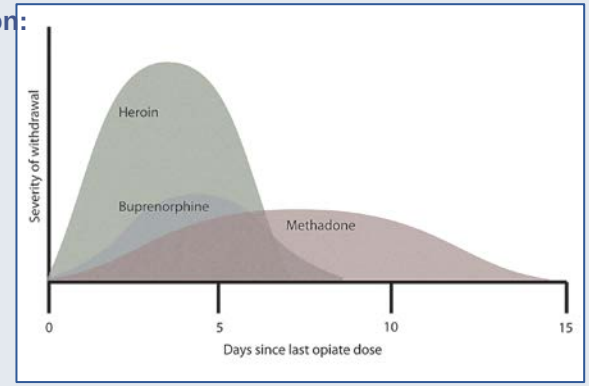
Nutritional Supplementation

- All pts need **thiamine (B_1) 100mg daily** (and potentially **500mg QD**) for a minimum of **5d** and must be given **before glucose** containing fluids to avoid **Wernicke syndrome**
- All pts should get **folate 1mg BID;** pts may also be deficient in **pyridoxine (B_6)**
- All pts should get **magnesium 2-4 mEq/kg IV day 1 and 0.5 mEq/kg IV or PO days 2-4** regardless of admission magnesium level since it is a cofactor for thiamine metabolism
- **Niacin (B_3)** absorption may be impaired, leading to **pellagra** – the clinical picture includes the three "D's" – **diarrhea, dementia, and dermatitis** – treat with **niacin 100-300mg PO TID (or extended release niacin 500mg QD) for 3-4 wks** – *Cresce, Clev Clin, 2014*

Heroin and Opiate Withdrawal

Clinical Presentation:

- It is said that opioid withdrawal syndrome resembles a severe case of influenza with rhinorrhea, anorexia, nausea, vomiting, and diarrhea.
- The onset and duration of symptoms depend upon the drug of abuse (see figure).



Treatment:

- Substitution of a long-acting, oral opioid such as **methadone** is preferred approach. Typically start at **20-35mg daily**. – *Kosten, NEJM, 2003*
- Pts whose **methadone dose is reduced each week by 3 percent** of the initial dose are less likely to drop out or experience severe symptoms than pts titrated at 10 percent per week – *Senay, Arch Gen Psych, 1977*
- **Clonidine** decreases neuronal activity at adrenergic autoreceptors and reduces withdrawal symptoms. For heroin withdrawal, start clonidine at a dose of **0.1-0.2 mg Q4 hrs**, begin taper on day 3 and taper over 10d (taper over 14d for methadone withdrawal).

Cocaine and Amphetamine Withdrawal

Clinical Presentation:

- Typical symptoms include dysphoria with insomnia, anorexia, and motor disturbances similar to depressive disorders.
- Severe withdrawal symptoms can last up to 48 hours; more mild symptoms tend to last up to 2 weeks

Treatment:

- Although no meds have shown efficacy in reducing the severity of withdrawal sx, longer acting benzodiazepines such as **chlordiazepoxide** used in the **first 48 hours** may reduce severity drug toxicity
- Treating more severe cocaine withdrawal symptoms with **propranolol 100mg QD** may improve treatment retention. – *Kampman, Alc Dep, 2001*

Withdrawal and Toxicity

Alcohol Withdrawal

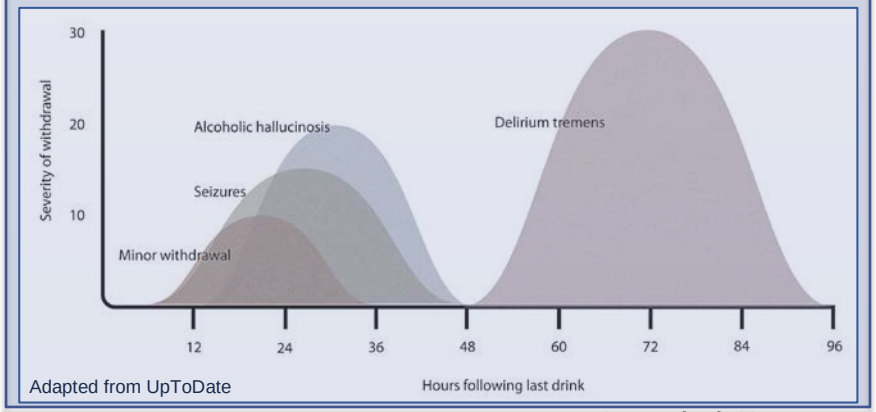
General Considerations:

A structured approach should be adopted when evaluating patients suspected of substance abuse including alcohol abuse – consider the following questions during the evaluation:

1. **Timing: where in the withdrawal process is the patient?** The time of the last drink in conjunction with a blood alcohol level can provide an estimated timeline
2. **Severity: how severe is the withdrawal syndrome likely to be?** The predicted severity is based upon a) withdrawal symptom scores, b) symptoms in relationship to timing of last drink and BAL, c) a history of withdrawal seizures or seizure disorder
3. **Seizures: how likely is the patient to experience seizures?** This is based on a documented history of prior seizures or presence of seizure disorder
4. **Other substances: what co-occurring withdrawal syndromes are likely present?** Other substances may contribute to a confusing clinical picture if not identified
5. **Complications: what complications of withdrawal will require treatment?** Common issues include arrhythmias, electrolyte derangement, malnourishment, and hypertension

Understanding the Timeline

- In an observational study of admitted medical and surgical patients, for those patients without sx at time of admission, **median time to onset of sx following *admission* was 5 hrs**; **90% had sx within 20 hrs**; nearly all had sx within 40 hrs; all sx had resolved in 99% of pts within 120 hrs – *Foy et al, QJM, 1997*
- **Minor withdrawal** includes tremulousness, anxiety, diaphoresis, and GI upset
- **Alcoholic hallucinosis** tend to be short lived – sx include visual, auditory, or tactile hallucinations – median time of onset approx 20 hrs following admission; median duration approx 6 hrs; 90% had resolved within 48 hrs
- **Delirium of delirium tremens** is more variable – sx include confusion, tachycardia, hypertension, agitation, fever, diaphoresis – median time of onset approx 48 hrs following admission; median duration 24 hrs; 90% had resolved within 100 hrs
- It can be challenging to estimate time since last drink – hence the reason observational studies measure from time of admission – **measurement of blood alcohol level** can provide useful information, particularly if the BAL is zero – *Claassen, CNS Drugs, 1999*



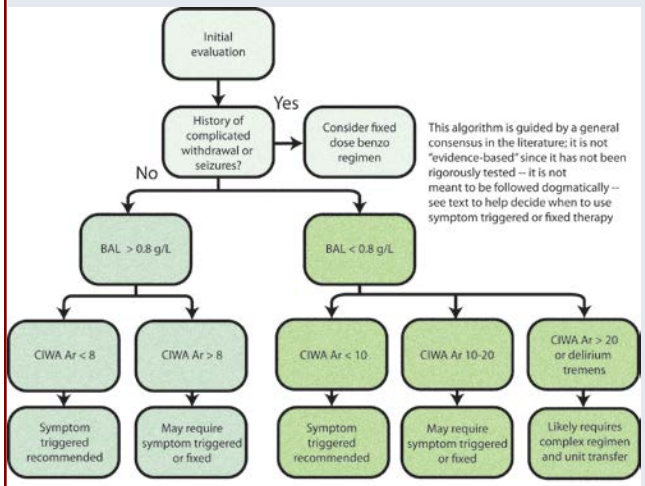
Adapted from UpToDate

Risk Stratification

- To **assess withdrawal risk**, consider application of a standardized screening instrument. The **Alcohol Use Disorders Identification Test (AUDIT)** and the condensed 3 item version (AUDIT-C) are practical, valid screening tests – *Bush, Arch IM, 1998*
- To assess **likelihood of seizures**, look for documented reports of prior seizure activity
- To **estimate severity of withdrawal**, a validated tool should be applied to guide administration of medications and help with triage – the best validated tool is the **Clinical Institute Withdrawal Assessment for Alcohol (CIWA-A)** symptom scale and the 10 item revised scale (**CIWA-Ar**) –*it should be noted that the CIWA has not been well validated in acutely ill medical and surgical populations (as opposed to detoxification units) – hence, it should not be reflexively adopted without considering alternative causes of delirium and tailoring tx for patients with higher seizure risk*
- Scores **< 8** suggest mild withdrawal; scores **> 8** should be receiving medication; scores **> 15** suggest increased risk for seizures; scores **> 20** may require ICU level monitoring

Clinical Institute Withdrawal Assessment for Alcohol (CIWA-Ar)

Category	Range of Scores	Examples
Agitation	0-7	0 = normal activity 7 = constantly thrashing
Anxiety	0-7	0 = no anxiety, at ease 7 = acute panic states
Auditory disturbances	0-7	0 = not present 7 = continuous hallucinations
Clouding of sensorium	0-4	0 = oriented, can do serial additions 4 = disoriented as to place, person, or both
Headache	0-7	0 = not present 7 = extremely severe
Nausea or vomiting	0-7	0 = no nausea or vomiting 7 = constant nausea, vomiting or dry heaves
Paroxysmal sweats	0-7	0 = no sweat visible 7 = drenching sweats
Tactile disturbances	0-7	0 = none 7 = continuous hallucinations
Tremor	0-7	0 = no tremor 7 = severe, even with arms not extended
Visual disturbances	0-7	0 = not present 7 = continuous hallucinations



Adapted from Classen et al, CNS Drugs, 1999; Holbrook et al, CMAJ, 1999; Asplund et al, JFP, 2004

Symptom-triggered therapy is a reasonable "go-to" strategy and is generally favored in the elderly and most medical/surgical patients with co-morbidities unless there is a documented history of severe or complicated withdrawal (including seizures) – this helps avoid unneeded medication, prolonged sedation, falls, and functional impairment – *Kraemer, Drugs Aging, 1999*

Patients requiring IV therapy or with difficult to control symptoms or requiring complex pharmacotherapy or that are heavily sedated are **best served in the ICU**

Benzodiazepine Therapy

- Two major reviews of pharmacotherapy for withdrawal (11 trials) concluded **benzodiazepines are the treatment of choice**. They are likely effective due to cross-tolerance with EtOH at the type A gamma-amionbutyric acid receptor. – *Mayo-Smith, JAMA, 1997; Lejoyeux, Alcohol, 1998; Kosten, NEJM, 2003; Amato, Cochrane Review, 2011; Mayo-Smith, Arch IM, 2004*
- Dosing can be given in a "**fixed-dose**" or "**symptom-triggered**" manner. With fixed dose, a set dose of medication is given at regular intervals. The advantage of fixed dosing is that medication is always delivered to those requiring it (e.g., pts with past history of withdrawal seizure). With symptom triggered dosing, the timing and dose of medication is based upon a symptom score using a standardized instrument such as the **(CIWA)** scale. The benefit of sx-triggered dosing is that pts tend not to get oversedated, typically require less drug, and enjoy a shorter length of stay – *Saitz, JAMA, 1994; Daeppen, Arch IM, 2002; Kraemer, Drugs Aging, 1999*
- Symptom-triggered therapy has shown to be superior in patients on chemical-dependence wards without comorbid illness (two double-blind RCTs); **it has NOT been well-studied in general acute medical populations** (only one quasi-randomized non-blinded study on a GIM ward) and **has NOT been as well studied in patients with a history of severe withdrawal or prior seizures**; for this reason, it is important to recognize that efficacy data is limited in a complex medical population and the appropriateness of the regimen should take into consideration a) the current condition/withdrawal state of the patient, b) the likelihood of withdrawal seizures, and c) the age and clearance ability of the patient – *Saitz, JAMA, 1994; Daeppen, Arch IM, 2002; Weaver, Addictive Dis, 2006*
- The CIWA scoring system is typically paired with the **Sedation-Agitation Scale (SAS)** to track level of anxiolytic-induced sedation - the goal is to calm or lightly sedate the patient (i.e., patient should be easily arousable but should drift off if left undisturbed (1 = unarousable; 7 = dangerously agitated; 3-4 = goal)
- Most benzos are reasonable for mgt – diazepam, chlordiazepoxide, and lorazepam appear to be equally efficacious – **longer acting agents** tend to reduce incidence of seizures and "smooth" withdrawal – **shorter acting agents** are more appropriate for pts > 70y or with cirrhosis – *Kosten, NEJM, 2003; Asplund, J Fam Prac, 2004; Kraemer, Drugs Aging, 1999; Mayo-Smith, Arch IM, 2004*

Benzodiazepine	Dose Equivalency	Time to onset	Peak activity	Half-Life	Suggested schedule (see text above for details regarding tx regimens)
Lorazepam	1 mg	20-30 min	60-90 min	10-20 hrs	2-4 mg Q6 hrs x 4 doses, then 1-2mg Q6 hrs x 8 doses
Chlordiazepoxide	25 mg	20-30 min	60-120 min	10-30 hrs	50-100mg Q6 hrs x 4 doses, then 25-50mg Q6 hrs x 8 dose
Diazepam	5 mg	15-30 min	60-120 min	20-80 hrs	10-20mg Q6 hrs x 4 doses, then 5-10mg Q6 hrs x 8 doses

Adjunctive Therapy

- Although treatments other than benzos may be useful as adjuvants, they are often **unsuitable if used alone** during withdrawal and have **relatively limited outcomes data** to support routine use
- **Haloperidol** may reduce signs and symptoms of withdrawal but is less effective than benzodiazepines in preventing delirium or seizures – although it can reduce agitation, it can also decrease sz threshold; a reasonable strategy is to combine with benzos (e.g., 2mg lorazepam + 5mg haloperidol) for DT-related agitation since the benzodiazepine should protect against seizure activity – *Palestine, Curr Ther Res, 1976; Kraemer, Drugs Aging, 1999; Claassen, CNS Drugs, 1999*
- **Beta-blockers** reduce autonomic manifestations of withdrawal and (insert Gil Perot data here). However, they do not have anticonvulsant activity and they may mask signs of early withdrawal
- **Clonidine** may ameliorate symptoms in pts with mild-to-moderate withdrawal and may be considered in pts with co-morbid CAD and significant hypertension
- **Carbamazepine** has been used successfully for many years in Europe; it has compared favorably to oxazepam in 2 double-blind RCTs; it may be used in 7 day protocols since it reduces emotional distress, has anticonvulsant activity, and prevents withdrawal seizures; it is typically **given as 200mg QID for 48 hours and then tapered by 200mg/day in 48 hr time blocks**; it can be considered in select patients that are less suitable for benzodiazepines; it is contraindicated if liver enzymes are > 2.5 times normal range – *Asplund, J Fam Prac, 2004; Stuppaeck, Alcoh, 1992; Malcolm, Am J Psych, 1989; Chu, Neurology, 1979*