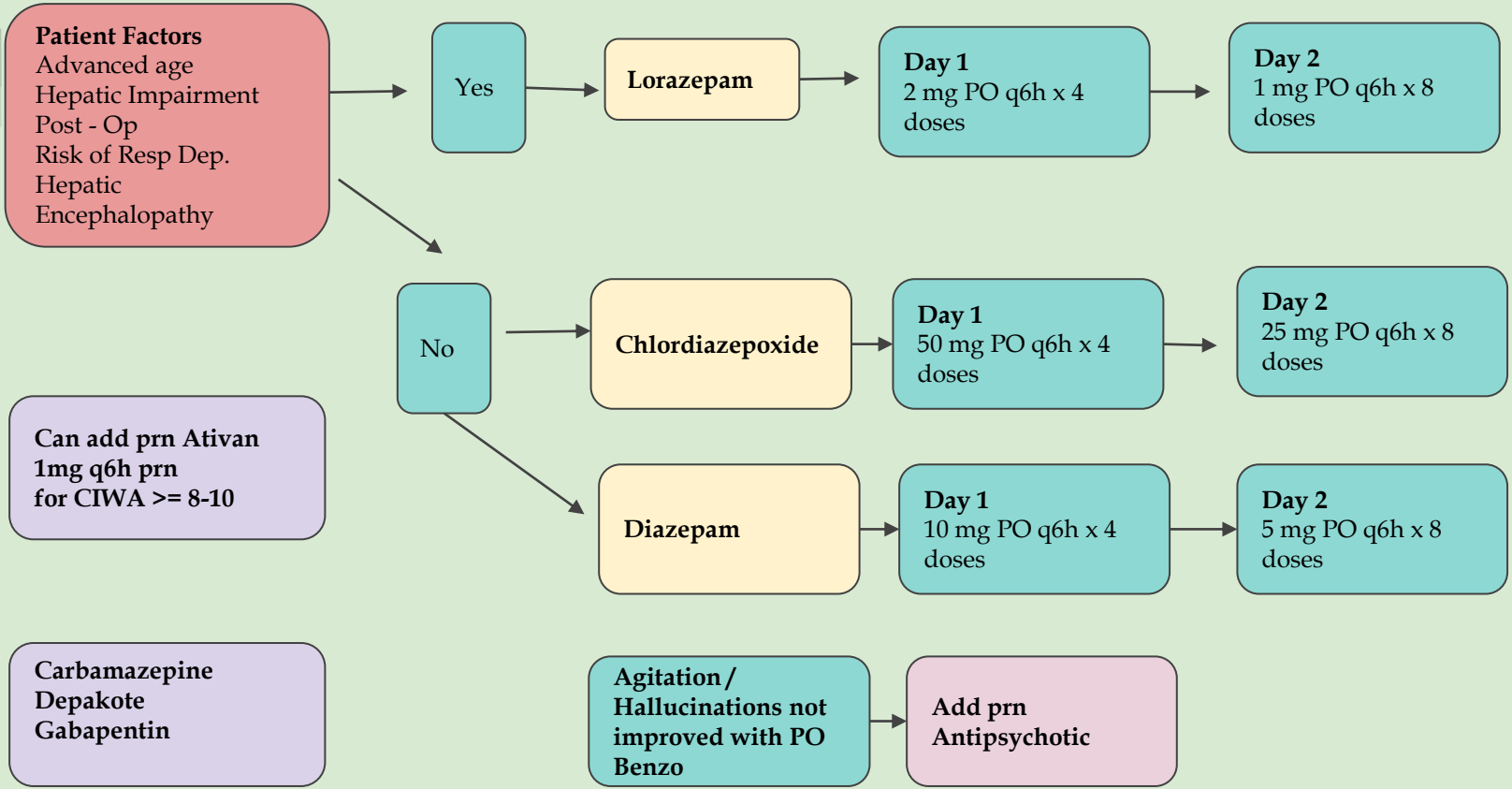
Lack of reliable support network

ICU - Age > 65, Significant cardiac disease, Hemodynamic instability, Marked acid-base disturbances, Severe respiratory disease, Serious infection, Active delirium tremens, Serious GI pathology, Temp > 103 F, Rhabdomyolysis, ARF, IV benzodiazepine drip (Ativan 12+ mg/day)

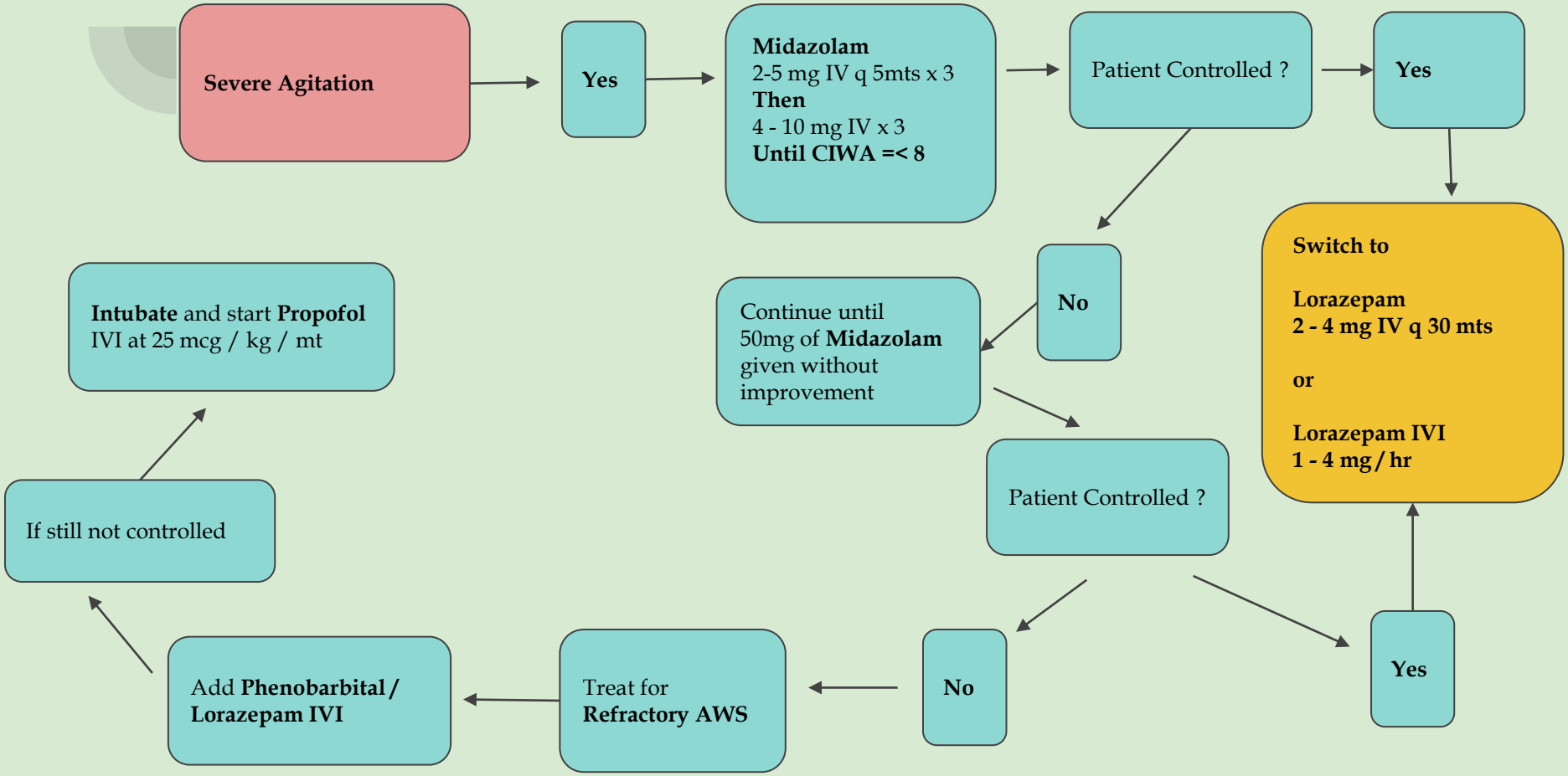
Symptom driven medication regimen



Structured medication regimen



ICU admissions



Benzo Withdrawal Syndrome

An important difference between patients dependent on BZPs as part of their polydrug addiction and those dependent on BZPs for therapeutic purposes, such as panic disorder or a combination of both.

Symptoms of **BZP withdrawal** range from mild to severe and include anxiety, agitation, sleep disturbances, tremor, perceptual disturbances, paranoia, and seizures.

Besides withdrawal, patients discontinuing BZPs can experience recurrence and rebound.

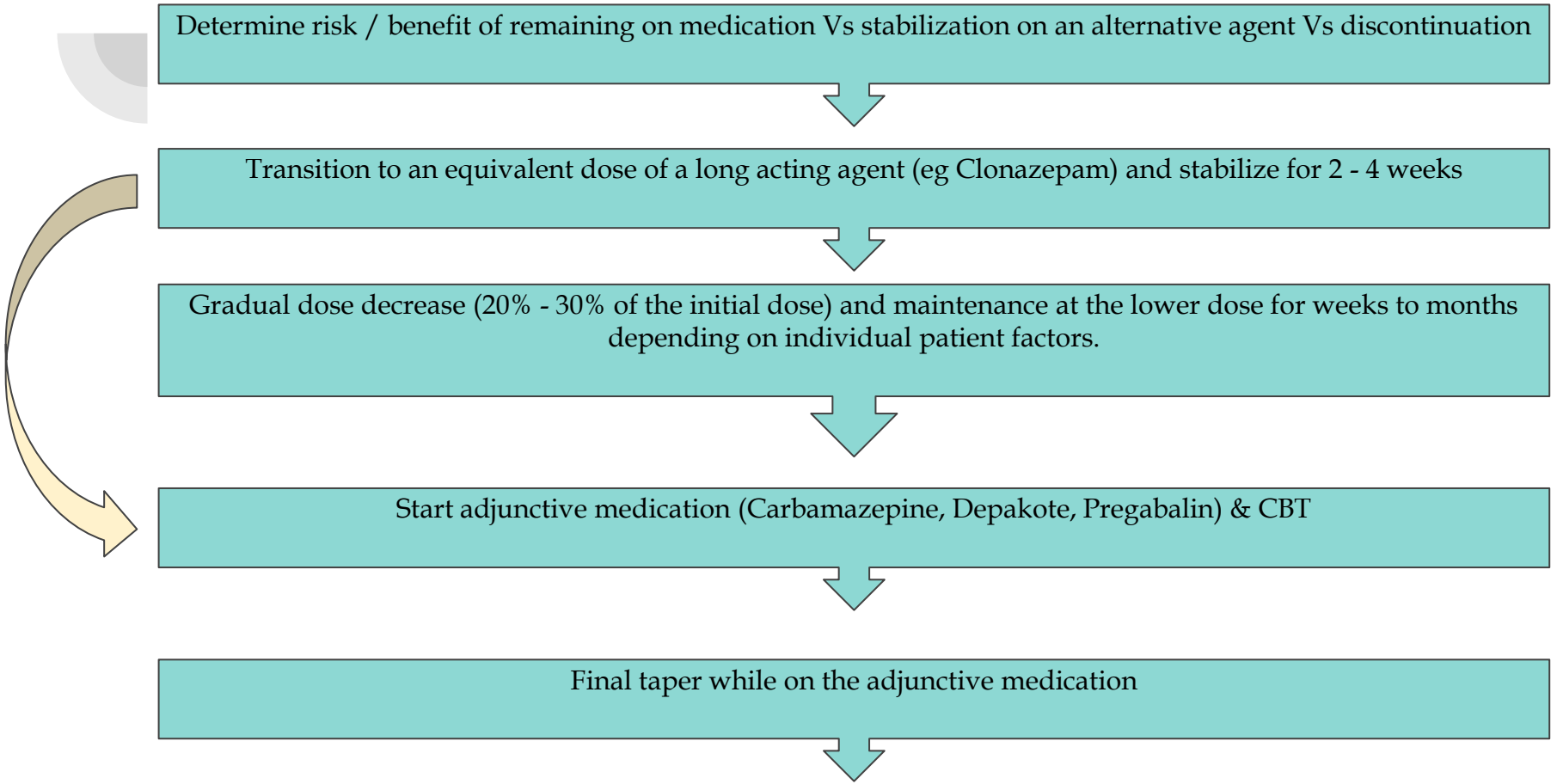
Recurrence is the slow return of the originally targeted psychiatric symptoms for which the patient was receiving BZP treatment. These symptoms may return over weeks or months and should be of no greater intensity than the original symptoms.

Rebound is a syndrome occurring more rapidly than recurrence. Patients with rebound will experience symptoms within hours to days of BZP discontinuation. Although the symptoms are qualitatively similar to the original symptoms, they may be transiently more intense. Both rebound insomnia and rebound anxiety have been well described. Rebound tends to be self-limited and of short duration.

Withdrawal is differentiated from either recurrence or rebound by the prominence of additional autonomic symptoms.

Finally, some authors have described a controversial **protracted withdrawal syndrome** that may cause mild autonomic and subjective distress over several weeks or months

Sedative Hypnotic Detox



REFERENCES

1. GBD 2016 Alcohol Collaborators. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 2018; 392:1015.
2. Kosten TR, O'Connor PG. Management of drug and alcohol withdrawal. N Engl J Med 2003; 348:1786.
3. Wood E, Albargouni L, Tkachuk S, et al. Will This Hospitalized Patient Develop Severe Alcohol Withdrawal Syndrome?: The Rational Clinical Examination Systematic Review. JAMA 2018; 320:825.
4. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse. Withdrawal and treatment. Med Clin North Am 1997; 81:881.
5. Grzywacz A, Jasiewicz A, Mateckaj, et al. Influence of DRD2 and ANKK1 polymorphisms on the manifestation of withdrawal syndrome symptoms in alcohol addiction. Pharmacol Rep 2012; 64:1126.
6. ISBELL H, FRASER HF, WIKLER A, et al. An experimental study of the etiology of rum fits and delirium tremens. Q J Stud Alcohol 1955; 16:1.
7. Mihic SJ, Ye Q, Wick MJ, et al. Sites of alcohol and volatile anaesthetic action on GABA(A) and glycine receptors. Nature 1997; 389:385.
8. Morrow AL, Suzdak PD, Karanian JW, Paul SM. Chronic ethanol administration alters gamma-aminobutyric acid, pentobarbital and ethanol-mediated 36Cl- uptake in cerebral cortical synaptoneurosomes. J Pharmacol Exp Ther 1988; 246:158.
9. Hoffman PL, Grant KA, Snell LD, et al. NMDA receptors: role in ethanol withdrawal seizures. Ann N Y Acad Sci 1992; 654:52.
10. Tsai G, Gastfriend DR, Coyle JT. The glutamatergic basis of human alcoholism. Am J Psychiatry 1995; 152:332.
11. Laine TP, Ahonen A, Torniainen P, et al. Dopamine transporters increase in human brain after alcohol withdrawal. Mol Psychiatry 1999; 4:189.
12. Etherington JM. Emergency management of acute alcohol problems. Part 1: Uncomplicated withdrawal. Can Fam Physician 1996; 42:2186.
13. Victor M, Brausch C. The role of abstinence in the genesis of alcoholic epilepsy. Epilepsia 1967; 8:1.
14. Alldredge BK, Lowenstein DH, Simon RP. Placebo-controlled trial of intravenous diphenylhydantoin for short-term treatment of alcohol withdrawal seizures. Am J Med 1989; 87:645.
15. Chance JF. Emergency department treatment of alcohol withdrawal seizures with phenytoin. Ann Emerg Med 1991; 20:520.
16. Rathlev NK, D'Onofrio G, Fish SS, et al. The lack of efficacy of phenytoin in the prevention of recurrent alcohol-related seizures. Ann Emerg Med 1994; 23:513.
17. VICTOR M, ADAMS RD. The effect of alcohol on the nervous system. Res Publ Assoc Res Nerv Ment Dis 1953; 32:526.
18. Abraham E, Shoemaker WC, McCartney SF. Cardiorespiratory patterns in severe delirium tremens. Arch Intern Med 1985; 145:1057.
19. Berglund M, Risberg J. Regional cerebral blood flow during alcohol withdrawal related to consumption and clinical symptomatology. Acta Neurol Scand Suppl 1977; 64:480.
20. Elisaf M, Liberopoulos E, Bairaktari E, Siamopoulos K. Hypokalaemia in alcoholic patients. Drug Alcohol Rev 2002; 21:73.
21. Wadstein J, Skude G. Does hypokalaemia precede delirium tremens? Lancet 1978; 2:549.
22. Victor M. The role of hypomagnesemia and respiratory alkalosis in the genesis of alcohol-withdrawal symptoms. Ann N Y Acad Sci 1973; 215:235.
23. Ferguson JA, Suelzer CJ, Eckert GJ, et al. Risk factors for delirium tremens development. J Gen Intern Med 1996; 11:410.
24. Cushman P Jr. Delirium tremens. Update on an old disorder. Postgrad Med 1987; 82:117.
25. Schuckit MA, Tipp JE, Reich T, et al. The histories of withdrawal convulsions and delirium tremens in 1648 alcohol dependent subjects. Addiction 1995; 90:1335.
26. Maldonado JR, Sher Y, Ashouri JF, et al. 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 2014; 48:375.
27. Maldonado JR, Sher Y, Das S, et al. Prospective Validation Study of the Prediction of Alcohol Withdrawal Severity Scale (PAWSS) in Medically Ill Inpatients: A New Scale for the Prediction of Complicated Alcohol Withdrawal Syndrome. Alcohol Alcohol 2015; 50:509.
28. Turner RC, Lichstein PR, Peden JG Jr, et al. Alcohol withdrawal syndromes: a review of pathophysiology, clinical presentation, and treatment. J Gen Intern Med 1989; 4:432.
29. DeBellis R, Smith BS, Choi S, Malloy M. Management of delirium tremens. J Intensive Care Med 2005; 20:164.
30. Pristach CA, Smith CM, Whitney RB. Alcohol withdrawal syndromes - prediction from detailed medical and drinking histories. Drug Alcohol Depend 1983; 11:177.
31. Boston, LN. Alcohol withdrawal. Lancet 1908; 1:18.
32. Yost DA. Alcohol withdrawal syndrome. Am Fam Physician 1996; 54:657.
33. TAVEL ME, DAVIDSON W, BATTERTON TD. A critical analysis of mortality associated with delirium tremens. Review of 39 fatalities in a 9-year period. Am J Med Sci 1961; 242:18.
34. Mayo-Smith MF, Beecher LH, Fischer TL, et al. Management of alcohol withdrawal delirium. An evidence-based practice guideline. Arch Intern Med 2004; 164:1405.
35. Hecksel KA, Bostwick JM, Jaeger TM, Cha SS. Inappropriate use of symptom-triggered therapy for alcohol withdrawal in the general hospital. Mayo Clin Proc 2008; 83:274.
36. Hack JB, Hoffman RS. Thiamine before glucose to prevent Wernicke encephalopathy: examining the conventional wisdom. JAMA 1998; 279:583.
37. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. JAMA 1995; 274:562.

REFERENCES

38. Hoffman RS, Goldfrank LR. Ethanol-associated metabolic disorders. Emerg Med Clin North Am 1989; 7:943.
39. Mayo-Smith MF. Pharmacological management of alcohol withdrawal. A meta-analysis and evidence-based practice guideline. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal. JAMA 1997; 278:144.
40. Amato L, Minozzi S, Vecchi S, Davoli M. Benzodiazepines for alcohol withdrawal. Cochrane Database Syst Rev 2010; :CD005063.
41. Amato L, Minozzi S, Davoli M. Efficacy and safety of pharmacological interventions for the treatment of the Alcohol Withdrawal Syndrome. Cochrane Database Syst Rev 2011; :CD008537.
42. Schmidt KJ, Doshi MR, Holzhausen JM, et al. Treatment of Severe Alcohol Withdrawal. Ann Pharmacother 2016; 50:389.
43. Bird RD, Makela EH. Alcohol withdrawal: what is the benzodiazepine of choice? Ann Pharmacother 1994; 28:67.
44. Saitz R, Mayo-Smith MF, Roberts MS, et al. Individualized treatment for alcohol withdrawal. A randomized double-blind controlled trial. JAMA 1994; 272:519.
45. Jaeger TM, Lohr RH, Pankratz VS. Symptom-triggered therapy for alcohol withdrawal syndrome in medical inpatients. Mayo Clin Proc 2001; 76:695.
46. Daeppen JB, Gache P, Landry U, et al. Symptom-triggered vs fixed-schedule doses of benzodiazepine for alcohol withdrawal: a randomized treatment trial. Arch Intern Med 2002; 162:1117.
47. Cassidy EM, O'Sullivan I, Bradshaw P, et al. Symptom-triggered benzodiazepine therapy for alcohol withdrawal syndrome in the emergency department: a comparison with the standard fixed dose benzodiazepine regimen. Emerg Med J 2012; 29:802.
48. Sullivan JT, Sykora K, Schneiderman J, et al. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). Br J Addict 1989; 84:1353.
49. Spies CD, Otter HE, Hüske B, et al. Alcohol withdrawal severity is decreased by symptom-orientated adjusted bolus therapy in the ICU. Intensive Care Med 2003; 29:2230.
50. Cagetti E, Liang J, Spigelman I, Olsen RW. Withdrawal from chronic intermittent ethanol treatment changes subunit composition, reduces synaptic function, and decreases behavioral responses to positive allosteric modulators of GABAA receptors. Mol Pharmacol 2003; 63:53.
51. Nolop KB, Natow A. Unprecedented sedative requirements during delirium tremens. Crit Care Med 1985; 13:246.
52. Hack JB, Hoffmann RS, Nelson LS. Resistant alcohol withdrawal: does an unexpectedly large sedative requirement identify these patients early? J Med Toxicol 2006; 2:55.
53. Ma Y, Thomas MC, Laskey CS, et al. Current Practice Patterns in the Management Of Alcohol Withdrawal Syndrome. P T 2018; 43:158.
54. Rosenson J, Clements C, Simon B, et al. Phenobarbital for acute alcohol withdrawal: a prospective randomized double-blind placebo-controlled study. J Emerg Med 2013; 44:592.
55. Riggan MA, Hayman K, Chen BC, Hoffman RS. Regarding "Phenobarbital for Acute Alcohol Withdrawal: A Prospective Randomized Double-Blind Placebo-Controlled Study". J Emerg Med 2016; 50:895.
56. Nguyen TA, Lam SW. Phenobarbital and symptom-triggered lorazepam versus lorazepam alone for severe alcohol withdrawal in the intensive care unit. Alcohol 2020; 82:23.
57. Ibarra F Jr. Single dose phenobarbital in addition to symptom-triggered lorazepam in alcohol withdrawal. Am J Emerg Med 2020; 38:178.
58. Sullivan SM, Dewey BN, Jarrell DH, et al. Comparison of phenobarbital-adjunct versus benzodiazepine-only approach for alcohol withdrawal syndrome in the ED. Am J Emerg Med 2019; 37:1313.
59. Oks M, Cleven KL, Healy L, et al. The Safety and Utility of Phenobarbital Use for the Treatment of Severe Alcohol Withdrawal Syndrome in the Medical Intensive Care Unit. J Intensive Care Med 2018; :885066618783947.
60. McCowan C, Marik P. Refractory delirium tremens treated with propofol: a case series. Crit Care Med 2000; 28:1781.
61. Brotherton AL, Hamilton EP, Kloss HG, Hammond DA. Propofol for Treatment of Refractory Alcohol Withdrawal Syndrome: A Review of the Literature. Pharmacotherapy 2016; 36:433.
62. Tolonen J, Rossinen J, Alho H, Harjola VP. Dexmedetomidine in addition to benzodiazepine-based sedation in patients with alcohol withdrawal delirium. Eur J Emerg Med 2013; 20:425.
63. Hodges B, Mazur JE. Intravenous ethanol for the treatment of alcohol withdrawal syndrome in critically ill patients. Pharmacotherapy 2004; 24:1578.
64. Blum K, Eubanks JD, Wallace JE, Hamilton H. Enhancement of alcohol withdrawal convulsions in mice by haloperidol. Clin Toxicol 1976; 9:427.
65. Minozzi S, Amato L, Vecchi S, Davoli M. Anticonvulsants for alcohol withdrawal. Cochrane Database Syst Rev 2010; :CD005064.
66. Woods AD, Giometti R, Weeks SM. The use of dexmedetomidine as an adjuvant to benzodiazepine-based therapy to decrease the severity of delirium in alcohol withdrawal in adult intensive care unit patients: a systematic review. JBI Database System Rev Implement Rep 2015; 13:224.
67. Crispo AL, Daley MJ, Pepin JL, et al. Comparison of clinical outcomes in nonintubated patients with severe alcohol withdrawal syndrome treated with continuous-infusion sedatives: dexmedetomidine versus benzodiazepines. Pharmacotherapy 2014; 34:910.
68. Colombo G, Serra S, Brunetti G, et al. Suppression by baclofen of alcohol deprivation effect in Sardinian alcohol-preferring (sP) rats. Drug Alcohol Depend 2003; 70:105.
69. Addolorato G, Caputo F, Capristo E, et al. Rapid suppression of alcohol withdrawal syndrome by baclofen. Am J Med 2002; 112:226.
70. Addolorato G, Leggio L, Abenavoli L, et al. Baclofen in the treatment of alcohol withdrawal syndrome: a comparative study vs diazepam. Am J Med 2006; 119:276.e13.
71. Liu J, Wang LN. Baclofen for alcohol withdrawal. Cochrane Database Syst Rev 2017; 8:CD008502.