Management of Unhealthy Alcohol Use: From Research to Practice

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Opportunities to discuss alcohol with patients and/or trainees

- Esophageal cancer
- Chronic pancreatitis
- Cirrhosis and chronic hepatitis
- Lip, oral cavity, pharynx, larynx cancer
- Acute pancreatitis
- Pulmonary tuberculosis
- Hepatic neoplasm
- Esophageal, stomach, duodenal diseases
- Hypertension
- Cerebrovascular disease
- Medication interactions
- Renal failure
- Medical conditions worsening
- Fetal harm
- Cirrhosis
- Alcoholism
- Atrial fibrillation (holiday heart)
- Cardiomyopathy
- Hypertension
- Nutritional
- Malnutrition
- Thiamine and folate deficiency
- Endocrine/Metabolic
- Osteoporosis
- Magnesium, calcium, potassium, phosphorus
- Hypo- and hyperglycemia
- Acidoses (primary and secondary, due to ingestions)
- Impaired fertility (men and women) and sexual function
- Anemia (folate, toxic, iron, chronic disease, hemolysis)
- Pancytopenia
- Coagulopathy
- Hepatitis
- Toxic (alcohol, acetaminophen)
- Cirrhosis
- Ascites and edema
- Coagulopathy and bleeding
- Spontaneous bacterial peritonitis, Encephalopathy
- Hepatoma
- Gastrointestinal
- GI bleeding: varices, Mallory-Weiss, gastritis, ulcer, esophagitis, gastritis
- Esophageal stricture, malignancy
- Gastric cancer
- Malabsorption and diarrhea, with or without Pancreatitis (acute and chronic)
- Social problems
- Stroke
- Violent death
- Infertility
- Tremor
- Ecchymosis/purpura
- Palmar erythema
- Scars from trauma
- Gynecomastia
- Hepatomegaly
- Spiders
- Uric acid, glucose
- MCV, AST, HDL, GGT
- Heartburn
- Gastrointestinal upset
- AM cough or HA
- Anxiety, stress
- Insomnia
- Concentration
- Memory
- Tachycardia
- Hypertension
- Apnea
- Impaired gag
- Cough
- Myopathy
- Gout
- Rhabdomyolysis
- Kidney failure
- Pneumonia, lung abscess
- TB
- Central nervous system infection
- Diabetes
- Pneumonia
- Hypokalemia
- Hypomagnesemia
- Hypocalcemia
- Intoxication, blackouts, overdose
- Withdrawal seizures
- Head trauma and subdural hematoma
- Sensory, motor or autonomic neuropathy
- Wernicke’s syndrome
- Korsakoff’s (amnestic) syndrome
- Cerebellar degeneration
- Stroke (hemorrhagic, ischemic)
- Marchiafava-Bignami (corpus callosum)
- Confusion, language, dementia, seizures
- Breast cancer
- Depression
A 43 year old man presents because he bumped his head after slipping and falling. No loss of consciousness.
Breath alcohol is 210 mg/dL (0.21 g/100mL).
He reports no hematemesis, hematochezia, melena, tremors, past seizures, liver disease, gastrointestinal bleeding, pancreatitis or delirium.
He lives alone and reports drinking all day since he became disabled from lumbar disc disease ten years ago. He takes no medications, has no allergies, and smokes one pack of cigarettes daily.

T 98, RR 18, HR 110 (regular), BP 136/82 standing, 100, 140/70 lying down.
Unable to visualize fundi, EOMI, supple neck, clear chest, no murmur, no tremor; frontal ecchymosis.
He is awake, alert and oriented to place, time and person. Speech is fluent. Gait normal. Sensorimotor exam non-focal.
The patient is seen having a generalized tonic-clonic convulsion.

- What is the most likely etiology?
- What is the appropriate work-up?
ALCOHOL WITHDRAWAL SEIZURES

- Recurrent detox and prior seizure are risk factors
- Generalized, single or a few (79% <3, <3% status), over a short time (86%/1st 6 hrs)
- Fever, delirium, focal exam, head trauma, focal or multiple seizures, 1st seizure ever, or status suggest other diagnoses
- CT scanning unhelpful if clinical picture consistent
LORAZEPAM PREVENTS RECURRENCE

• 186 subjects with alcohol withdrawal seizures
• RPCDBT
• 2 mg of lorazepam IV
• Also decreased hospital admission

D’Onofrio G et al New Engl J Med
Four hours later (15-20 mg/dL/hr [1 drink] elimination), the patient becomes tremulous, anxious, and complains of nausea. BP 134/84, HR 90, ethanol level 146 mg/dl.

- What is the diagnosis?
- What is appropriate management?
DSM-5 ALCOHOL WITHDRAWAL DEFINITION

• Cessation or reduction in alcohol use that has been heavy and prolonged
• Two or more of the following, developing in hours to days, causing distress or impairment, not due to other condition
  – Autonomic hyperactivity (sweating, tachycardia)
  – Increased hand tremor
  – Insomnia
  – Nausea or vomiting
  – Transient tactile, visual or auditory hallucinations or illusions
  – Psychomotor agitation
  – Anxiety
  – Generalized tonic-clonic seizures
Benzodiazepines reduce seizures

ANY 1/188 (0.5%)
Placebo 16/201 (8%)

RRR 93%, p<0.001

Benzodiazepines reduce delirium

Chlordiazepoxide 3/172 (2%)
Placebo 11/186 (6%)

RRR 71%, p=0.04

Rosenfeld 1961, Sereny 1965, Kaim 1969, Zilm 1980,
summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51
He did predictably suffer from delirium tremens. This was quelled with p.o. alcohol.
**Nausea and vomiting.** Ask “Do you feel sick to your stomach? Have you vomited?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—No nausea and no vomiting</th>
<th>1—Mild nausea with no vomiting</th>
<th>2—</th>
<th>3—</th>
<th>4—Intermittent nausea with dry heaves</th>
<th>5—</th>
<th>6—</th>
<th>7—Constant nausea, frequent dry heaves, and vomiting</th>
</tr>
</thead>
</table>

**Tremor.** Ask patient to extend arms and spread fingers apart.

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—No tremor</th>
<th>1—Tremor not visible but can be felt, fingertip to fingertip</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderate tremor with arms extended</th>
<th>5—</th>
<th>6—</th>
<th>7—Severe tremor, even with arms not extended</th>
</tr>
</thead>
</table>

**Paroxysmal sweats**

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—No sweat visible</th>
<th>1—Barely perceptible sweating; palms moist</th>
<th>2—</th>
<th>3—</th>
<th>4—Beads of sweat obvious on forehead</th>
<th>5—</th>
<th>6—</th>
<th>7—Drenching sweats</th>
</tr>
</thead>
</table>

**Anxiety.** Ask “Do you feel nervous?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—No anxiety (at ease)</th>
<th>1—Mildly anxious</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderately anxious or guarded, so anxiety is inferred</th>
<th>5—</th>
<th>6—</th>
<th>7—Equivalent to acute panic states as occur in severe delirium or acute schizophrenic reactions</th>
</tr>
</thead>
</table>

**Agitation**

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—Normal activity</th>
<th>1—Somewhat more than normal activity</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderately fidgety and restless</th>
<th>5—</th>
<th>6—</th>
<th>7—Paces back and forth during most of the interview or constantly thrashes about</th>
</tr>
</thead>
</table>

**Tactile disturbances.** Ask “Do you have you any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—None</th>
<th>1—Very mild itching, pins-and-needles sensation, burning, or numbness</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderately severe hallucinations</th>
<th>5—</th>
<th>6—</th>
<th>7—Continuous hallucinations</th>
</tr>
</thead>
</table>

**Auditory disturbances.** Ask “Are you more aware of sounds around you? Are they harsh? Do they frighten you? Are you hearing anything that is disturbing to you? Are you hearing things you know are not there?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—Not present</th>
<th>1—Very mild harshness or ability to frighten</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderately severe hallucinations</th>
<th>5—</th>
<th>6—</th>
<th>7—Continuous hallucinations</th>
</tr>
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</table>

**Visual disturbances.** Ask “Does the light appear to be too bright? Is its color different? Does it hurt your eyes? Are you seeing anything that is disturbing to you? Are you seeing things you know are not there?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—Not present</th>
<th>1—Very mild sensitivity</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderately severe hallucinations</th>
<th>5—</th>
<th>6—</th>
<th>7—Continuous hallucinations</th>
</tr>
</thead>
</table>

**Headache, fullness in head.** Ask “Does your head feel different? Does it feel like there is a band around your head?”

Do not rate for dizziness or lightheadedness; otherwise, rate severity.

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—Not present</th>
<th>1—Very mild</th>
<th>2—</th>
<th>3—</th>
<th>4—Moderate</th>
<th>5—</th>
<th>6—</th>
<th>7—Extremely severe</th>
</tr>
</thead>
</table>

**Orientation and clouding of sensorium.** Ask “What day is this? Where are you? Who am I?”

<table>
<thead>
<tr>
<th>Observation:</th>
<th>0—Orientated and can do serial additions</th>
<th>1—Cannot do serial additions or is uncertain about date</th>
<th>2—</th>
<th>3—</th>
<th>4—Date disorientation by more than two calendar days</th>
<th>5—</th>
<th>6—</th>
<th>7—Date disorientation by more than two calendar days</th>
</tr>
</thead>
</table>

**Disorientation for place and/or person**
Decreased Duration of Treatment

Saitz R et al JAMA 1994;272:519-23
American Society of Addiction Medicine Practice Guidelines

- Symptom-triggered (q 1 when CIWA-Ar > 8)
  - Chlordiazepoxide 50-100 mg
  - Diazepam 10-20 mg
  - Lorazepam 2-4 mg

- Fixed schedule (q 6 for 4/8 doses + PRN)
  - Chlordiazepoxide 50 mg/25 mg
  - Diazepam 10 mg/5 mg
  - Lorazepam 2 mg/1 mg

Protocol increased mortality and LOS though decreased ICU transfer


Mayo-Smith and ASAM working group JAMA 1997;278:144-51
The patient tells you he is at the racetrack with his friends, BP 170/100, HR 110, Temp 99.

- What is the diagnosis?
- What if he were febrile?

**DSM-5 DEFINITION: alcohol withdrawal delirium**

A. A disturbance in **attention** (i.e., reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment) and

B. The disturbance develops over a short period of time (usually hours to days), represents a change from baseline attention and awareness, and **fluctuates** in severity during the course of a day

C. An additional disturbance in **cognition** (e.g., memory deficit, disorientation, language, visuospatial ability, or perception)
DTs: Treatment time to light somnolence/adequate control

- N=34, RCT
- Diazepam 10 mg IV then 5mg q 5” vs. paraldehyde 30cc PR q 30” until calm but awake
- All complications in paraldehyde group
  - sudden death (2), apnea (2), brachial plexus injury (2), 3rd floor jump attempt (1), bitten nurse (1), bitten intern (1)
- Diazepam 200 mg mean dose required

Systematic evidence review and practice guideline
Thompson, Maddrey, Osler Medical Housestaff. Ann Int Med 1978;82:175
DT Treatment Trials
Sedative-hypnotics Rx of choice

• Decreased duration of delirium by 22-90 hours
  – 3 of 4 trials; paraldehyde vs. neuroleptics
• Decreased mortality RR 0.15 (95% CI 0.03-0.83)
  – 5 trials (no placebo) vs. neuroleptics; N=386, 1 vs. 8 deaths
• Requirements variable and sometimes high
  – Case reports
    • >2000 mg of diazepam in 2 days
    • 12,424 mg of diazepam, 121 mg of lorazepam, 3,050 mg of chlordiazepoxide, and 2,025 mg of midazolam in 8 weeks
      – “Refractory” DTs—theory=benzodiazepine receptor saturation
      – Pentobarbital; or propofol (GABA and NMDA mechanisms)

Systematic evidence review and practice guideline*
DTs: Recommendation

- **Parenteral benzodiazepines, prefer long-acting**
- **Example regimen:**
  - Diazepam, 5 mg intravenously (2.5 mg/min)
  - If not effective, repeat in 5 to 10“
  - if not satisfactory, use 10 mg for the third and fourth doses
  - if not effective, use 20 mg for the fifth and subsequent doses until sedation
  - Then 5 to 20 mg q 1h PRN to maintain light somnolence
ALCOHOL WITHDRAWAL TRIAGE

• Outpatient
  – Last drink >36 hrs: symptoms unlikely to develop
  – No other risk factors, responsible other

• Consider inpatient
  – Past seizure, drug use, anxiety disorder, multiple detoxifications, alcohol >150 (risks more severe symptoms)

• Inpatient
  – Older age (>60), concurrent acute illness, seizure, moderate to severe symptoms (risks DTs)

• ICU level
  – DTs
MANAGEMENT OF UNHEALTHY ALCOHOL USE: BEYOND WITHDRAWAL

- Detoxification is not treatment
- Brief Intervention
- Treatment
  - Counseling, removal from environment/access
  - Pharmacotherapy
- Self (online, books) and mutual help (e.g. AA, Smart Recovery)
- Manage comorbidity (medical and psychiatric)

CASE

A 53 year old woman drinks $\frac{1}{2}$ to 1 pint of vodka daily and wishes to quit. She has a history of EGD-proven esophagitis, and has had recurrent hematemesis after drinking. She has no current acute medical problem. You are seeing her as an outpatient after hospital discharge. She feels she will drink even though she realizes she will bleed again. She refuses “inpatient rehab.”
PATIENT SELECTION FOR PHARMACOTHERAPY

• All people with moderate to severe alcohol use disorder who are:
  – currently drinking
  – experiencing craving or at risk for return to drinking

• Considerations
  – Specific medication contraindications
  – Psychosocial support/therapy and follow-up
    • Primary care med mgt (O’Malley; Anton, Oslin*) as effective as specialized behavioral therapy**
  – Prescriber, access to monitoring (e.g. visits, liver enzymes)


RCT: naltrexone effective without obligatory therapy
### Prescribing

Neurochemical Circuits Involved in Alcohol Dependence and Craving
Efficacy of Naltrexone


Relapse to heavy drinking

37% vs. 48%
NALTREXONE

- 50 RCTs, 7793 patients
- Heavy drinking NTX RR 0.83 (95% CI 0.76 to 0.90)
- Drinking days, MD -3.89% (95% CI -5.75 to -2.04)
- Heavy drinking days, MD - 3.25 (95% CI -5.51 to -0.99)
- Consumed amount of alcohol, MD - 10.83 (95% CI -19.69 to -1.97)
- GGT, MD - 10.37 (95% CI -18.99 to -1.75)
- Any drinking, RR 0.96 (95 CI 0.92 to 1.00)
- Side effects—GI (e.g. nausea: RD 0.10; 95% CI 0.07 to 0.13) and sedative effects (e.g. daytime sleepiness: RD 0.09; 95% CI 0.05 to 0.14)

Receipt of Naltrexone
14% got 80% of a 6-mo course

Stephenson JJ et al. (abstract) AAAP 2006.
Medstat MarketScan Commercial Claims data
Injectable Naltrexone
Primary Efficacy Analysis: Mean Heavy Drinking Event Rate

Decreased heavy drinking days 25%;
Median 6 vs 3 days/month

Prescribing Naltrexone

Naltrexone 12.5 mg/d --> 25 mg/d --> 50 mg/d or 380 mg IM per month

- Main contraindication: opiates, pregnancy
- Main side effects: nausea, dizziness
### The COMBINE Study

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Good Clinical Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Management and Placebo</td>
<td>58%</td>
</tr>
<tr>
<td>Medical Management and Placebo and CBI</td>
<td>71%</td>
</tr>
<tr>
<td>Medical Management and Naltrexone</td>
<td>74%</td>
</tr>
</tbody>
</table>

CBI = Combined Behavioral Intervention

Good Clinical Outcome = Abstinence or drinking moderate amounts without problems.

P < 0.025 (interaction p-value 0.02)

Anton RF et al. *JAMA* 2006 May 3;295:2003-17 (NCT00006206)
Efficacy of Acamprosate
“stabilizes activity in the glutamate system”

ACAMPROSATE: COCHRANE REVIEW

• 24 RCTs, 6915 participants, compared to placebo
• Any drinking RR 0.86 (95% CI 0.81 to 0.91); NNT 9.09 (95% CI 6.66 to 14.28)
• Cumulative abstinence duration MD 10.94 (95% CI 5.08 to 16.81)
• Secondary outcomes: GGT and heavy drinking NSD
• Diarrhea was the only side effect more frequent RD 0.11 (95% 0.09 to 0.13)
• Same effect in industry-sponsored and non-profit funded trials (RR 0.88 (95% 0.80 to 0.97) and RR 0.88 (95% CI 0.81 to 0.96)

Prescribing Acamprosate

Acamprosate 666 mg tid

- Main contraindication: renal insufficiency
- Main side effect: diarrhea; pregnancy category C
Disulfiram

Ethanol → Acetaldehyde

• Flushing
• Headache
• Palpitations
• Dizziness
• Nausea

ACDH

Acetate

ALDH

Disulfiram
Disulfiram (DS)

2 RCTs
DS 250 mg; DS 1 mg (subtherapeutic); or riboflavin.

DS groups informed about the DS-ethanol reaction; riboflavin not.

N = 605
No difference between groups for abstinence
  DS 250 mg--Fewer drinking days (subsample who drank, complete assessments

N = 128
Similar rates of abstinence for DS groups (21%, 25%); lower with riboflavin (12%).
Monitored Disulfiram: Small Randomized studies

<table>
<thead>
<tr>
<th>Author, Yr</th>
<th>Follow-up</th>
<th>Disulfiram</th>
<th>Abstinence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerrein, 1973</td>
<td>85%, 39%</td>
<td>Monitored</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>7%</td>
</tr>
<tr>
<td>Azrin, 1976</td>
<td>90%</td>
<td>Monitored</td>
<td>90-98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>55%</td>
</tr>
<tr>
<td>Azrin, 1982</td>
<td>100%</td>
<td>Monitored</td>
<td>73%*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>47*</td>
</tr>
<tr>
<td>Liebson, 1978</td>
<td>78%</td>
<td>Monitored</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unmonitored</td>
<td>79%</td>
</tr>
</tbody>
</table>


*Thirty-day abstinence at 6 months.
Prescribing Disulfiram

Disulfiram 250 mg/d --> 500 mg/d

- Main contraindications:
  recent alcohol use, cognitive impairment, risk of harm from disulfiram--ethanol reaction, drug interactions, pregnancy, rubber, nickel or cobalt allergy

- Main side effects:
  hepatitis, neuropathy
The COMBINE Study

• One year after treatment ended, the groups did not differ significantly on drinking outcomes
  – Alcohol dependence is an illness that, like other chronic diseases, requires ongoing care
Thanks to Tom McLellan for the concept
Figures published in NIDA Principles of Drug Treatment
The following medications are not approved by the FDA for the treatment of alcohol use disorder.
The following medications are not approved by the FDA for the treatment of alcohol use disorder

Consider using: topiramate (7 RCTs).

Maybe (a few RCTs) ondansetron, gabapentin, varenicline, buspirone if anxiety, SSRI (e.g. fluoxetine) if depression

Don’t consider using: baclofen (1 positive, several negative trials), rimonabant (1 trial; not available)
Prescribing Topiramate

25 mg hs, increase by 25-50mg each week and dose bid. Target 200 mg. May respond to lower doses

- Main contraindication: Narrow angle glaucoma, kidney stones, renal or hepatic impairment, severely underweight, use of CNS depressants.
- Main side effects: Paresthesias, taste perversion, anorexia, weight loss, somnolence, cognitive dysfunction; pregnancy category C
AUD AND COMORBID ANXIETY

• 5 RPCTs with 290 participants
• PTSD, Social anxiety disorder, generalized anxiety disorder
• Paroxetine, buspirone, sertraline, desipramine
• Some effects on anxiety, none on depression or alcohol
• Very low quality evidence

Pharmacotherapy

- Efficacious though modest; future promise for individualization
- Naltrexone first line (considerations re oral/injectable)
  - Acamprosate tid (renal), disulfiram (monitored), topiramate (SEs)
  - Ondansetron (early onset), gabapentin, varenicline
  - Targeted (vs. daily) may be as effective
- Psychotherapy or medical-type counseling
- Address depression and anxiety – medication can help*
  though not necessarily for alcohol use

TREATMENT EFFECTIVENESS

- At one year, 2/3\textsuperscript{rd}s of patients have a reduction in
  - alcohol consequences (injury, unemployment)
  - consumption (by 50%)
- 1/3\textsuperscript{rd} are abstinent or drinking moderately without consequences
- Monetary benefits of alcohol and drug treatment to society outweigh costs 4 to 12-fold (depending on drug and treatment type)

Anon. Journal of Studies on Alcohol 1997;58:7-29,
SUMMARY

- Benzodiazepines for withdrawal; individualize
- Pharmacotherapy