Management of Unhealthy Alcohol Use: From Research to Practice

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Boston Medical Center is the primary teaching affiliate of the Boston University School of Medicine.
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
- Occur 24-48 hrs after abstinence or decreased intake
- Often occur prior to autonomic hyperactivity
- 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

% with 2nd seizure

lorazepam

0 10 20 30 40 50

3 24

CRIT/FIT 2013
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 IV 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
  – Grand mal seizures
GABA 
GABA<sub>A</sub> Receptor 
Glycine Receptor 
NMDA receptor 
glutamate 
Ca++ 
Cl⁻ 
NO 
ETHANOL 
VOCC<sub>L,N</sub> 
CNS Neuron 
Cl⁻ 
Ca++
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

He did predictably suffer from delirium tremens. This was quelled with p.o. alcohol.
Alcohol
Not for withdrawal
(or hangover)

• Pros
  – The perfect cross-tolerant drug
  – The alcoholic’s drug of choice

• Cons
  – Controlled trials are either absent (most circumstances) or show no advantage
    (Ungur 2013, meta-analysis, no controlled trial for treatment in ICU)
  – Narrow TI
  – Many toxicities (hepatitis, gastritis, pancreatitis, marrow)
  – Need to monitor and adjust levels (and target unknown)
  – The alcoholic’s drug of choice (reinforces acceptability, use)

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).
<table>
<thead>
<tr>
<th>Nausea and vomiting. Ask “Do you feel sick to your stomach? Have you vomited?”</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>3—</td>
</tr>
<tr>
<td>4—Intermittent nausea with dry heaves</td>
</tr>
<tr>
<td>5—</td>
</tr>
<tr>
<td>6—</td>
</tr>
<tr>
<td>7—Constant nausea, frequent dry heaves, and vomiting</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Tremor. Ask patient to extend arms and spread fingers apart.</th>
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</thead>
<tbody>
<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>
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<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>
</tr>
<tr>
<td>7—Severe tremor, even with arms not extended</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Paroxysmal sweats</th>
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<tbody>
<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>
</tr>
<tr>
<td>6—</td>
</tr>
<tr>
<td>7—Drenching sweats</td>
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<thead>
<tr>
<th>Anxiety. Ask “Do you feel nervous?”</th>
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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>
</tr>
<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>
</tbody>
</table>

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<thead>
<tr>
<th>Agitation</th>
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</thead>
<tbody>
<tr>
<td>Observation:</td>
</tr>
<tr>
<td>0—Normal activity</td>
</tr>
<tr>
<td>1—Somewhat more than normal activity</td>
</tr>
<tr>
<td>2—</td>
</tr>
<tr>
<td>3—</td>
</tr>
<tr>
<td>4—Moderately fidgety and restless</td>
</tr>
<tr>
<td>5—</td>
</tr>
<tr>
<td>6—</td>
</tr>
<tr>
<td>7—Varies back and forth during most of the interview or constantly thrashes about</td>
</tr>
</tbody>
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<thead>
<tr>
<th>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?”</th>
</tr>
</thead>
<tbody>
<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>
</tr>
<tr>
<td>4—Moderately severe hallucinations</td>
</tr>
<tr>
<td>5—Severe hallucinations</td>
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<tr>
<td>6—Extremely severe hallucinations</td>
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<tr>
<td>7—Continuous hallucinations</td>
</tr>
</tbody>
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<thead>
<tr>
<th>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?”</th>
</tr>
</thead>
<tbody>
<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>
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<td>7—Continuous hallucinations</td>
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<thead>
<tr>
<th>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?”</th>
</tr>
</thead>
<tbody>
<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>
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<td>5—Severe hallucinations</td>
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<td>6—Extremely severe hallucinations</td>
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<td>7—Continuous hallucinations</td>
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</tbody>
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<thead>
<tr>
<th>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.</th>
</tr>
</thead>
<tbody>
<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>
</tbody>
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<table>
<thead>
<tr>
<th>Orientation and clouding of sensorium. Ask “What day is this? Where are you? Who am I?”</th>
</tr>
</thead>
<tbody>
<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

- Fixed-Schedule Therapy
- Symptom-Triggered Therapy

Receiving Treatment, %

Hours 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

Mayo-Smith and ASAM working group JAMA 1997;278:144-51
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)

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 IV DEFINITION**

A. Disturbance of consciousness (ie, reduced clarity of awareness of the environment), with reduced ability to focus, sustain, or shift attention.

B. A change in cognition (such as memory deficit, disorientation, or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a preexisting, established, or evolving dementia.

C. The disturbance develops in a short period (usually hours to days) and tends to fluctuate during the day.

D. There is evidence from the history, physical examination, or laboratory findings that the symptoms in criteria A and B developed during, or shortly after, a withdrawal syndrome.
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
  – Pharmacotherapy
• Self and mutual help
What is Brief Intervention?

• 10-15”, empathic
• Feedback
  – Ask permission
  – Ask what patient thinks of it
• Advice (clear)
• Goal setting
  – Negotiate
  – Menu of options
    • Cut down, quit, refer
  – Support self-efficacy
• Follow-up

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"You are drinking more than is safe for your health."

"My best medical advice is that you cut down or quit."

"What do you think? Are you willing to consider making changes?"


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Table 1. Brief Counseling and Referral

<table>
<thead>
<tr>
<th>Example or Explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;What do you think about your drinking? Are you ready to make a change in your alcohol use?&quot;</td>
</tr>
</tbody>
</table>
| "I am concerned about your drinking; my medical advice is that the healthiest choice for you is to cut down or abstain."
| "My best medical advice is that you cut down or quit."
| "What do you think? Are you willing to consider making changes?"

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CRIT/FIT 2013
evidence-based
EFFICACY of BI among screen-identified patients with non-dependent unhealthy alcohol use

- Efficacious: 10-15” multi-contact
  - >23 original RCTs,* 9 systematic reviews, primary care
- Lower proportion of drinkers of risky amounts
  - 57% vs. 69% at 1 year (n=2784)**; 11% risk diff (n=5973)*
- Lower consumption (n=5639)
  - by 15% (38 grams per week)(n=5639)***; 3.6 drinks/wk (n=4332)*
- Accidents, injuries, liver problems, hospital/ER/primary care use, legal problems, quality of life: insufficient evidence*
  - Decreased hospital utilization (≥2 RCTs)
  - Cost-effective (spend $166, save $546 medical, $7780 society)
  - Decreased mortality (RR 0.47)(4 RCTs (n=1640))

**Beich et al. BMJ 2003;327:536
KNOWN UNKNOWNS

As we know,
There are known knowns.
There are things we know we know.
We also know
There are known unknowns.
That is to say
We know there are some things
We do not know.
But there are also unknown unknowns,
The ones we don't know
We don't know.

US Secretary of Defense Donald Rumsfeld
Details of BI literature with relevance to practice

• Key concept: “identified by screening”
• Best evidence: nondependent unhealthy use, primary care
  – Self-report and social desirability a limitation
    • Efficacy results modest
  – Studies find the right ‘zone’
    • More than minimally risky amounts, but not too much
• Almost all studies exclude dependence and even (very) heavy drinking (Saitz R. Drug Alcohol Rev 2010; 29:631-640)
  – Little evidence for linkage to specialty care
• Evidence of efficacy for outcomes beyond consumption is limited
• Studies that include >1 substance or co-occurring medical condition: negative (Kaner EFS et al. Ment Health Subst Use. 2011;4(1):38–61)
• Literature regarding ED and hospital mixed
• Implementation: FAILURE except screening at VA (maybe)

Bradley KA, et al. Am J Managed Care, 2006
SETTING

- Most people identified by screening in hospitals have dependence
- Different expectations and goals
  - Comprehensive care?
  - Preventive care?
  - Longitudinal care? Long-term therapeutic alliance?
  - Teachable vs. learnable moments?

Belen Martinez et al INEBRIA 2007
Bischoff G et al. Drug Alcohol Depend 2008
Bischof et al. Int J Pub Health 2010
Saitz et al. Int J Pub Health 2010
SBI for other drugs: Promising, but more complicated, severe

- **RCT in urgent care** (Bernstein et al Drug Alcohol Depend 2005;77:49-59)
  - 9% difference in opioid abstinence (40% vs. 31%)
  - 5% difference in cocaine abstinence (22% vs. 17%)
  - No difference in linkage to treatment

- **Multi-site RCT (international) in varied outpatient settings** (Humeniuk et al Addiction 2012;107:957-66)
  - Excluded mild and severe
  - Small (clinically insignificant) decreases in point scales representing marijuana and stimulant use but not opioid use
  - No effect in US

- **Breaking news** (Saitz et al J Gen Intern Med 2013 abstract)
  - BI for drug in primary care: no efficacy
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.”
MAINTENANCE AND RELAPSE

• Anticipate difficult situations (triggers)
• Emphasize prior successes and use relapse as a learning experience, cope w/craving
• Help patient develop a plan to manage early relapses
• Facilitate involvement in treatment
  – 12-step groups
  – Counseling
  – Pharmacotherapy
  – Comorbid psychiatric disorders

PATIENT SELECTION FOR PHARMACOTHERAPY

• All people with alcohol dependence 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*) as effective as specialized behavioral therapy**
  – Prescriber, access to monitoring (e.g. visits, liver enzymes)


RCT: naltrexone effective without obligatory therapy
Medication-Assisted Treatment
Medication-Assisted Treatment

Counseling-Assisted Pharmacotherapy
### Medications for Treating Alcohol Dependence

The chart below highlights some of the properties of each medication. It does not provide complete information about all these medications and other drugs. The National Library of Medicine provides Medline Plus (http://medlineplus.gov).

Whether or not a medication should be prescribed in an individual circumstance, and in what amount is a matter between the provider and the patient. The prescribing information provided here is not a substitute for a provider’s judgment in an individual circumstance, and the NIAAA accepts no liability or responsibility for use of the information with regard to particular patients.

<table>
<thead>
<tr>
<th>Action</th>
<th>Disulfiram (Antabuse®)</th>
<th>Naltrexone (ReVia®)</th>
<th>Acamprosate (Campral®)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Generic</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Use</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Indications</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Precautions</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Serious adverse reactions</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Common side effects</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Examples of drug interactions</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
</tr>
<tr>
<td><strong>Usual adult dosage</strong></td>
<td>Antabuse®</td>
<td>ReVia®</td>
<td>Campral®</td>
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</tbody>
</table>

The information in this chart was drawn primarily from NIAAA, 2007.
Disulfiram

Ethanol → Acetaldehyde → Acetate

- Flushing
- Headache
- Palpitations
- Dizziness
- Nausea

Disulfiram inhibits ADH, blocking the conversion of acetaldehyde to acetate.

Fuller RK et al. JAMA 1986;256:1449
## Monitored Disulfiram: 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
Efficacy of Acamprosate
“stabilizes activity in the glutamate system”

**Comparison: 03 Acamprosate vs Placebo**

**Outcome: 02 Cumulative abstinence duration (CAD)**

<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>Paillé 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[12.54,61.16]</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[1.20,92.60]</td>
</tr>
<tr>
<td>**Total(95%CI)</td>
<td>1195</td>
<td>152.67(139.00)</td>
<td>1027</td>
<td>115.67(109.00)</td>
<td></td>
<td>100.0</td>
<td>26.55[17.56,35.54]</td>
</tr>
</tbody>
</table>

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

Complete abst. 1 yr. 23% vs 15%
Prescribing Acamprosate

Acamprosate 666 mg tid

- Main contraindication: renal insufficiency
- Main side effect: diarrhea; pregnancy category C
Neurochemical Circuits Involved in Alcohol Dependence and Craving

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, 1.89]</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 95</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 97</td>
<td>17 / 48</td>
<td>26 / 49</td>
<td></td>
<td>5.5</td>
<td>0.48 [0.22, 0.99]</td>
</tr>
</tbody>
</table>

Total (95% CI): 428 / 1142 vs. 445 / 930
Test for heterogeneity chi-square = 15.97 df = 13 p = 0.25
Test for overall effect z = -4.97 p = 0.00001

37% vs. 48%
Relapse to heavy drinking

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>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</td>
<td>71</td>
</tr>
<tr>
<td>CBI</td>
<td>74</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)
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
Medical management alone (no CBI). Genotype vs. medication interaction $p=0.005$.

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 b</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>DrNc-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>
Baclofen


Complete Abstinence: 71% vs. 29%

Not replicated
Rimonabant

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

Ondansetron

- 5HT3 antagonist

Pharmacotherapy

- Efficacious though modest; future promise for individualization
- Naltrexone first line (considerations re oral/injectable)
  - Acamprosate tid (renal), disulfiram (monitored)
  - Targeted (vs. daily) may be as effective
- Therapy or medical-type counseling
- Medication treatment of anxiety (buspirone) and depression (fluoxetine) can decrease alcohol consumption
TREATMENT EFFECTIVENESS

• At one year, 2/3\(^{rd}\)s of patients have a reduction in
  – alcohol consequences (injury, unemployment)
  – consumption (by 50%)
• 1/3\(^{rd}\) 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,
O’Brien CP, McLellan AT. Lancet 1996;347:237-240 and
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
Poorest Quality of Care

- 10.5% of recommended care is received by people with alcohol dependence
  - Lowest of 25 conditions (54.9% overall)

- National survey and record review, n=6712
# 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
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

SUMMARY

- Recognize intoxication, consider differential
- Benzodiazepines for withdrawal
- Brief intervention—to decrease use, consequences, link with or begin treatment (be aware of evidence, limitations)
- Prevent relapse
  - Assess
  - Counsel
  - Medications
  - Support (e.g. 12-step)
### Duration and frequency may matter: Brief and Very Brief (VB) vs. Brief Multi-contact

#### Brief and very brief

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>N</th>
<th>Difference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richmond et al. (VB)</td>
<td>378</td>
<td>-</td>
<td>Nonrandom</td>
</tr>
<tr>
<td>WHO (VB)</td>
<td>1559</td>
<td>+ B &amp; VB</td>
<td>NS for women</td>
</tr>
<tr>
<td>Anderson &amp; Scott</td>
<td>154</td>
<td>+</td>
<td>Men</td>
</tr>
<tr>
<td>Nilssen</td>
<td>338</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Senft et al.</td>
<td>516</td>
<td>Borderline</td>
<td></td>
</tr>
<tr>
<td>Maisto et al.</td>
<td>301</td>
<td>-</td>
<td>Outside clinic</td>
</tr>
<tr>
<td>Scott &amp; Anderson</td>
<td>72</td>
<td>-</td>
<td>Women</td>
</tr>
</tbody>
</table>

#### Brief multi-contact

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>N</th>
<th>Difference</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maisto et al.</td>
<td>301</td>
<td>-</td>
<td>Decrease but NS</td>
</tr>
<tr>
<td>Curry et al.</td>
<td>307</td>
<td>+</td>
<td>Good quality</td>
</tr>
<tr>
<td>Fleming et al.</td>
<td>774</td>
<td>+</td>
<td>Good quality</td>
</tr>
<tr>
<td>Fleming et al.</td>
<td>158</td>
<td>+</td>
<td>Good quality; Elderly</td>
</tr>
<tr>
<td>Nilssen</td>
<td>338</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Ockene</td>
<td>530</td>
<td>+</td>
<td>Good quality</td>
</tr>
<tr>
<td>Wallace</td>
<td>909</td>
<td>+</td>
<td>Good quality</td>
</tr>
</tbody>
</table>

**Example intervention (Fleming)**

Health booklet + 2 10-15” physician discussions And follow-up nurse phone call

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