Case

- 48 year old man admitted complaining of hallucinations. Mild hallucinations for a year. Worsened tremor for 3 weeks and then markedly worse hallucinations last 2 days.
  - History of psoriatic arthritis, htn, essential tremor
  - Meds: propranolol, etodolac, etanercept
  - No history of prior psychiatric disease.
Examination

- Hr 80  RR 18  Temp 36.6  BP 125/80
- Chest and cardiovascular exam normal
- Neuro: marked tremor, dysarthria, truncal ataxia with normal finger to nose testing. Oriented to person and place
Hospital Course:
- Patient spent a long time in the ED waiting for a bed
- He started to become agitated
- Needed multiple doses of IV lorazepam and then oral chlordiazepoxide
- Needed to be held down by 2 security guards, 2 EMTs and 3 RNs
- It then became apparent that he was in alcohol withdrawal
- Admitted to internal medicine
- Assessment: Hallucinations / Tremor due to alcohol withdrawal
- Plan:
  - Admitted to ICU
  - B12, ammonia, TSH
  - Alcohol withdrawal protocol (lorazepam)
  - Neurology and psychiatry consults
  - RUQ ultrasound to evaluate elevated LFTs
  - RUQ Ultrasound: Fatty liver
  - B12, ammonia, TSH normal

Hospital Course—Cont’d:
- Agitation increased over next few hours
- Initially given intermittent IV lorazepam with some response then became ineffective
- Became hypertensive, tachycardic
- Lorazepam infusion started, titrated to up to 6mg/hour
- Patient remained tremulous, delirious, barely responding to voice, gurgling airway secretions
- Tachycardic 150s-160s
- Hypertensive 170s systolic
- It had been ~15 hours since presentation to ED
- Decision made to intubate patient for airway protection and facilitate use of propofol for benzodiazepine-refractory alcohol withdrawal
- Propofol infusion started and lorazepam infusion continued
- Hospital Day #2: Febrile 38.9 C, tachycardic 120s, BP improved
- Dx remained alcohol withdrawal (delirium tremens)
Subsequent Course

- 12 days on ventilator
  - Complicated by MSSA pneumonia
- 22 days on IV lorazepam
- Subsequently transferred to psychiatry; needed antipsychotic medications for hallucinations
- Had some benzodiazepine withdrawal on psychiatry
- Discharged to chem dep facility after 38 days.
Alcohol Withdrawal

Hospitalist Case conference
21 May, 2009
William Dickey MD
Alcohol Withdrawal
Why talk about it?

- Work on a new ICU alcohol withdrawal order set
- Maybe things not going so well
  - Frequent lorazepam infusions
  - No charting of assessments when meds administered
  - Lots of dogmatic pronouncements about what is best.
  - No subspecialist to punt to
DSM IV Definition

- Cessation of prolonged or heavy EtOH use
- 2 or more of following: autonomic hyperactivity, increased hand tremor, insomnia, visual tactile or auditory hallucinations, nausea and vomiting, psychomotor agitation, anxiety and grand mal seizures
DSM IV Definition

- Symptoms from #2 causing significant distress or impairment
- Symptoms not resulting from a general medical condition or not better accounted for by another mental disorder.
Time frame: A review

- 24
- 48
- 72
- 96

- | Tremors
- | Irritability
- | Seizures
- | Hallucinosis
- | Delirium, disoriented

- Autonomic activity increases 1st 5 days
Time Frame

- Withdrawal seizures—within 2-24 hours from last drink (3% of alcoholics and 3% of those get status)
- Minor withdrawal symptoms (6-24 hours resolve by 48 hours) anxiety, headache, nausea, GI upset.
- Alcoholic hallucinosis (onset 12-24 resolved by 24-48 hrs after last drink). Rare—hallucinations without altered sensorium or delirium.
Time Frame

- Alcohol Withdrawal/Delirium tremens, onset 48-96 hours after last drink with duration 1-5 days typical.
- Delirium (acute onset and fluctuating course, inattention and either disordered thinking or altered level of consciousness).
Delirium tremens

- A delirium with all the features, developing in context of alcohol withdrawal and with signs of autonomic hyperactivity: fever, tachycardia, diaphoresis.
- As with all delirium, underlying cause is primary; consider differential dx.
- Maybe as much as 5% risk of mortality.
- Hallucinations usually visual
Pathophysiology

- GABA an inhibitory neurotransmitter. In EtOH withdrawal, receptors downregulated and decreased neural activity.

- Increased CSF norepinephrine felt to be due to decreased Alpha2 inhibition of presynaptic norepinephrine release.
Assessment

- CIWA Ar Assessment tool
- RASS tool for patients on ventilator
### Appendix: Clinical Institute Withdrawal Assessment for Alcohol.*

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

*The Clinical Institute Withdrawal Assessment for Alcohol measures 10 categories of symptoms, with a range of scores in each. The maximal score is 67. Minimal-to-mild withdrawal symptoms result in a total score below 8; moderate withdrawal symptoms (marked autonomic arousal), in a total score of 8 to 15; and severe withdrawal symptoms, in a total score of more than 15. High scores are predictive of seizures and delirium.*
CIWA Ar

☐ None to minimal  < 8
☐ Moderate 8-15
☐ Severe 16-67
Are there randomized controlled trials comparing drugs?

- Old studies comparing benzodiazepines and antipsychotics have shown benzodiazepines superior in terms of mortality reduction and seizure prevention.
Treatment

- Most people pretty certain about what is right
- Not a lot of clinical trials
- One guideline paper
- Universal recommendation for benzodiazepines as cornerstone of therapy.
Benzodiazepines
The evidence

- No trials re mortality sedative/hypnotics vs. placebo
- 5 trials re mortality sedative/hypnotics vs antipsychotic agents: metaanalysis 6.6 relative risk of death treated with antipsychotics vs. sedative/hypnotics
- BUT old trials 1959-1972 e.g. chlorpromazine vs paraldehyde
Benzodiazepines: the evidence

- Cochrane review Ntais, C et al. Cochrane Library 2008 Issue 1
  - 57 trials with total of 4051 patients
  - “Benzodiazepines offered a large benefit against alcohol withdrawal seizure compared to placebo.”
  - “Data on other comparisons were very limited, thus making quantitative synthesis for various outcomes not very informative.”
  - No conclusive evidence or even hints of superiority of one benzo over another
  - Nonsignificant benefit in prevention of delirium
Benzodiazepines
The evidence

- No trials showing more benefit from one benzodiazepine compared to another. Most commonly used in US: diazepam, chlordiazepoxide and lorazepam
- No trials comparing intermittent dosing with IV infusion; Some retrospective studies suggest infusion may lead to higher cumulative dose and longer duration of delirium
- Despite this pretty much universal recommendation of benzodiazepines as first choice medications
Antipsychotics

☐ Inferior to benzodiazepines in old studies

☐ Side effects: Seizures, QT prolongation, neuroleptic malignant syndrome

☐ No trials with “atypical” agents
Other Drugs

- Beta blockers not studied and risk of delirium
- No controlled studies of magnesium
- Case studies of alcohol only for prevention
- Small uncontrolled studies of Carbamazepine, other anticonvulsants, clonidine
Definition of Success in improving alcohol withdrawal management

- Mortality? Benchmark in DTs is 1-5% mortality and most studies show lower making comparison difficult
- Avoidance of intubation?
- Symptom control

- Little guidance from literature about strategies to improve any of these
Two strategies to consider

- Symptom triggered therapy
- Rapidly escalating doses to *avoid* intubation
Symptom Triggered Therapy

- CIWA Ar developed in outpatient Detox units.
- Before and after study: benzodiazepines by symptom algorithm
  - No difference in dose; decreased risk of progression to DTs
- That is what is on the order sets
Symptom Triggered Therapy in the ICU


- Retrospective review of symptoms triggered therapy to no protocol
- CIWA not used; they used own scale
- Started with lorazepam boluses but went to infusions if no response to 16mg (sic) IV lorazepam

- Time to adequate therapy reduced
- Total benzodiazepine dose reduced.
Aggressive Dose Escalation


- 54 patients with severe alcohol withdrawal

  - IV diazepam 10 mg IV with rapid escalation to doses of 100-150 mg per dose until sedation achieved.
  
  - Moved to ICU if they needed either 40 mg doses or 200 mg in 4 hours
Aggressive Dose escalation

- 47% pre and 21% post guideline needed mechanical ventilation—all but one for inadequately controlled agitation rather than respiratory depression

- In cases where >100-200 mg doses of diazepam were needed, phenobarbital was added
Expert opinion

- Benzodiazepines first choice therapy
- Antipsychotic medications as additional therapy controversial
- Phenobarbital or propofol in patients with benzodiazepine resistance.
Lorazepam vs Diazepam

- Rapid onset of action: diazepam or lorazepam beneficial
- Longer duration diazepam smoother control with less breakthrough symptoms—autotitration
- Lorazepam when there is concern about prolonged sedation (age or liver disease)
- Only lorazepam reliable IM
Lorazepam vs Diazepam

- IV lorazepam contains propylene glycol to keep it in solution: can be responsible for hypersosmolarity, anion gap acidosis and renal failure. Recommendation: check osmolarity daily in patients on > 1mg/kg/day lorazepam
Examples of dosing for Severe withdrawal

- Up to Date: Diazepam 5-10 mg IV every 5 minutes until calm but alert state achieved
- Lohr, RH in [Hospital Medicine]: Diazepam 15-20 mg or lorazepam 3-4 mg reassess every 2 hours
- Mayo-Smith Guideline paper: diazepam dose Q 5-10 minutes: 5,5,10,10, then 20 mg. Or Lorazepam 1-4 mg every 5-15 minutes.
- Some have gone higher
Haloperidol: Expert opinion

- Mayo Smith Haloperidol as adjunct to benzodiazepines: 0.5-5 mg iv every 30-60 minutes
- Lohr not mentioned
- Kosten NEJM review “significantly less effective than benzodiazepines in preventing delirium and seizures”
- Up to Date: “should not be used in the withdrawing alcoholic”
Benzodiazepine-refractory Withdrawal

- Gold et al phenobarbital (patients needing more than 40 mg diazepam in an hour) escalate dose (up to 100-150 mg per dose) and if still refractory add IV phenobarbital or propofol
Other Medications

- Clonidine or beta blockers primarily for effects on vital signs
- Obviously thiamine and other nutritional supports (check PO4)
- Some support for baclofen
Summary

- There is much certainty and dogma about management but not a lot of controlled trials
- Benzodiazepines cornerstone of therapy
- Lorazepam a good choice in liver disease or the elderly, but in others there may be reason to push practice toward diazepam
Summary

- Massive doses of benzodiazepines may be necessary in severe withdrawal
- Antipsychotics only as adjunct to benzodiazepines and even there, quite controversial
- Consider phenobarbital or propofol with consultation for benzodiazepine refractory withdrawal
Summary

- Symptom triggered therapy may lead to shorter duration than scheduled doses or infusions.
- Nutritional supports particularly thiamine and PO4 and consider other diagnoses in differential as cause of delirium.
References


References
