Management of Unhealthy Alcohol Use: From Research to Practice

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PREVALENCE

% of pop

% of pop

Drug

Hvy Alcohol

NSDUH 2012
ALCOHOL AND DRUG RELATED ED VISITS 2000

- Drug: 601,776
- Alcohol: 8,376,000

DAWN (doesn’t mention alcohol alone), NAHMCS
past year 1st time use

- Alcohol: 46,000,000
- Other drug: 28,000,000
- Tobacco: 21,000,000
WHAT IS WRONG WITH THIS PICTURE?

• Cost in the US:
  – Tobacco $193, drug $181
  – Alcohol $224 billion

• Causes of preventable death:
  – 1. tobacco
  – 2. overweight
  – 3. alcohol…
  – 9. drugs

• NIDA $1 billion, NIAAA $460 Million
• CRIT opioid talk 40”, alcohol talk 40”
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

summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51
Benzodiazepines reduce delirium

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

RRR 71%, p=0.04

<table>
<thead>
<tr>
<th>Clinical Institute Withdrawal Assessment, for Alcohol, revised (CIWA-Ar)</th>
</tr>
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<tbody>
<tr>
<td>Nausea and vomiting. Ask “Do you feel sick to your stomach? Have you vomited?”</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—No nausea and no vomiting</td>
</tr>
<tr>
<td>1—Mild nausea with no vomiting</td>
</tr>
<tr>
<td>2—</td>
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<td>3—</td>
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<tr>
<td>4—Intermittent nausea with dry heaves</td>
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<tr>
<td>5—</td>
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<tr>
<td>6—</td>
</tr>
<tr>
<td>7—Constant nausea, frequent dry heaves, and vomiting</td>
</tr>
<tr>
<td>Tremor. Ask patient to extend arms and spread fingers apart.</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—No tremor</td>
</tr>
<tr>
<td>1—Tremor not visible but can be felt, fingertip to fingertip</td>
</tr>
<tr>
<td>2—</td>
</tr>
<tr>
<td>3—</td>
</tr>
<tr>
<td>4—Moderate tremor with arms extended</td>
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<tr>
<td>5—</td>
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<tr>
<td>6—</td>
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<tr>
<td>7—Severe tremor, even with arms not extended</td>
</tr>
<tr>
<td>Paroxysmal sweats</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—No sweat visible</td>
</tr>
<tr>
<td>1—Barely perceptible sweating; palms moist</td>
</tr>
<tr>
<td>2—</td>
</tr>
<tr>
<td>3—</td>
</tr>
<tr>
<td>4—Beads of sweat obvious on forehead</td>
</tr>
<tr>
<td>5—</td>
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<tr>
<td>6—</td>
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<tr>
<td>7—Drenching sweats</td>
</tr>
<tr>
<td>Anxiety. Ask “Do you feel nervous?”</td>
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<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—No anxiety (at ease)</td>
</tr>
<tr>
<td>1—Mildly anxious</td>
</tr>
<tr>
<td>2—</td>
</tr>
<tr>
<td>3—</td>
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<tr>
<td>4—Moderately anxious or guarded, so anxiety is inferred</td>
</tr>
<tr>
<td>5—</td>
</tr>
<tr>
<td>6—</td>
</tr>
<tr>
<td>7—Equivalent to acute panic states as occur in severe delirium or acute schizophrenic reactions</td>
</tr>
<tr>
<td>Tactile disturbances. Ask “Do you have any itching, pins-and-needles sensations, burning, or numbness, or do you feel like bugs are crawling on or under your skin?”</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—None</td>
</tr>
<tr>
<td>1—Very mild itching, pins-and-needles sensation, burning, or numbness</td>
</tr>
<tr>
<td>2—Mild itching, pins-and-needles sensation, burning, or numbness</td>
</tr>
<tr>
<td>3—Moderate itching, pins-and-needles sensation, burning, or numbness</td>
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<tr>
<td>4—Moderately severe hallucinations</td>
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<tr>
<td>5—Severe hallucinations</td>
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<tr>
<td>6—Extremely severe hallucinations</td>
</tr>
<tr>
<td>7—Continuous hallucinations</td>
</tr>
<tr>
<td>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?”</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—Not present</td>
</tr>
<tr>
<td>1—Very mild harshness or ability to frighten</td>
</tr>
<tr>
<td>2—Mild harshness or ability to frighten</td>
</tr>
<tr>
<td>3—Moderate harshness or ability to frighten</td>
</tr>
<tr>
<td>4—Moderately severe hallucinations</td>
</tr>
<tr>
<td>5—Severe hallucinations</td>
</tr>
<tr>
<td>6—Extremely severe hallucinations</td>
</tr>
<tr>
<td>7—Continuous hallucinations</td>
</tr>
<tr>
<td>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?”</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—Not present</td>
</tr>
<tr>
<td>1—Very mild sensitivity</td>
</tr>
<tr>
<td>2—Mild sensitivity</td>
</tr>
<tr>
<td>3—Moderate sensitivity</td>
</tr>
<tr>
<td>4—Moderately severe hallucinations</td>
</tr>
<tr>
<td>5—Severe hallucinations</td>
</tr>
<tr>
<td>6—Extremely severe hallucinations</td>
</tr>
<tr>
<td>7—Continuous hallucinations</td>
</tr>
<tr>
<td>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.</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—Not present</td>
</tr>
<tr>
<td>1—Very mild</td>
</tr>
<tr>
<td>2—Mild</td>
</tr>
<tr>
<td>3—Moderate</td>
</tr>
<tr>
<td>4—Moderately severe</td>
</tr>
<tr>
<td>5—Severe</td>
</tr>
<tr>
<td>6—Very severe</td>
</tr>
<tr>
<td>7—Extremely severe</td>
</tr>
<tr>
<td>Orientation and clouding of sensorium. Ask “What day is this? Where are you? Who am I?”</td>
</tr>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—Orientated and can do serial additions</td>
</tr>
<tr>
<td>1—Cannot do serial additions or is uncertain about date</td>
</tr>
<tr>
<td>2—Date disorientation by no more than two calendar days</td>
</tr>
<tr>
<td>3—Date disorientation by more than two calendar days</td>
</tr>
<tr>
<td>4—Disoriented for place and/or person</td>
</tr>
</tbody>
</table>
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

Protocol applied to patients w/no recent use or who couldn’t communicate; all AE’s among ineligible

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)
"He did predictably suffer from delirium tremens. This was quelled with p.o. alcohol"
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 (sedative hypnotics vs. neuroleptics); N=386, 1 vs. 8 deaths
- Requirements variable and sometimes high
  - Case reports
    - “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)

Poor Quality of Care: Alcohol Use Disorder

• 10% receive any treatment (survey)
  – Not happening in specialty treatment ($, prescribers)
• 10% receive any recommended care (medical record)

“The number of addiction medicine patients we see is so great, the quality of care is so poor…”

--Sim Kimmel, FIT’t 4/24/2016

OAS, CSAT, SAMHSA NSDUH 2006
Green-Hennessey 2002; NSDUH 2009; NAMCS 2008
Mark et al. Drug Alcohol Depend 1 January 2009, Pages 345–349 10% receive 1 prescription in a year (medication databases)
Compared to 11 prescriptions in a year for depression

“When the facts change — and they’ve changed a lot — the minds have not,” Dr. Willenbring said.

“When we publish studies in our field, nobody who is running these centers reads them. If it counters what they already know, they discount them,” he continued. “In the addiction world, the knee-jerk response is typically, ‘We know what to do.’ And when that doesn’t work, we blame patients if they fail.”

“What we simply need is a nice bulldozer, so that we could level the entire industry and start from scratch.”

“We used to treat breast cancer with prayer, too. We don’t do that anymore.”
CASE

A 53 year old woman drinks ½ 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
Friedmann PD, Schwartz RP. Just call it “treatment.”
Addiction Science & Clinical Practice 2012, 7:10
Helping Patients Who Drink Too Much
NIAAA, 2015
Neurochemical Circuits Involved in Alcohol Dependence and Craving
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
NALMEFENE

- Not FDA approved. Approved by European Medications Agency 2014
- PRN use 1-2 hrs prior to perceived risk
- Trial 1, n=604: reduced HDDs, total use, ALT, GGT; more dizziness, nausea, fatigue
- Trial 2, n=718: reduced HDDs, ALT; more dizziness, nausea


Targeted NTX: fewer drinks per day and drinks per drinking day.
Medical management alone (no CBI). Genotype vs. medication interaction p=0.005

Good clinical outcome based on OPRM1 and medication group
The COMBINE Study

<table>
<thead>
<tr>
<th>N=1383, 16 wk trial</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 <strong>Naltrexone</strong></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)
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% CI 0.09 to 0.13)
- Same effect in industry-sponsored and non-profit funded trials (RR 0.88 (95% CI 0.80 to 0.97) and RR 0.88 (95% CI 0.81 to 0.96)

Prescribing Acamprosate: stabilizes activity on the glutamate system

Acamprosate 666 mg tid

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

Ethanol $\rightarrow$ Acetaldehyde $\rightarrow$ Acetate

- Flushing
- Headache
- Palpitations
- Dizziness
- Nausea

Disulfiram

ADH

ALDH
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\%).

Fuller RK et al. JAMA 1986;256:1449
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 Unmonitored</td>
<td>40% 7%</td>
</tr>
<tr>
<td>Azrin, 1976</td>
<td>90%</td>
<td>Monitored Unmonitored</td>
<td>90-98% 55%</td>
</tr>
<tr>
<td>Azrin, 1982</td>
<td>100%</td>
<td>Monitored Unmonitored</td>
<td>73%* 47*</td>
</tr>
<tr>
<td>Liebson, 1978</td>
<td>78%</td>
<td>Monitored Unmonitored</td>
<td>98% 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 following medications are not approved by the FDA for the treatment of alcohol use disorder
A META-ANALYSIS OF TOPIRAMATE'S EFFECTS FOR INDIVIDUALS WITH ALCOHOL USE DISORDERS

Difference/SD 0.5 = moderate effect

Alcoholism: Clinical and Experimental Research
Volume 38, Issue 6, pages 1481-1488, 5 MAY 2014 DOI: 10.1111/acer.12411
OTHER MEDICATIONS

• Limited evidence
  – Gabapentin
  – Varenicline
  – Ondansetron
  – Baclofen
  – Rimonabant (CB-1 blocker)

• Buspirone (anxiety), SSRI (depression)
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

The COMBINE Study

• One year after treatment ended, the groups did not differ significantly on drinking outcomes
  – Alcohol use disorder 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
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

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

Monetary benefits of alcohol and drug treatment to society outweigh costs
4 to 12-fold (depending on drug and treatment type)
SUMMARY

- Benzodiazepines for withdrawal; individualize
- Pharmacotherapy

- *To be discussed later* (because it applies to alcohol and other drugs):
  - Counseling (brief, psychotherapy)
  - Social networks
EXTRA SLIDES
Caution with Protocols

• SFGH: Fixed-schedule plus PRN
  – Decreased transfers to ICU (OR 0.6); increased mortality (OR 2.1) and LOS (by 18%)
• Mayo Clinic: STT protocol
  – 55% had no recent drinking (57% of whom couldn’t communicate); 14% drank but couldn’t communicate
  – 7 of 11 AEs in people ineligible (9 DTs (2 w/seizure), 1 seizure, 1 death)

Specialty Treatment

- 2 of 175 programs had a physician director
  - 54% have no physician
  - 34% have a part-time physician
  - 12% have a full-time physician

Alcohol
Not for withdrawal

• Dose/therapeutic index
• Effectiveness
• Toxicities

Take a Hair of the Dog that Bit You.
After a debauch, take a little wine the next day. Take a cool draught of ale in the morning, after a night’s excess. “If a dog bites you, put a hair of the dog into the wound.”
“Similia similibus curantur” (like cures like).
Alcohol Use Disorder: Treatment Gap

1,600,000 (8%) received treatment

17,900,000 (92%) did not

OAS, CSAT, SAMHSA NSDUH 2006
Green-Hennessey 2002; NSDUH 2009; NAMCS 2008
## Prescriptions for the 4 FDA approved Rxs

<table>
<thead>
<tr>
<th></th>
<th>Disulfiram</th>
<th>Naltrexone</th>
<th>Acamprosate</th>
<th>Injectable naltrexone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriptions</td>
<td>179,000</td>
<td>221,000</td>
<td>306,000</td>
<td>15,000</td>
</tr>
<tr>
<td>Cost per rx</td>
<td>$78</td>
<td>$100</td>
<td>$114</td>
<td>$489</td>
</tr>
</tbody>
</table>

- 9% of the 7.9 million people with alcohol dependence received the equivalent of 1 prescription in a year (720,000 prescriptions)
  - Compared with 170 million antidepressant Rxs
    - 14.8 million people have depression

Mark et al. Drug Alcohol Depend 1 January 2009, Pages 345–349
### Table 3. Difference Between Topiramate and Placebo on Physical and Psychosocial Measures of Health by the Primary (Mixed Model) Analytic Approach

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mean Difference Between Study Groups (95% CI)</th>
<th>Effect Size</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma AST, U/L</td>
<td>4.70 (1.86 to 7.54)</td>
<td>0.30</td>
<td>.001</td>
</tr>
<tr>
<td>Plasma ALT, U/L</td>
<td>6.74 (2.99 to 10.49)</td>
<td>0.43</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma log GGT ratio</td>
<td>0.05 (0.03 to 0.08)</td>
<td>0.53</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma bicarbonate, mEq/L</td>
<td>2.50 (1.89 to 3.11)</td>
<td>1.01</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Plasma cholesterol, mg/dL</td>
<td>13.30 (5.09 to 21.44)</td>
<td>0.41</td>
<td>.002</td>
</tr>
<tr>
<td>Urine pH</td>
<td>-0.30 (-0.54 to -0.06)</td>
<td>0.32</td>
<td>.01</td>
</tr>
<tr>
<td>BMI</td>
<td>1.08 (0.81 to 1.34)</td>
<td>0.91</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>9.70 (6.81 to 12.60)</td>
<td>0.77</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>6.74 (4.57 to 8.90)</td>
<td>0.73</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pulse, bpm</td>
<td>1.59 (-0.96 to 4.14)</td>
<td>0.16</td>
<td>.07</td>
</tr>
<tr>
<td>Temperature, °C</td>
<td>0.08 (-0.02 to 0.17)</td>
<td>0.18</td>
<td>.92</td>
</tr>
<tr>
<td>OCDS total score</td>
<td>3.36 (1.98 to 4.73)</td>
<td>0.62</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CGI-I score</td>
<td>0.63 (0.38 to 0.87)</td>
<td>0.66</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>CGI-S score</td>
<td>0.72 (0.39 to 1.06)</td>
<td>0.57</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>DrlnC-2R Total Consequences scale score</td>
<td>10.08 (5.86 to 14.30)</td>
<td>0.61</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
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)
Intent to treat with baseline value imputed if follow-up missing

Received 1 dose and visit, no imputation

Also lower blood pressure, BMI and overall clinical improvement
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Prescribing Topiramate

- 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

25 mg hs, increase by 25-50mg each week and dose bid. Target 200 mg. May respond to lower doses
Gabapentin Effects on Rates of No Heavy Drinking and Complete Abstinence During the 12-Week Study in the Intention-to-Treat Population A, No heavy drinking; B, complete abstinence. Error bars indicate 95% confidence intervals (N = 150).
ANTICONVULSANTS: VALPROATE, GABAPENTIN, TOPIRAMATE

- 25 studies, 2641 participants
- Anticonvulsants reduced drinks/drinking days (11 studies, 1126 participants, mean difference (MD) -1.49, 95% CI -2.32 to -0.65) and heavy drinking (12 studies, 1129 participants, standardised mean difference (SMD) -0.35, 95% CI -0.51 to -0.19)
- No effect on dropouts or abstinence; fewer adverse effects in placebo group
- INSUFFICIENT EVIDENCE

Ondansetron

- 5HT3 antagonist

Johnson BA et al. JAMA 2000;284:963-7
Varenicline

- Partial α4β2 nicotinic acetylcholine agonist
- N=200; lower %HDD (by 10%), drinks/day, D/Dday, craving; similar among smokers and non-smokers; more nausea, abnormal dreams, constipation, chest pain.

Baclofen


Not replicated

GAMMA-HYDROXYBUTYRIC ACID (GHB)

- 1 study (71 participants, 3 months follow-up) favour GHB for abstinence rate (RR 5.35, 95% CI 1.28 to 22.4), controlled drinking (RR 2.13, 95% CI 1.07 to 5.54), relapses (RR 0.36, 95% CI 0.21 to 0.63), and number of daily drinks (MD -4.60, 95% CI -6.18 to -3.02)
- On abstinence, GHB performed better than Naltrexone (NTX) (2 studies, 64 participants) (RR 2.59, 95% CI 1.35 to 4.98 at 3 months) and than Disulfiram (1 study, 59 participants) (RR 1.66, 95% CI 0.99 to 2.80 at 12 months)
- The combination of GHB and NTX was better than NTX for abstinence (RR 12.3, 95% CI 1.79 to 83.9 at 3 months; 1 study, 35 participants)
- The combination of NTX, GHB and Escitalopram was better than Escitalopram alone for abstinence (RR 2.02 95% CI 1.03 to 3.94 at 3 months; RR 4.58, 95% CI 1.28 to 16.5 at 6 months; 1 study, 23 participants)
- For Alcohol Craving Scale, results favour GHB over placebo (MD -4.50, 95% CI -5.81 to -3.19 at 3 months; 1 study, 71 participants) and over Disulfiram at 12 months (MD -1.40, 95% CI -1.86 to -0.94, from 1 study with 41 participants)
- INSUFFICIENT EVIDENCE, AND RISK OF HARM (ADDICTION)

Rimonabant

- CB-1 (cannabinoid receptor) blocker
- Less relapse to heavy drinking

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

Thanks to Tom McLellan for the concept
Figures published in NIDA Principles of Drug Treatment

Hypertension Treatment

Addiction Treatment
Efficacy of Acamprosate "stabilizes activity in the glutamate system"


<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n</th>
<th>mean(sd)</th>
<th>Control n</th>
<th>mean(sd)</th>
<th>WMD (95% CI Fixed)</th>
<th>Weight %</th>
<th>WMD (95% CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besson 1998</td>
<td>55</td>
<td>137.00(147.00)</td>
<td>55</td>
<td>75.00(108.00)</td>
<td></td>
<td>3.5</td>
<td>62.00[13.79,110.21]</td>
</tr>
<tr>
<td>Geerlings 1997</td>
<td>128</td>
<td>61.00(70.00)</td>
<td>134</td>
<td>43.00(58.00)</td>
<td></td>
<td>33.2</td>
<td>18.00[2.40,33.60]</td>
</tr>
<tr>
<td>Gual 2001</td>
<td>141</td>
<td>93.00(75.00)</td>
<td>147</td>
<td>74.00(75.00)</td>
<td></td>
<td>26.9</td>
<td>19.00[1.67,36.33]</td>
</tr>
<tr>
<td>Paille 1995</td>
<td>361</td>
<td>210.00(134.00)</td>
<td>177</td>
<td>173.00(137.00)</td>
<td></td>
<td>13.5</td>
<td>37.00[12.54,61.46]</td>
</tr>
<tr>
<td>Poldrugo 1997</td>
<td>122</td>
<td>168.00(151.00)</td>
<td>124</td>
<td>120.00(147.00)</td>
<td></td>
<td>5.8</td>
<td>48.00[10.75,85.25]</td>
</tr>
<tr>
<td>Tempesta 2000</td>
<td>164</td>
<td>155.00(114.00)</td>
<td>166</td>
<td>127.00(115.00)</td>
<td></td>
<td>13.2</td>
<td>28.00[3.29,52.71]</td>
</tr>
<tr>
<td>Whitworth 1996</td>
<td>224</td>
<td>230.00(259.00)</td>
<td>224</td>
<td>183.00(235.00)</td>
<td></td>
<td>3.9</td>
<td>47.00[1.20,82.80]</td>
</tr>
</tbody>
</table>

Complete abst. 1 yr. 23% vs 15%

Test for heterogeneity chi-square=6.71 df=6 p=0.35
Test for overall effect z=5.79 p<0.00001

26.55[17.56,35.54] days/year
Six studies analyzed the role of A118G polymorphism in response to naltrexone for alcohol dependence.

Naltrexone-treated patients carrying the G allele had lower relapse rates than those who were homozygous for the A allele (OR: 2.02, 95% CI 1.26–3.22; \( P = 0.003 \)). There were no differences in abstinence rates.

The Proportion of Participants With Any Heavy Drinking Within a Given Treatment Week Separated by Genotype and Treatment Group

There were no significant differences in outcomes among the 4 groups when adjusting for site and baseline rates of heavy drinking.
Efficacy of Naltrexone


Comparison: 01 Naltrexone
Outcome: 01 Relapse rate

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment n/N</th>
<th>Control n/N</th>
<th>Peto OR (95%CI Fixed)</th>
<th>Weight %</th>
<th>Peto OR (95%CI Fixed)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anton 1999</td>
<td>26 / 68</td>
<td>38 / 63</td>
<td></td>
<td>7.5</td>
<td>0.42[0.21,0.82]</td>
</tr>
<tr>
<td>Chick 2000</td>
<td>59 / 90</td>
<td>54 / 85</td>
<td></td>
<td>9.2</td>
<td>1.09[0.59,2.03]</td>
</tr>
<tr>
<td>Guardia 2002</td>
<td>8 / 101</td>
<td>19 / 101</td>
<td></td>
<td>5.4</td>
<td>0.39[0.17,0.88]</td>
</tr>
<tr>
<td>Heinala 2001</td>
<td>49 / 63</td>
<td>51 / 58</td>
<td></td>
<td>4.0</td>
<td>0.50[0.19,1.27]</td>
</tr>
<tr>
<td>Hersch 1998</td>
<td>15 / 31</td>
<td>15 / 33</td>
<td></td>
<td>3.7</td>
<td>1.12[0.42,2.98]</td>
</tr>
<tr>
<td>Kranzler 2000</td>
<td>29 / 61</td>
<td>31 / 63</td>
<td></td>
<td>7.1</td>
<td>0.94[0.46,1.98]</td>
</tr>
<tr>
<td>Krystal 2001</td>
<td>142 / 378</td>
<td>83 / 187</td>
<td></td>
<td>27.4</td>
<td>0.75[0.53,1.08]</td>
</tr>
<tr>
<td>Latt 2002</td>
<td>19 / 56</td>
<td>27 / 51</td>
<td></td>
<td>6.0</td>
<td>0.46[0.22,0.99]</td>
</tr>
<tr>
<td>Monti 2001</td>
<td>16 / 64</td>
<td>19 / 64</td>
<td></td>
<td>5.8</td>
<td>0.79[0.36,1.72]</td>
</tr>
<tr>
<td>Morris 2001</td>
<td>19 / 55</td>
<td>26 / 56</td>
<td></td>
<td>6.1</td>
<td>0.61[0.29,1.30]</td>
</tr>
<tr>
<td>Oslin 1997</td>
<td>3 / 21</td>
<td>8 / 23</td>
<td></td>
<td>1.9</td>
<td>0.34[0.09,1.33]</td>
</tr>
<tr>
<td>O’Malley 1992</td>
<td>16 / 52</td>
<td>31 / 52</td>
<td></td>
<td>5.9</td>
<td>0.32[0.15,0.68]</td>
</tr>
<tr>
<td>Volpicelli 1995</td>
<td>10 / 54</td>
<td>17 / 45</td>
<td></td>
<td>4.5</td>
<td>0.38[0.16,0.93]</td>
</tr>
<tr>
<td>Volpicelli 1997</td>
<td>17 / 48</td>
<td>26 / 49</td>
<td></td>
<td>5.5</td>
<td>0.49[0.22,1.09]</td>
</tr>
<tr>
<td>Total (95%CI)</td>
<td>428 / 1142</td>
<td>445 / 930</td>
<td></td>
<td>100.0</td>
<td>0.62[0.52,0.75]</td>
</tr>
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Test for heterogeneity chi-square=15.97 df=13 p=0.25
Test for overall effect z=4.97 p<0.000001

37% vs. 48%
Relapse to heavy drinking
Helping Patients Who Drink Too Much
NIAAA, 2015
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 (sedative hypnotics 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*