Management of Unhealthy Alcohol Use:
From Research to Practice

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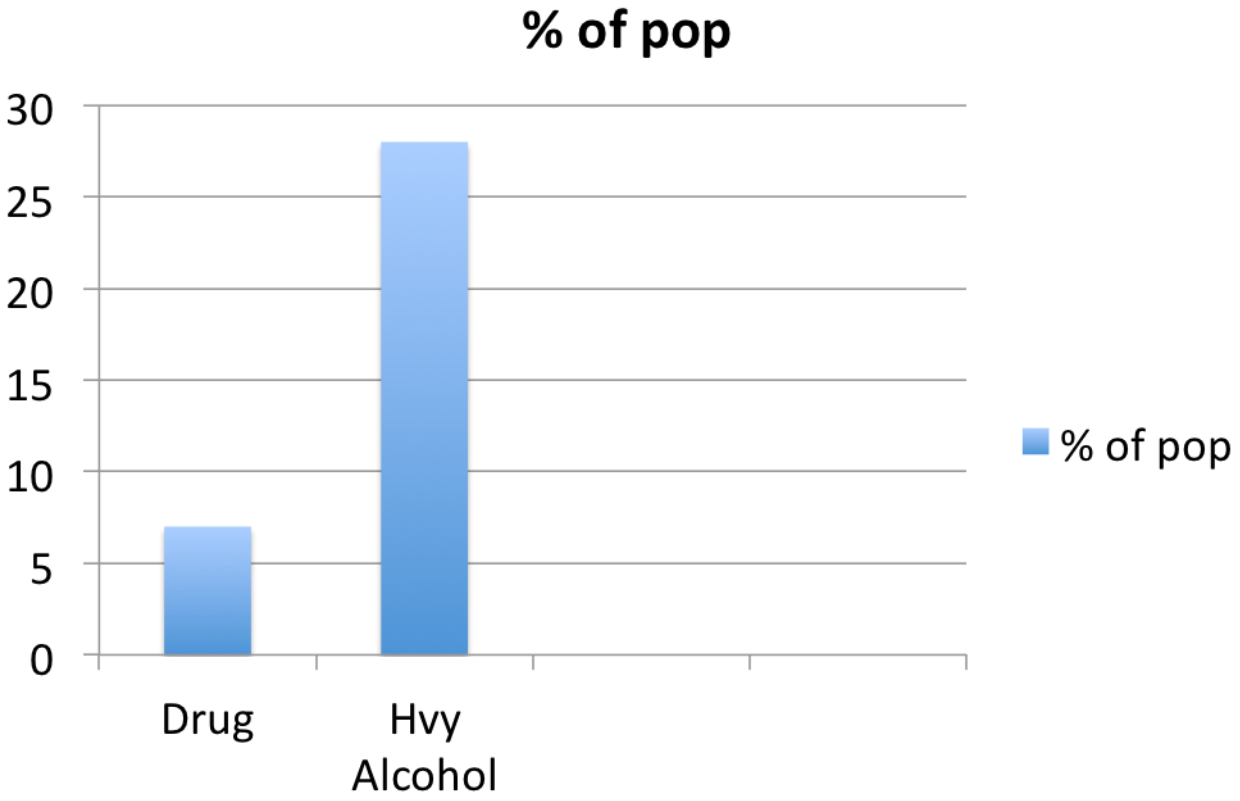
PREVALENCE

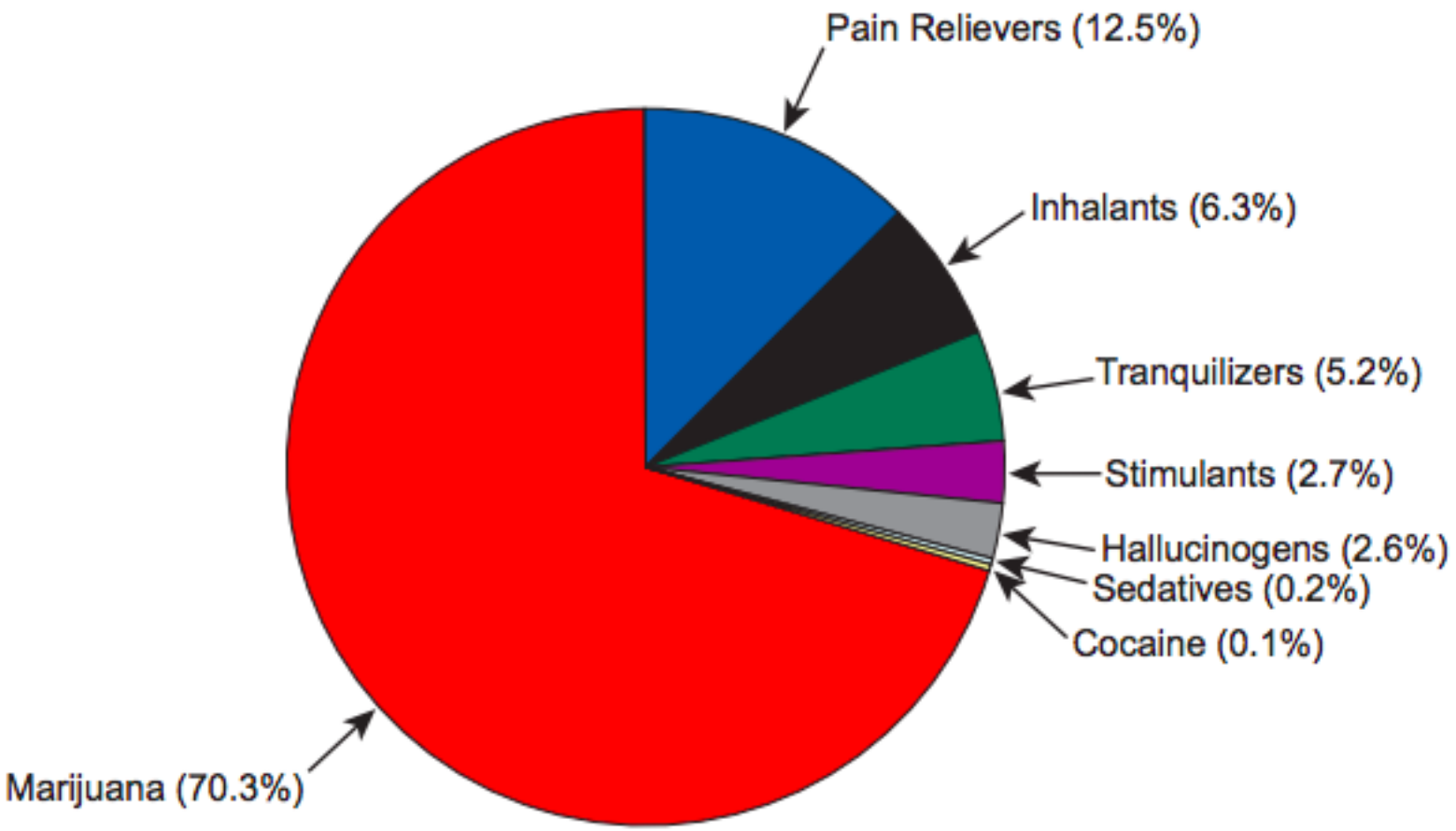


NSDUH 2012

ALCOHOL AND DRUG RELATED ED VISITS 2000

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

DAWN (doesn't mention alcohol alone), NAHMCS



2.8 Million Initiates of Illicit Drugs

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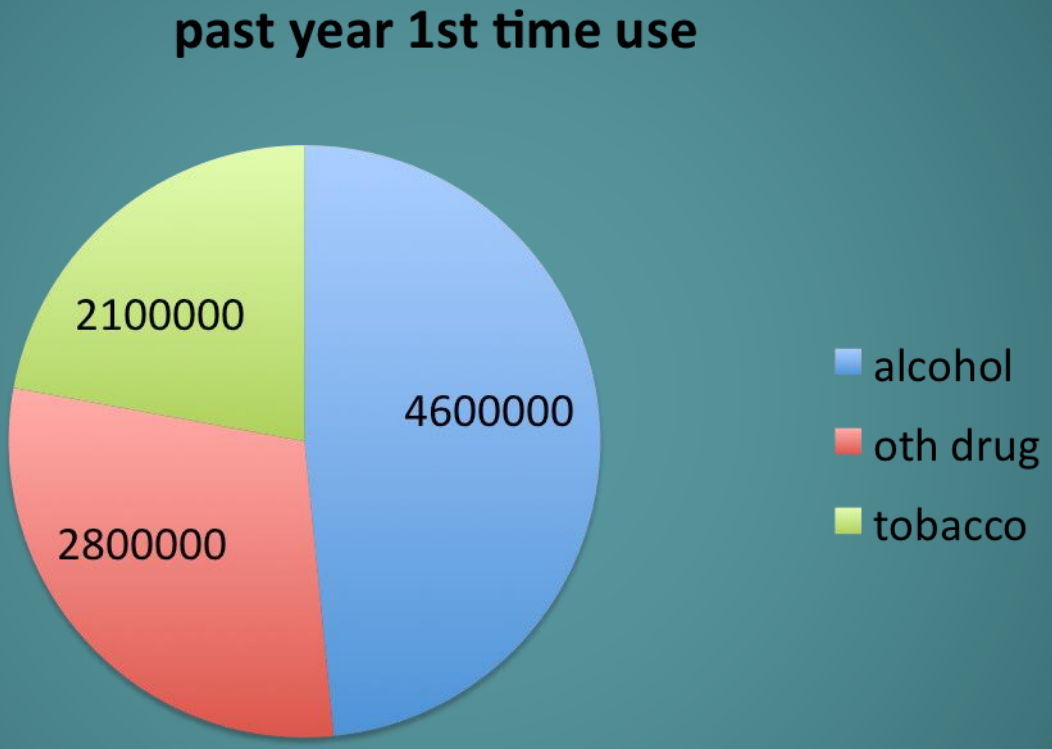

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WHAT IS WRONG WITH THIS PICTURE?

- Cost in the US:
  - Tobacco $193, drug $181, alcohol $235 billion
- Leading causes of preventable death:
  - 1. tobacco
  - 2. overweight
  - 3. alcohol
  - …
  - 9. drugs
- NIDA $ 1billion, 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.

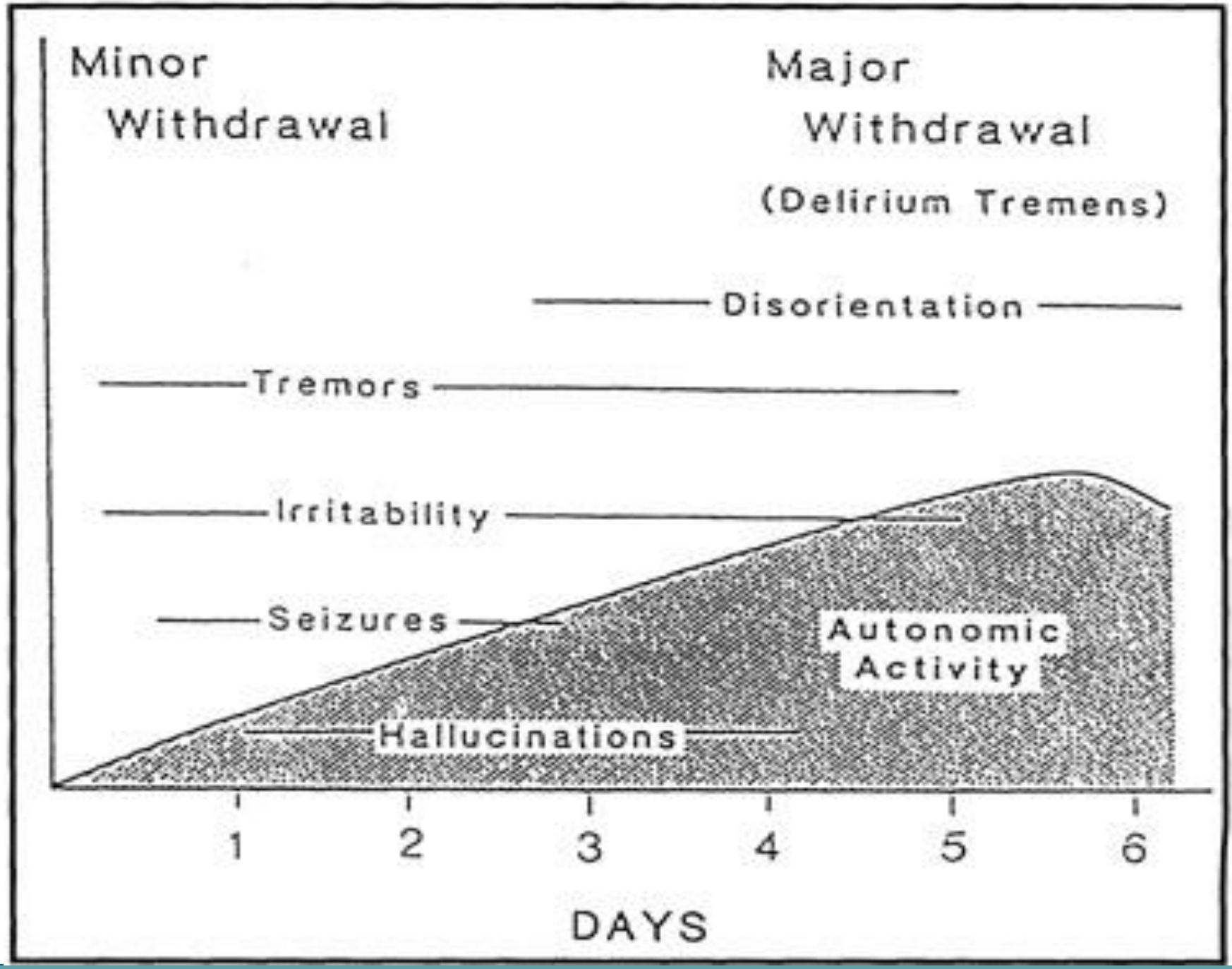
T 98, RR 18, HR 110 (regular), BP 136/82 standing, 100, 140/70 lying down.

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?

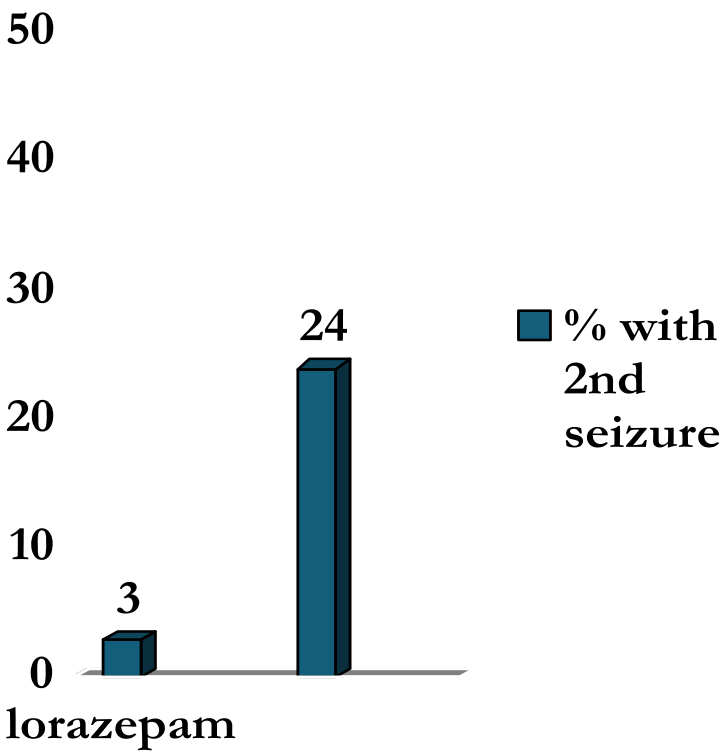

Minor
Withdrawal
Major
Withdrawal
(Delirium Tremens)
Disorientation
Tremors
Irritability
Seizures
Autonomic
Activity
Hallucinations
1
2
3
4
5
6
DAYS

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

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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

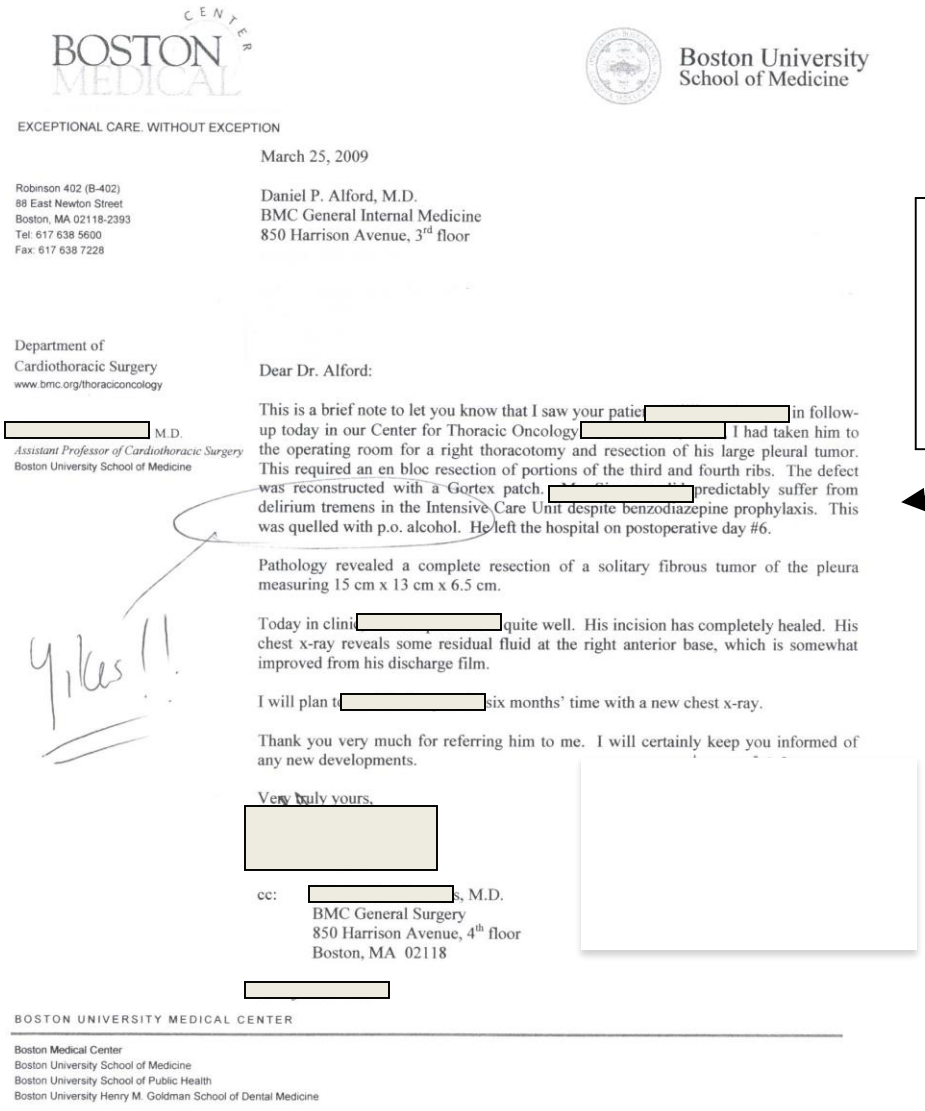
Sereny 1965, Kiam 1969, Zilm 1980, Sellers 1983, Naranjo 1983, summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51

Benzodiazepines reduce delirium

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

RRR 71%, p=0.04

Rosenfeld 1961, Sereny 1965, Kaim 1969, Zilm 1980,
summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51



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March 25, 2009

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Department of
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[redacted] M.D.
Assistant Professor of Cardiothoracic Surgery
Boston University School of Medicine

Dear Dr. Alford:

This is a brief note to let you know that I saw your patie[redacted] in follow-up today in our Center for Thoracic Oncology [redacted] I had taken him to the operating room for a right thoracotomy and resection of his large pleural tumor. This required an en bloc resection of portions of the third and fourth ribs. The defect was reconstructed with a Gortex patch. [redacted] predictably suffer from delirium tremens in the Intensive Care Unit despite benzodiazepine prophylaxis. This was quelled with p.o. alcohol. He left the hospital on postoperative day #6.

Pathology revealed a complete resection of a solitary fibrous tumor of the pleura measuring 15 cm x 13 cm x 6.5 cm.

Today in clini[redacted] quite well. His incision has completely healed. His chest x-ray reveals some residual fluid at the right anterior base, which is somewhat improved from his discharge film.

I will plan t[redacted] six months' time with a new chest x-ray.

Thank you very much for referring him to me. I will certainly keep you informed of any new developments.

Very truly yours,

[redacted]

cc: [redacted]s, M.D.
BMC General Surgery
850 Harrison Avenue, 4th floor
Boston, MA 02118

[redacted]

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Boston University School of Public Health
Boston University Henry M. Goldman School of Dental Medicine

"He did predictably suffer from delirium tremens. This was quelled with p.o. alcohol"

- Dose/therapeutic index
- Effectiveness
- Toxicities

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Clinical Institute Withdrawal Assessment, for Alcohol, revised (CIWA-Ar)

Nausea and vomiting. Ask "Do you feel sick to your stomach? Have you vomited?"

Observation:

0—No nausea and no vomiting
1—Mild nausea with no vomiting
2—
3—
4—Intermittent nausea with dry heaves
5—
6—
7—Constant nausea, frequent dry heaves, and vomiting

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

Observation:

0—No tremor
1—Tremor not visible but can be felt, fingertip to fingertip
2—
3—
4—Moderate tremor with arms extended
5—
6—
7—Severe tremor, even with arms not extended

Paroxysmal sweats

Observation:

0—No sweat visible
1—Barely perceptible sweating; palms moist
2—
3—
4—Beads of sweat obvious on forehead
5—
6—
7—Drenching sweats

Anxiety. Ask "Do you feel nervous?"

Observation:

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

Agitation

Observation:

0—Normal activity
1—Somewhat more than normal activity
2—
3—
4—Moderately fidgety and restless
5—
6—
7—Paces back and forth during most of the interview or constantly thrashes about

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?"

Observation:

0—None
1—Very mild itching, pins-and-needles sensation, burning, or numbness
2—Mild itching, pins-and-needles sensation, burning, or numbness
3—Moderate itching, pins-and-needles sensation, burning, or numbness
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

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?"

Observation:

0—Not present
1—Very mild harshness or ability to frighten
2—Mild harshness or ability to frighten
3—Moderate harshness or ability to frighten
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

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?"

Observation:

0—Not present
1—Very mild sensitivity
2—Mild sensitivity
3—Moderate sensitivity
4—Moderately severe hallucinations
5—Severe hallucinations
6—Extremely severe hallucinations
7—Continuous hallucinations

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 lightheadness; otherwise, rate severity.

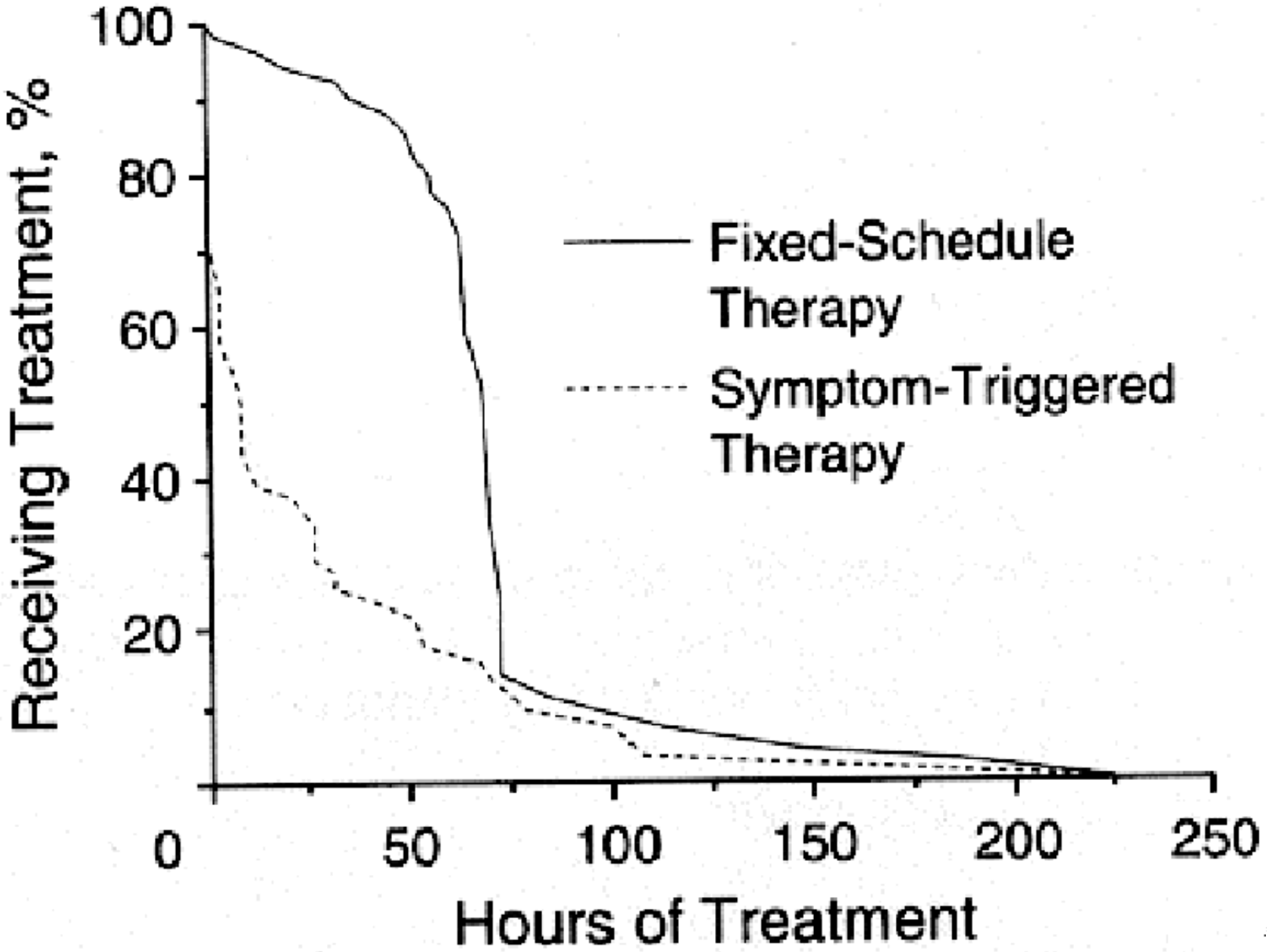
0—Not present
1—Very mild
2—Mild
3—Moderate
4—Moderately severe
5—Severe
6—Very severe
7—Extremely severe

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

Observation:

0—Orientated and can do serial additions
1—Cannot do serial additions or is uncertain about date
2—Date disorientation by no more than two calendar days
3—Date disorientation by more than two calendar days
4—Disorientated 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-A
  - Chlordiazepoxide 50-100 mg
  - Diazepam 10-20 mg
  - Lorazepam 2-4
- **Fixed sch** uses + PRN)
  - mg/25 mg
  - 10 mg/5 mg
  - azepam 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
Pletcher et al. J Qual Pat Safety 2005;31:148-57
Hecksel et al. Mayo Clin Proc 2008;83:274-9

Mayo-Smith and ASAM working group JAMA 1997;278:144-51
Saitz and O'Malley Med Clin N A 1997;81:881-907

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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)

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

Mayo-Smith et al. Arch Intern Med, Jul 2004; 164: 1405 – 1412
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)

Mayo-Smith et al. Arch Intern Med, Jul 2004; 164: 1405 – 1412
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
- Manage comorbidity

Friedmann PD, Saitz R, Samet JH. JAMA 1998;279(15):1227-31.

Poor Quality of Care: Alcohol Use Disorder

- 10% receive any treatment (survey)
- 10% receive 1 prescription in a year (medication databases)
  - Compared to 11 prescriptions in a year for depression
- 10% receive any recommended care (medical record)

OAS, CSAT, SAMHSA NSDUH 2006
Green-Hennessey 2002; NSDUH 2009; NAMCS 2008
Mark et al. Drug Alcohol Depend 1 January 2009, Pages 345–349
Harris KM et al. Psychiatr Serv 2004;55(3):221
McGlynn E et al. N Engl J Med 2003;348:2635-2645

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

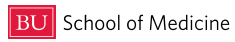
- All people with moderate to severe alcohol use disorder who are:
  - currently drinking
  - experiencing craving or at risk for return to drinking
- Considerations
  - Specific medication contraindications
  - Psychosocial support/therapy and follow-up
    - Primary care med mgt (O'Malley; Anton, Oslin*) as effective as specialized behavioral therapy**
  - Prescriber, access to monitoring (e.g. visits, liver enzymes)

*O' Malley SS et al. *Arch Int Med* 2003;163:1695-1704.
*Anton RF et al. *JAMA* 2006 May 3;295:2003-17.
*Oslin DW et al. J Gen Intern Med 2014;29:162-8.
**Latt NC, et al. *Med J Australia* 2002;176:530-534.
RCT: naltrexone effective without obligatory therapy

Medication-Assisted Treatment

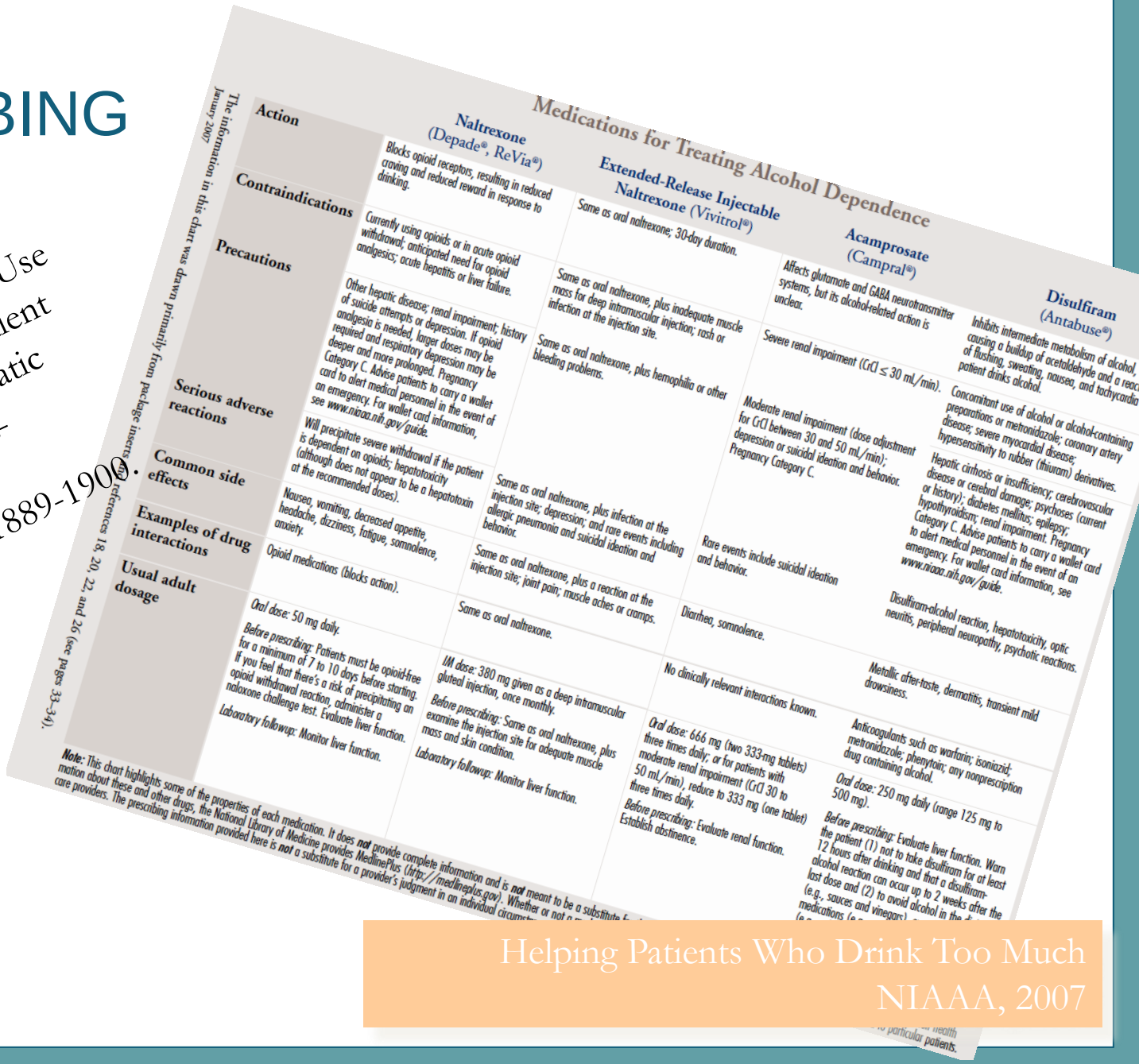
Medication-Assisted Treatment

Just call it Treatment



PRESCRIBING

Jonas DE, Amick HR, Feltner C, et al. Pharmacotherapy for Adults With Alcohol Use Disorders in Outpatient Settings: A Systematic Review and Meta-analysis. JAMA. 2014;311(18):1889-1900.



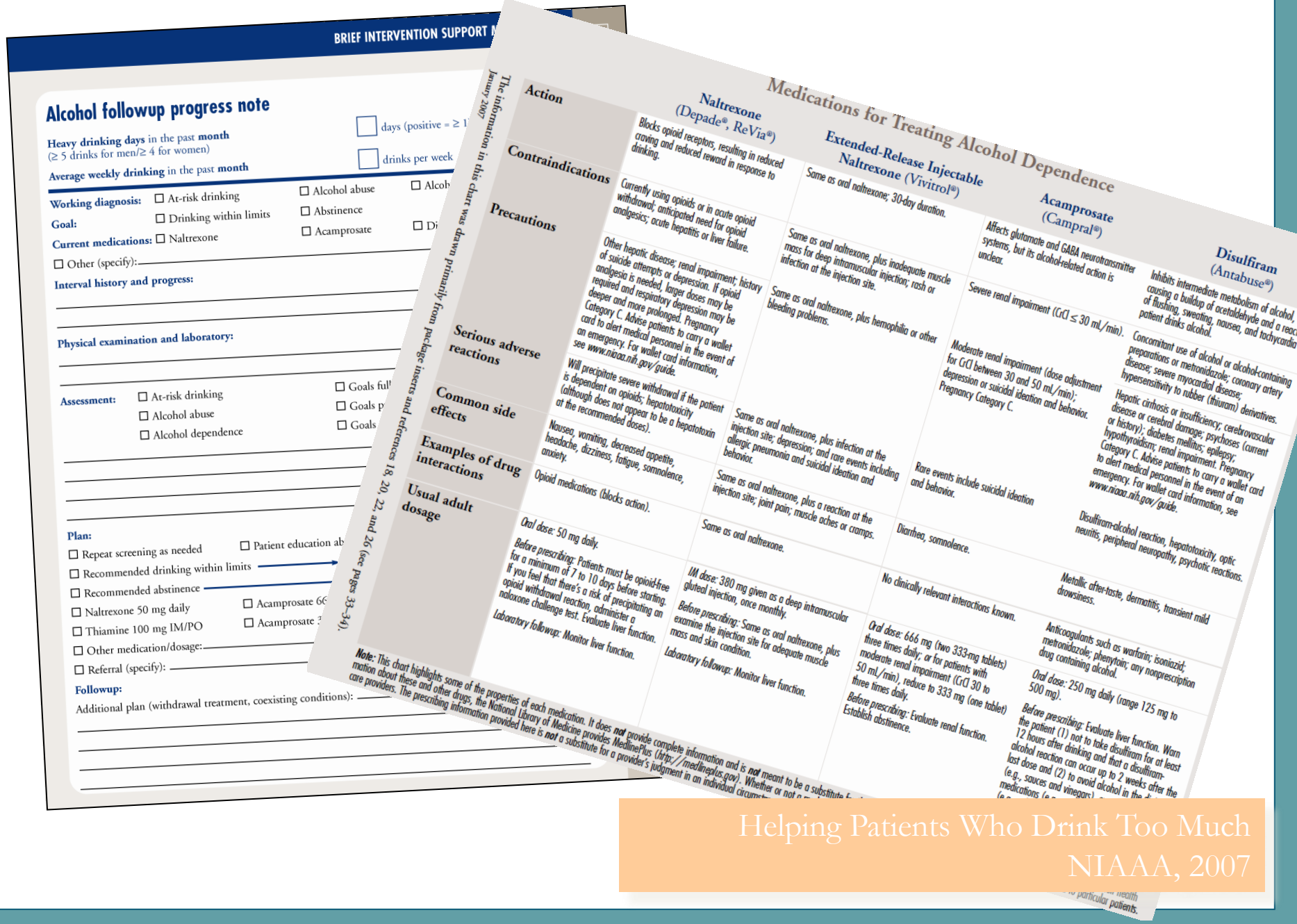
Medications for Treating Alcohol Dependence

The information in this chart was drawn primarily from package inserts (see references 18, 20, 22, and 26 (see pages 33–34). January 2007

Action	Naltrexone (Depade®, ReVia®)	Extended-Release Injectable Naltrexone (Vivitrol®)	Acamprosate (Campral®)	Disulfiram (Antabuse®)
	Blocks opioid receptors, resulting in reduced craving and reduced reward in response to drinking.	Same as oral naltrexone; 30-day duration.	Affects glutamate and GABA neurotransmitter systems, but its alcohol-related action is unclear.	Inhibits intermediate metabolism of alcohol, causing a buildup of acetaldehyde and a reaction of flushing, sweating, nausea, and tachycardia in patient drinks alcohol.
Contraindications	Currently using opioids or in acute opioid withdrawal; anticipated need for opioid analgesics; acute hepatitis or liver failure.		Severe renal impairment (CrCl ≤ 30 mL/min).	
Precautions	Other hepatic disease; renal impairment; history of suicide attempts or depression. If opioid analgesia is needed, larger doses may be required and respiratory depression may be deeper and more prolonged. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see www.niaaa.nih.gov/guide.	Same as oral naltrexone, plus inadequate muscle mass for deep intramuscular injection; rash or infection at the injection site.	Moderate renal impairment (dose adjustment for CrCl between 30 and 50 mL/min); depression or suicidal ideation and behavior. Pregnancy Category C.	Concomitant use of alcohol or alcohol-containing preparations or metronidazole; coronary artery disease; severe myocardial disease; hypersensitivity to rubber (thiuram) derivatives. Hepatic cirrhosis or insufficiency; cerebrovascular disease or cerebral damage; psychoses (current or history); diabetes mellitus; epilepsy; hypothyroidism; renal impairment. Pregnancy Category C. Advise patients to carry a wallet card to alert medical personnel in the event of an emergency. For wallet card information, see www.niaaa.nih.gov/guide.
Serious adverse reactions		Same as oral naltrexone, plus hemophilia or other bleeding problems.		
Common side effects	Will precipitate severe withdrawal if the patient is dependent on opioids; hepatotoxicity (although does not appear to be a hepatotoxin at the recommended doses).	Same as oral naltrexone, plus infection at the injection site; depression; and rare events including allergic pneumonia and suicidal ideation and behavior.	Rare events include suicidal ideation and behavior.	
Examples of drug interactions	Nausea, vomiting, decreased appetite, headache, dizziness, fatigue, somnolence, anxiety.	Same as oral naltrexone, plus a reaction at the injection site; joint pain; muscle aches or cramps.	Diarrhea, somnolence.	Disulfiram-alcohol reaction, hepatotoxicity, optic neuritis, peripheral neuropathy, psychotic reactions.
Usual adult dosage	Opioid medications (blocks action).	Same as oral naltrexone.	No clinically relevant interactions known.	Metallic after-taste, dermatitis, transient mild drowsiness.
	Oral dose: 50 mg daily.	*IM dose:* 380 mg given as a deep intramuscular gluteal injection, once monthly.	*Oral dose:* 666 mg (two 333-mg tablets) three times daily; or for patients with moderate renal impairment (CrCl 30 to 50 mL/min), reduce to 333 mg (one tablet) three times daily.	Anticoagulants such as warfarin; isoniazid; metronidazole; phenytoin; any nonprescription drug containing alcohol.
	Before prescribing: Patients must be opioid-free for a minimum of 7 to 10 days before starting. If you feel that there's a risk of precipitating an opioid withdrawal reaction, administer a naloxone challenge test. Evaluate liver function.	*Before prescribing:* Same as oral naltrexone, plus examine the injection site for adequate muscle mass and skin condition.	*Before prescribing:* Evaluate renal function. Establish abstinence.	*Oral dose:* 250 mg daily (range 125 mg to 500 mg).
	Laboratory followup: Monitor liver function.	*Laboratory followup:* Monitor liver function.		*Before prescribing:* Evaluate liver function. Warn the patient (1) not to take disulfiram for at least 12 hours after drinking and that a disulfiram-alcohol reaction can occur up to 2 weeks after the last dose and (2) to avoid alcohol in the [illegible] (e.g., sauces and vinegars) [illegible] medications [illegible]

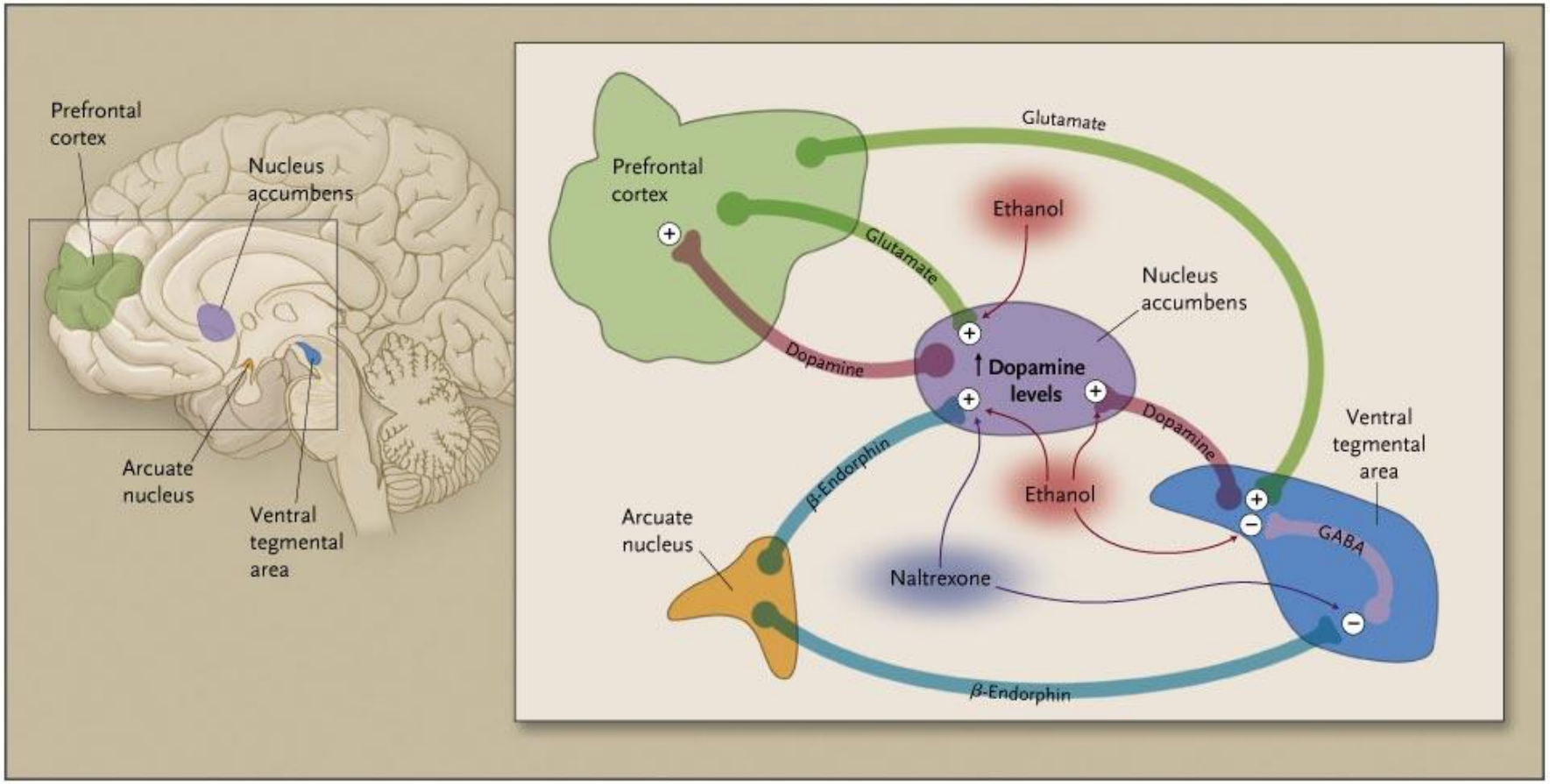
Note: This chart highlights some of the properties of each medication. It does **not** provide complete information and is **not** meant to be a substitute for [illegible] mation about these and other drugs, the National Library of Medicine provides MedlinePlus (http://medlineplus.gov). Whether or not [illegible] care providers. The prescribing information provided here is **not** a substitute for a provider's judgment in an individual circumstance

Helping Patients Who Drink Too Much
NIAAA, 2007



Helping Patients Who Drink Too Much
NIAAA, 2007

Neurochemical Circuits Involved in Alcohol Dependence and Craving



The NEW ENGLAND JOURNAL of MEDICINE

Anton R. N Engl J Med 2008;359:715-721

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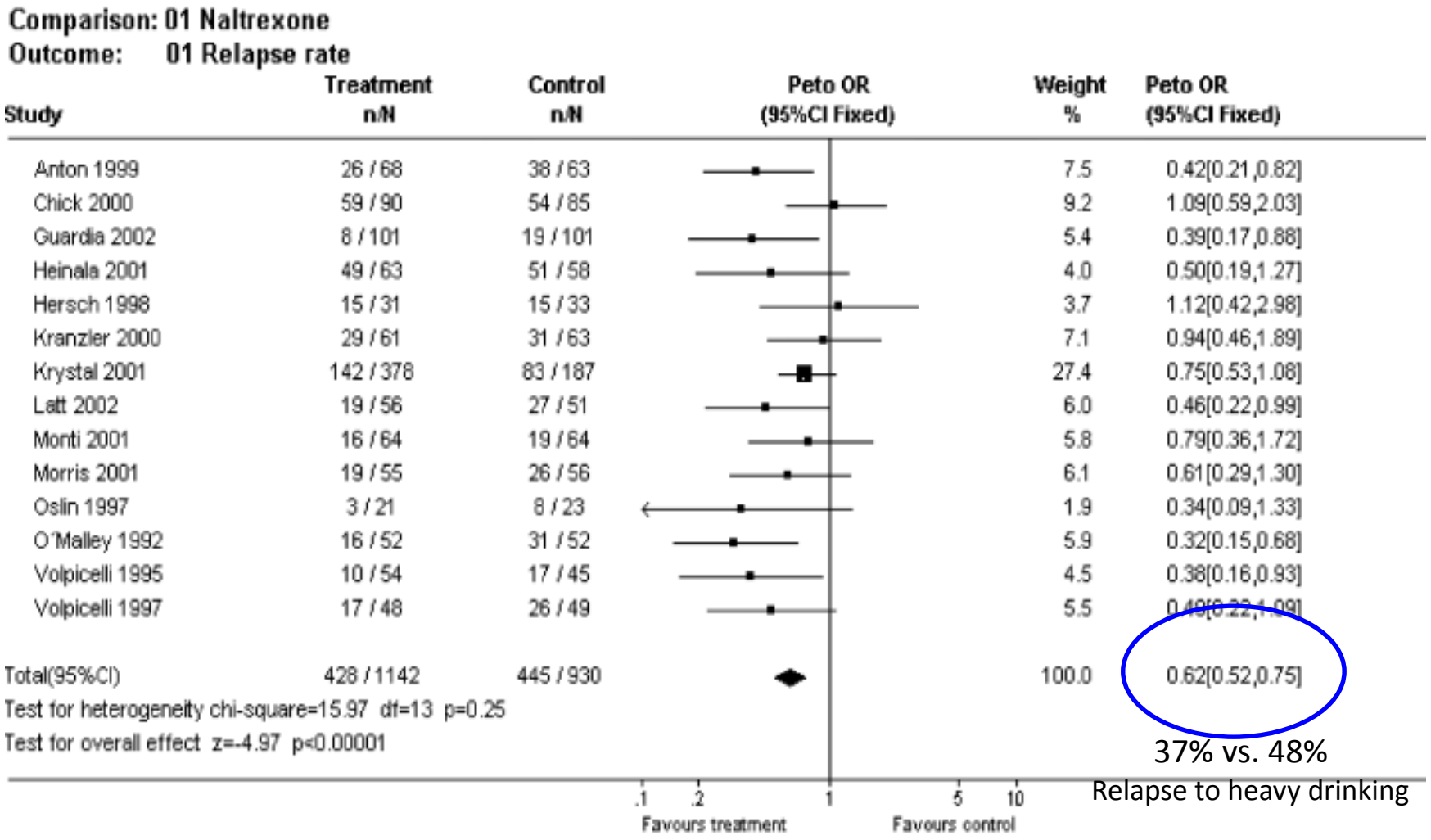
Efficacy of Naltrexone



37% vs. 48%

Relapse to heavy drinking

Bouza C et al. Addiction 2004;99:811

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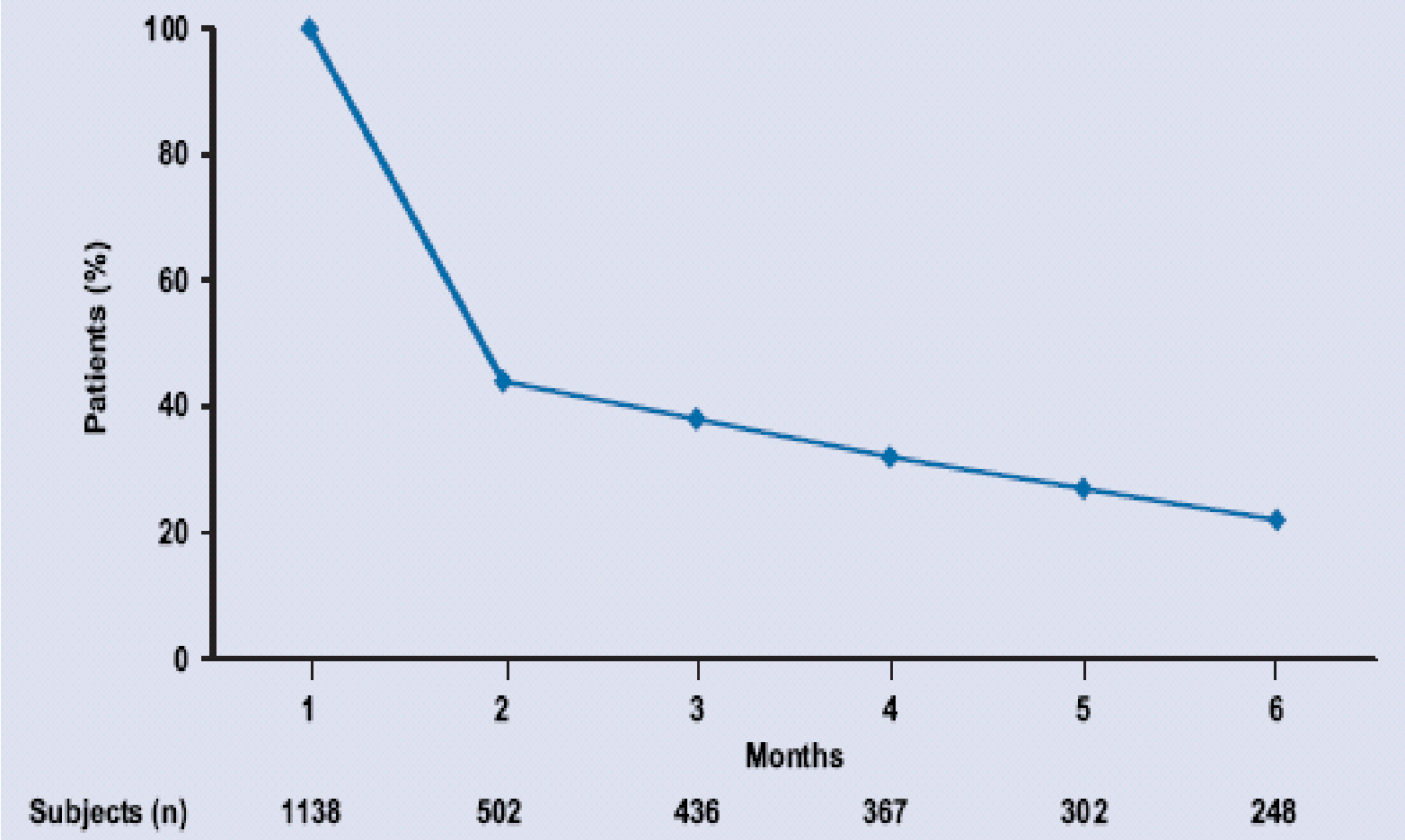
Receipt of Naltrexone

14% got 80% of a 6-mo course



Stephenson JJ et al. (abstract) AAAP 2006.
Medstat MarketScan Commercial Claims data

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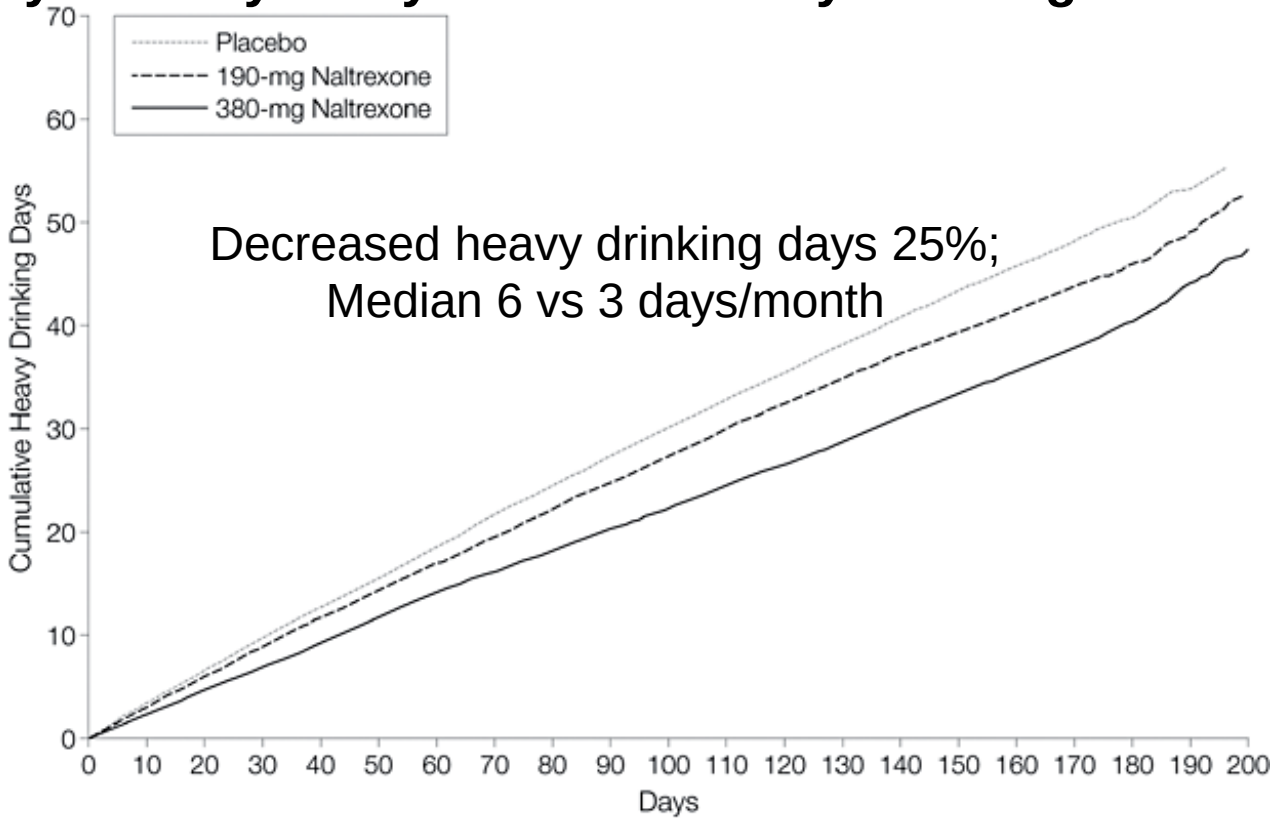
Injectable Naltrexone

Primary Efficacy Analysis: Mean Heavy Drinking Event Rate



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

Treatment Dose	1	2	3	4	5	6
No. of Patients						
Placebo	209	194	169	160	142	134
Naltrexone						
190 mg	210	187	169	156	144	137
380 mg	205	186	161	147	139	130

JAMA

Garbutt, J. C. et al. JAMA 2005;293:1617-1625.

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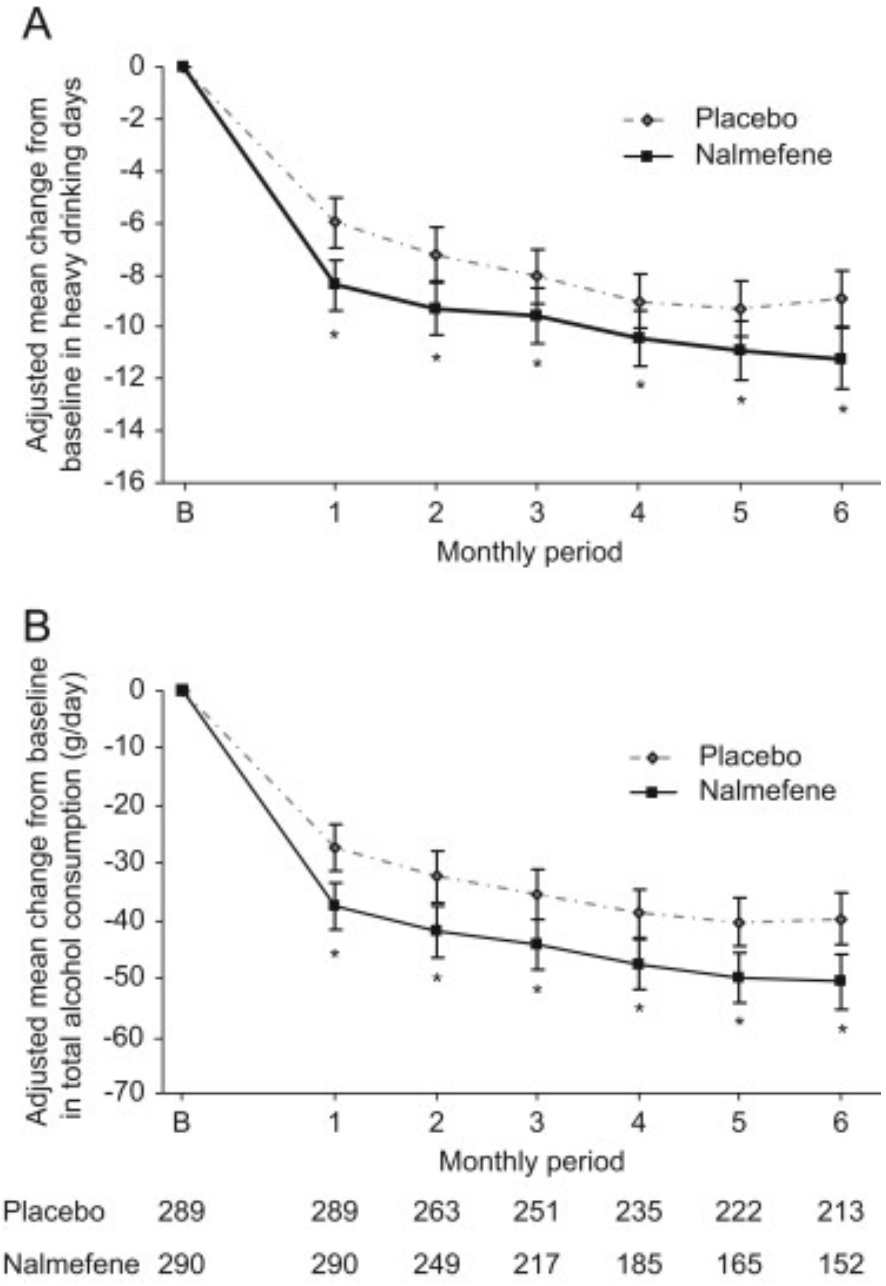
Prescribing Naltrexone

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

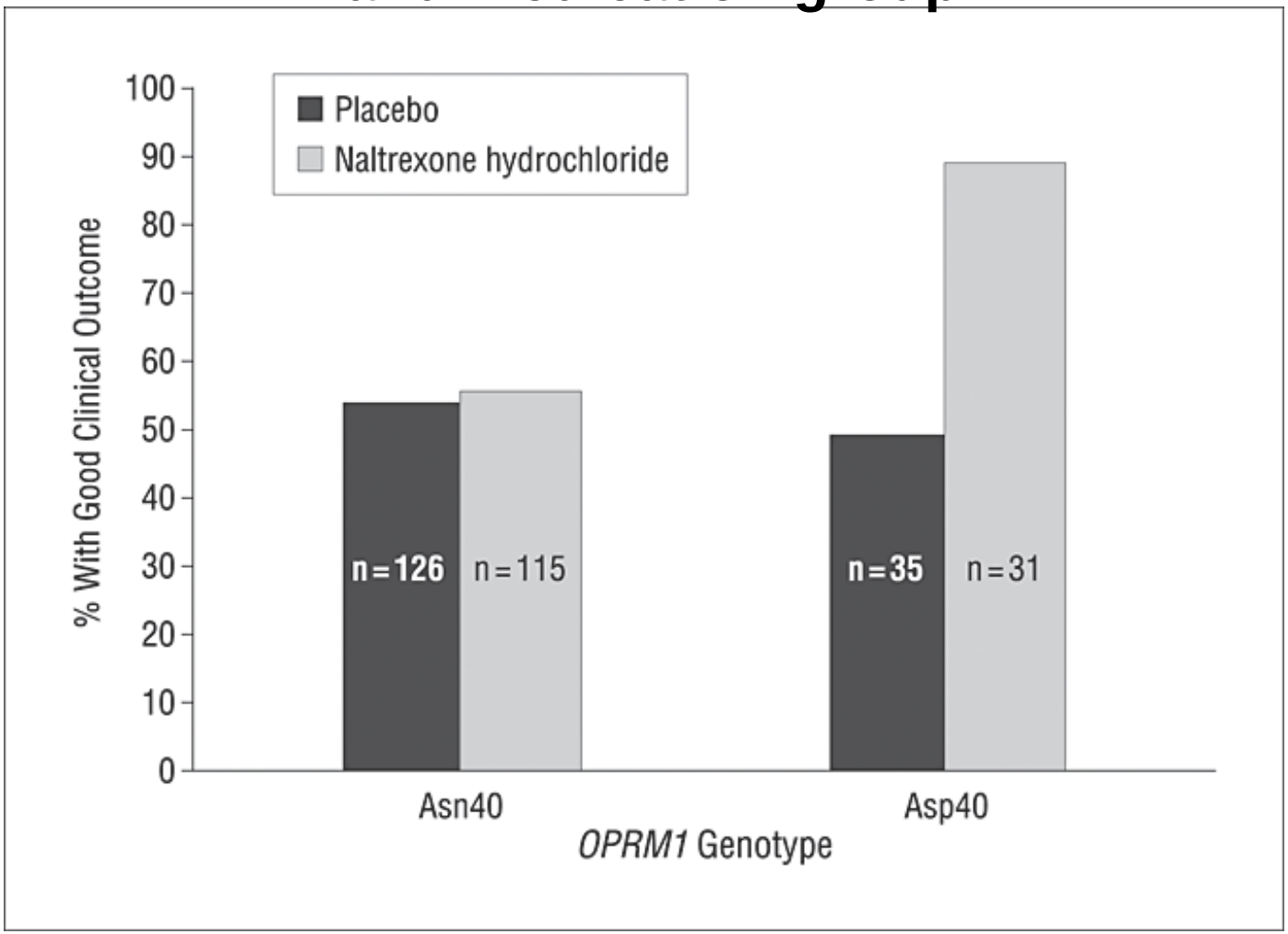
NALMEFENE

- 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



Mann K et al. Biol. Psychiatry 2013;73:706–713
Gual T et al. European Neuropsychopharm 2013;23:1432-42

Good clinical outcome based on OPRM1 and medication group



Medical management alone (no CBI). Genotype vs. medication interaction p=0.005
Anton, R. F. et al. Arch Gen Psychiatry 2008;65:135-144.

ARCHIVES OF GENERAL PSYCHIATRY

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The COMBINE Study

N=1383, 16 wk trial	Good Clinical Outcome %
Medical Management and Placebo	58
Medical Management and Placebo and **CBI**	71
Medical Management and **Naltrexone**	74

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)

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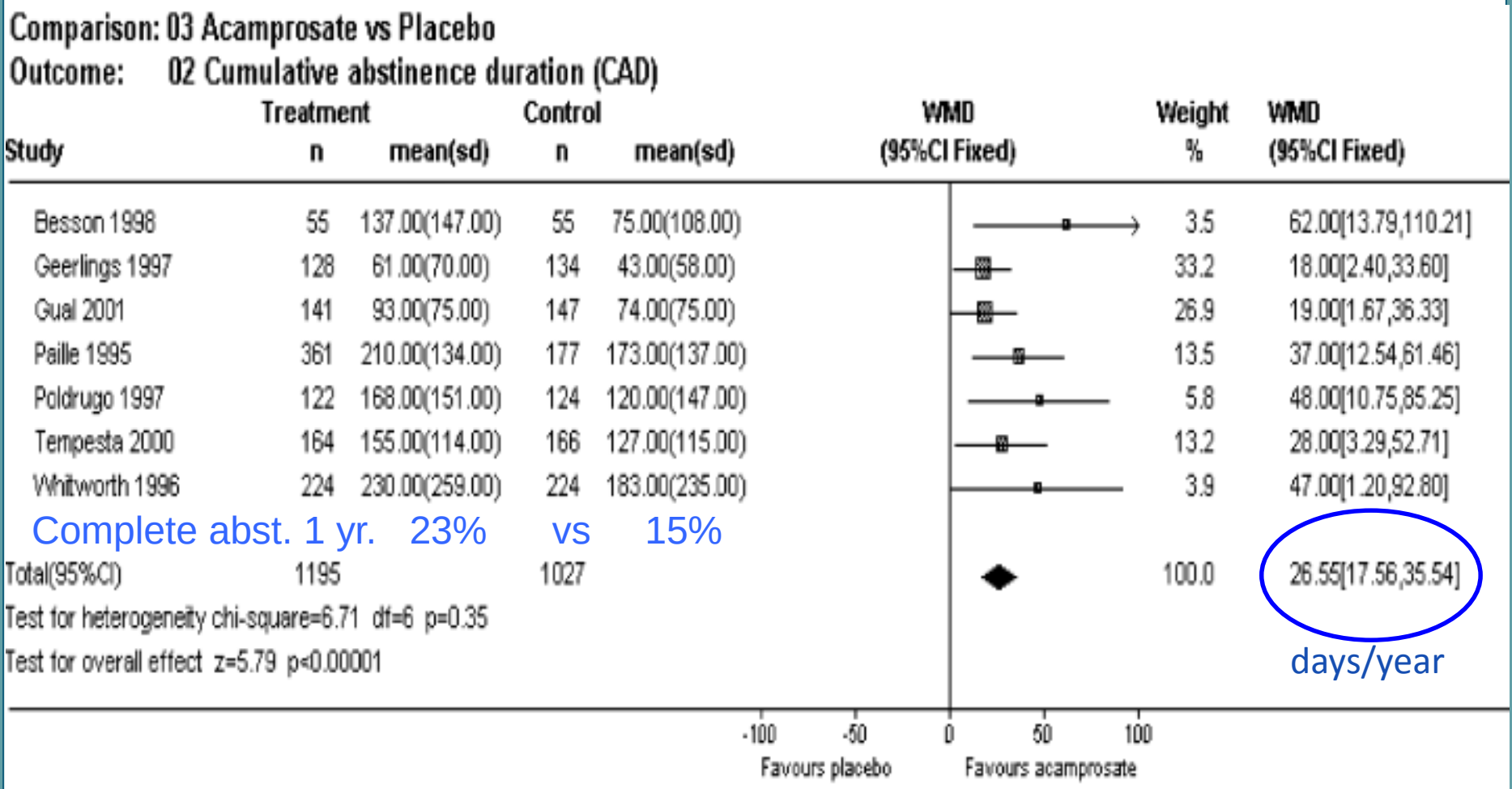
Efficacy of Acamprosate
"stabilizes activity in the glutamate system"



Bouza C et al. Addiction 2004;99:811

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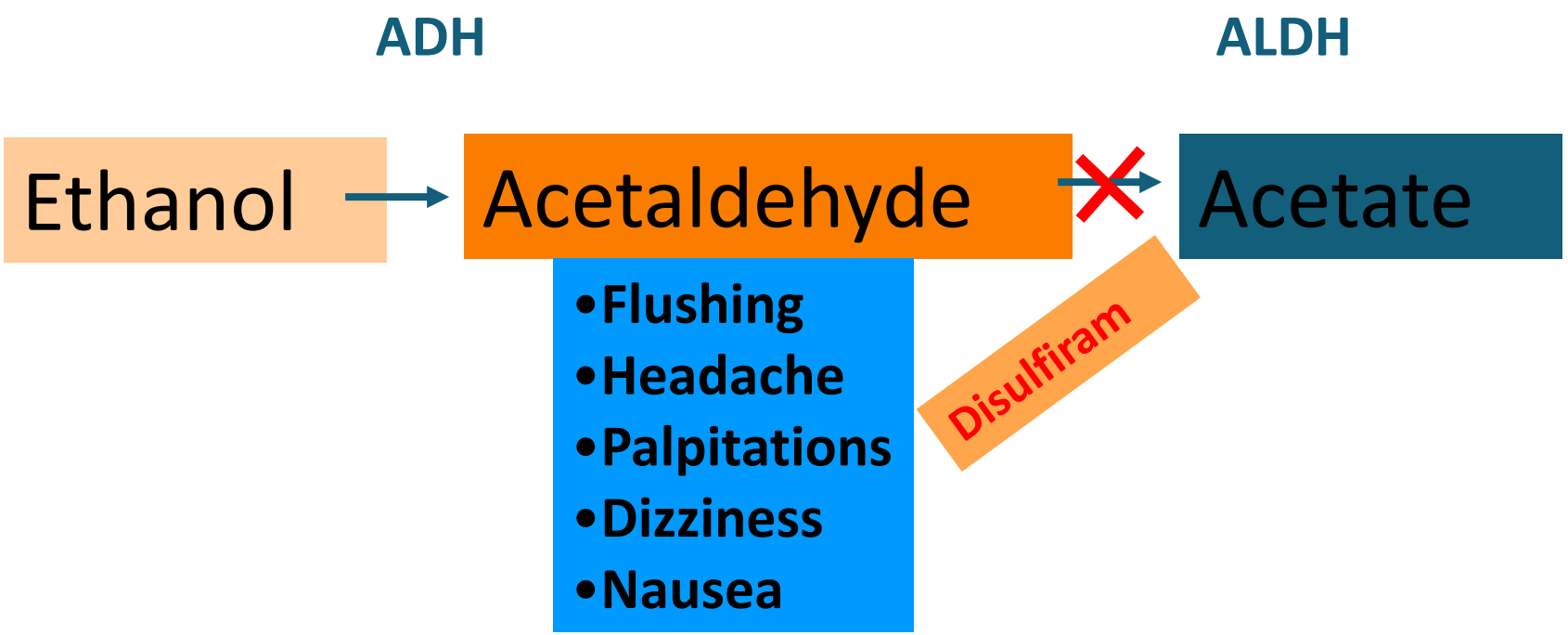
Prescribing Acamprosate

Acamprosate 666 mg tid

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

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%).

Fuller RK & Roth HP. Ann Intern Med. 1979;90(6):901-904.
Fuller RK et al. JAMA 1986;256:1449

Monitored Disulfiram: Small Randomized studies

Author, Yr	Follow-up	Disulfiram	Abstinence
Gerrein, 1973	85%, 39%	Monitored Unmonitored	40% 7%
Azrin, 1976	90%	Monitored Unmonitored	90-98% 55%
Azrin, 1982	100%	Monitored Unmonitored	73%* 47*
Liebson, 1978	78%	Monitored Unmonitored	98% 79%

Length of follow-up: Gerrein 1973: 8 weeks; Azrin 1976: 2 years, Azrin 1982: 6 months; Liebson 1978: 6 months.

*Thirty-day abstinence at 6 months.

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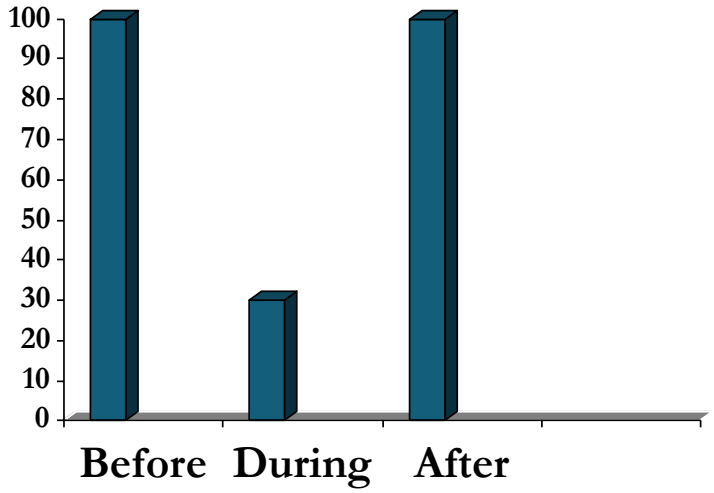
Prescribing Disulfiram

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



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The following medications are not approved by the FDA for the treatment of alcohol use disorder

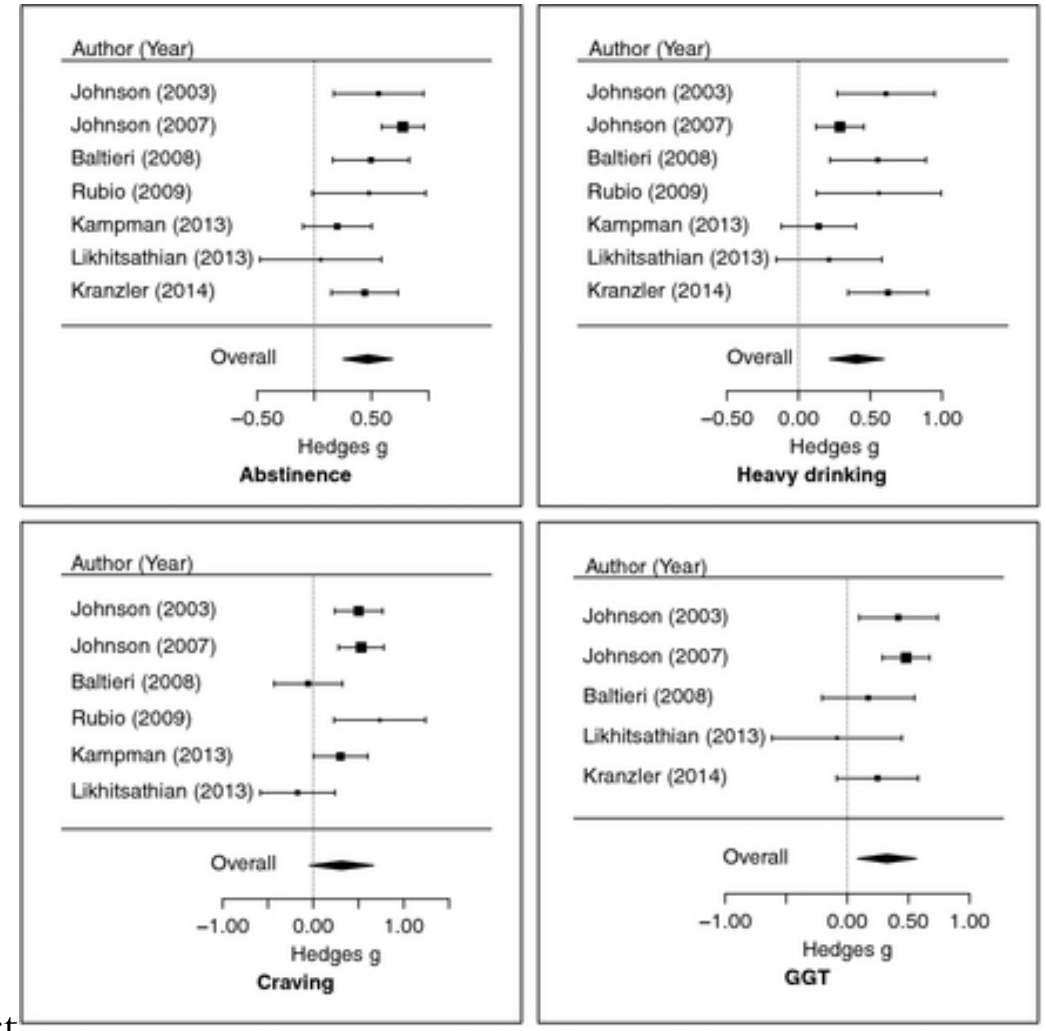
The following medications are not approved by the FDA for the treatment of alcohol use disorder

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)

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
http://onlinelibrary.wiley.com/doi/10.1111/acer.12411/full#acer12411-fig-0002

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From: **Topiramate for Treating Alcohol Dependence: A Randomized Controlled Trial**

JAMA. 2007;298(14):1641-1651. doi:10.1001/jama.298.14.1641

Intent to treat with baseline value imputed if follow-up missing

Received 1 dose and visit, no imputation

Table 3. Difference Between Placebo and Topiramate on the Self-Reported Drinking Measures and the Laboratory Marker of Drinking

Outcome	Mean (SD) Difference[a]				Mean Difference Between Study Groups (95% CI)[b]	*P* Value
	Baseline (Week 0)		Study End (Week 14)			
	Topiramate (n = 183)	Placebo (n = 188)	Topiramate (n = 183)	Placebo (n = 188)		
Primary Analytic Model of Imputing the Baseline Value for All Dropouts						
Self-reported and laboratory drinking measures[c]						
Heavy drinking days, %	81.91 (20.04)	81.97 (19.92)	43.81 (40.43)	51.76 (37.43)	8.44 (3.07 to 13.80)	.002
Days abstinent, %	9.64 (15.94)	9.35 (16.43)	37.56 (39.66)	29.06 (32.35)	–7.68 (–12.49 to –2.87)	.002
Drinks/drinking day	11.04 (4.62)	10.90 (5.11)	6.53 (5.44)	7.46 (4.93)	0.88 (0.25 to 1.51)	.006
Log GGT ratio[d]	3.88 (0.81)	4.00 (0.85)	–0.05 (0.09)	–0.02 (0.09)	0.03 (0.01 to 0.04)	<.001
Prespecified Mixed Model Analytic Approach						
Self-reported and laboratory drinking measures[e]	(n = 179)	(n = 185)	(n = 113)	(n = 144)		
Heavy drinking days, %	82.09 (20.08)	81.82 (20.02)	20.00 (30.46)	42.44 (36.38)	16.19 (10.79 to 21.60)	<.001
Days abstinent, %	9.48 (15.98)	9.45 (16.53)	54.94 (40.10)	34.48 (33.89)	–13.39 (–18.65 to –8.14)	<.001
Drinks/drinking day	11.05 (4.62)	10.94 (5.14)	3.62 (3.66)	6.33 (4.45)	1.77 (1.19 to 2.36)	<.001
Log GGT ratio[d]	3.89 (0.80)	3.99 (0.84)	–0.09 (0.12)	–0.02 (0.10)	0.05 (0.03 to 0.07)	<.001

Abbreviations: CI, confidence intervals; GGT, γ-glutamyl transferase.

Also lower blood pressure, BMI and overall clinical improvement

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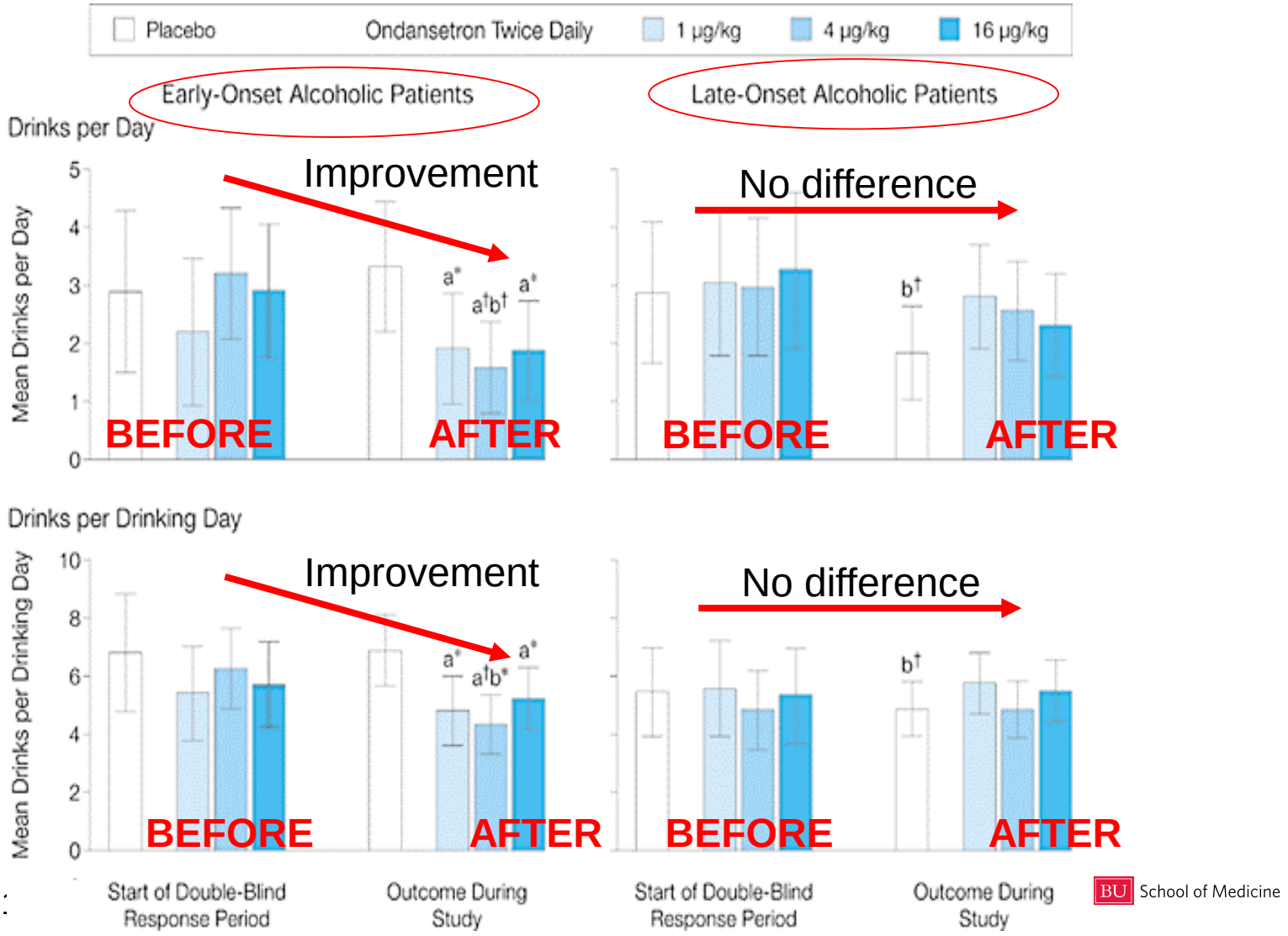
Prescribing Topiramate

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

Ondansetron

- 5HT3 antagonist



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

From: **Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial**

JAMA Intern Med. 2014;174(1):70-77. doi:10.1001/jamainternmed.2013.11950

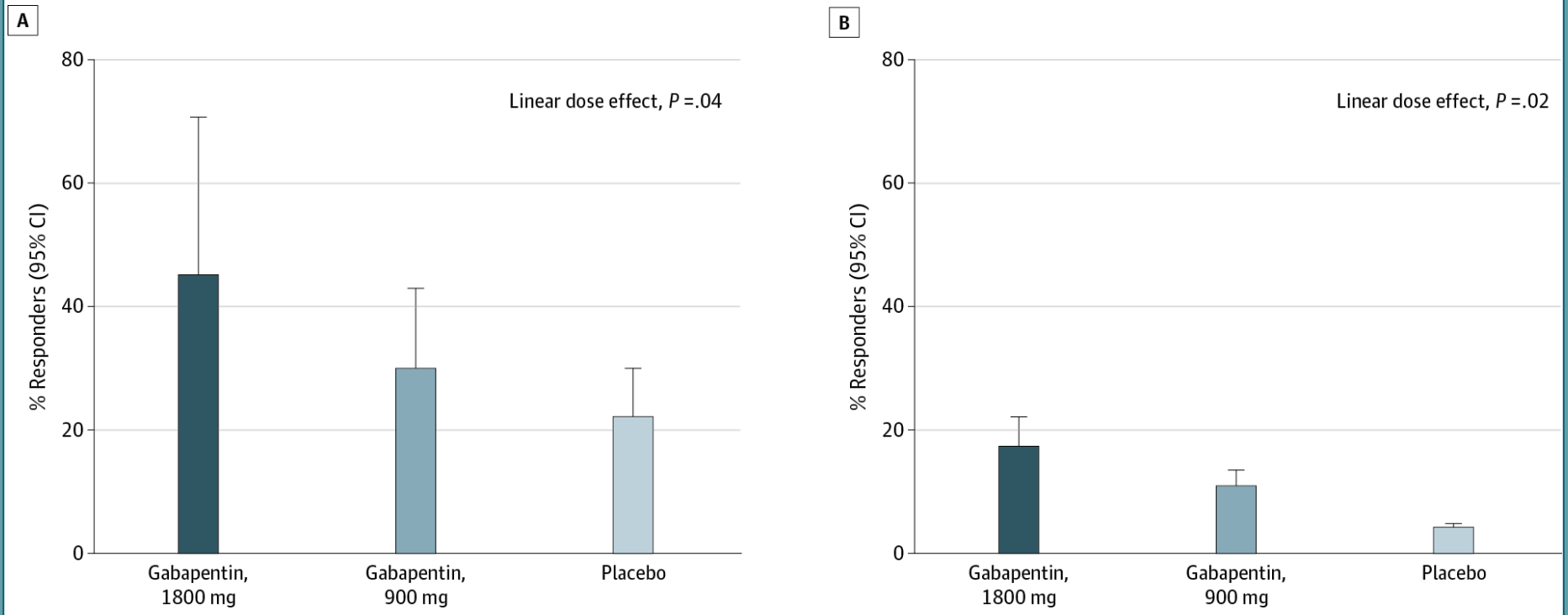
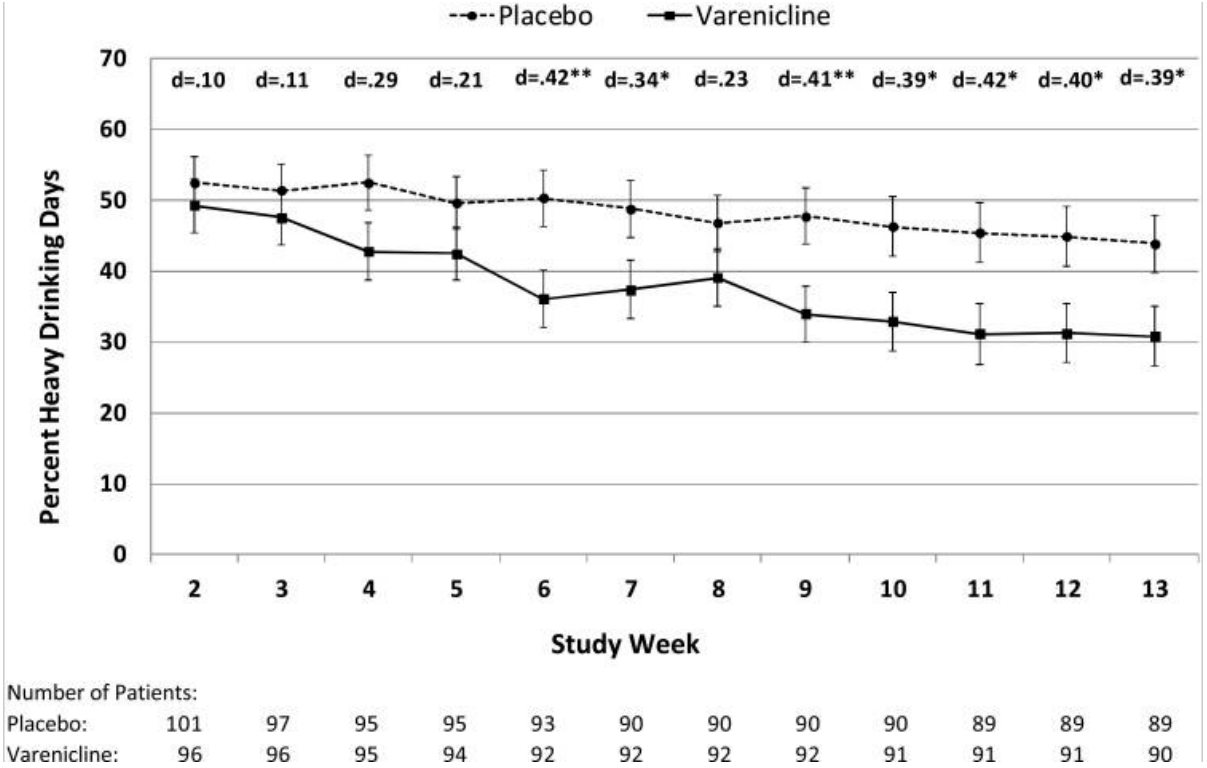


Figure Legend:

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).

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.



Litten RZ et al. J Addiction Med 2013;7:277-86.

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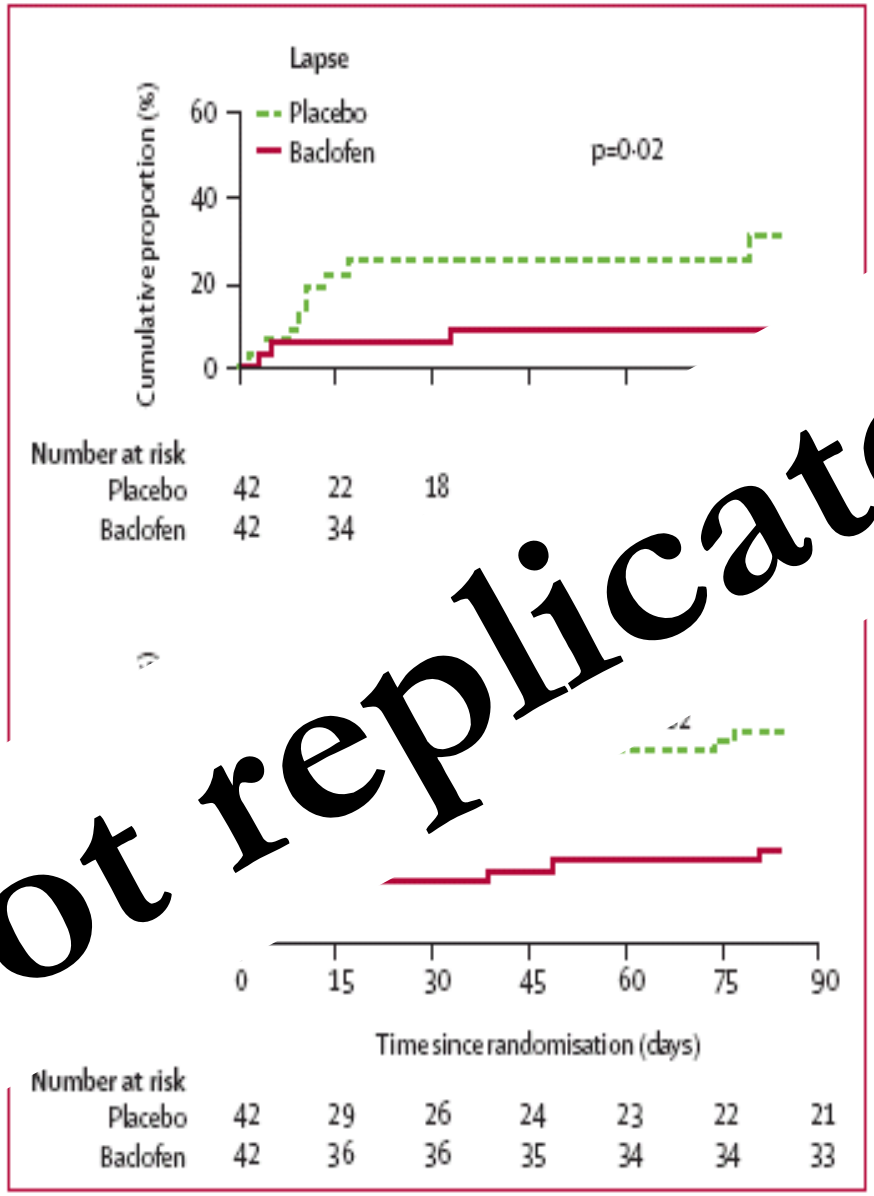
Baclofen



...unence:
71% vs. 29%

Not replicated

Addolorato G et al. *Lancet.* 2007;370(9603):1915–1922.

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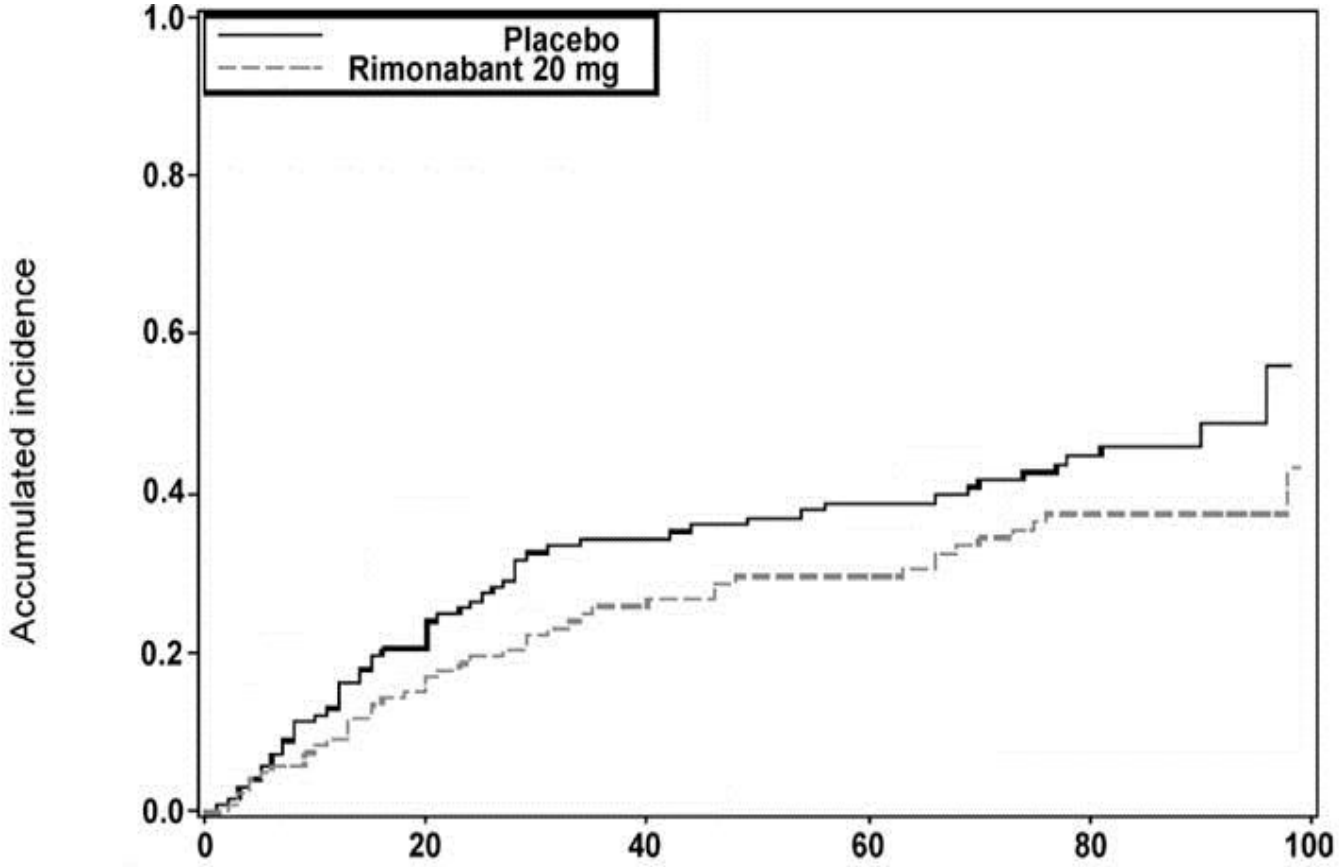
Rimonabant

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



Placebo	n	123	93	75	66	53
Rimonabant 20 mg	n	123	97	79	73	62

Soyka M et al. J Clin Psychopharm 2008;28(3):317-324

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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
- Medication treatment of anxiety (e.g. buspirone) and depression (e.g. fluoxetine) can decrease alcohol consumption (data not shown)

TREATMENT EFFECTIVENESS

- At one year, 2/3^{rds} of patients have a reduction in
  - alcohol consequences (injury, unemployment)
  - consumption (by 50%)
- 1/3rd 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)

Miller WR et al. J Stud Alcohol 2001;62:211-20
Anon. Journal of Studies on Alcohol 1997;58:7-29,
O'Brien CP, McLellan AT. Lancet 1996;347:237-240 and JAMA 2000:284:1689-95.

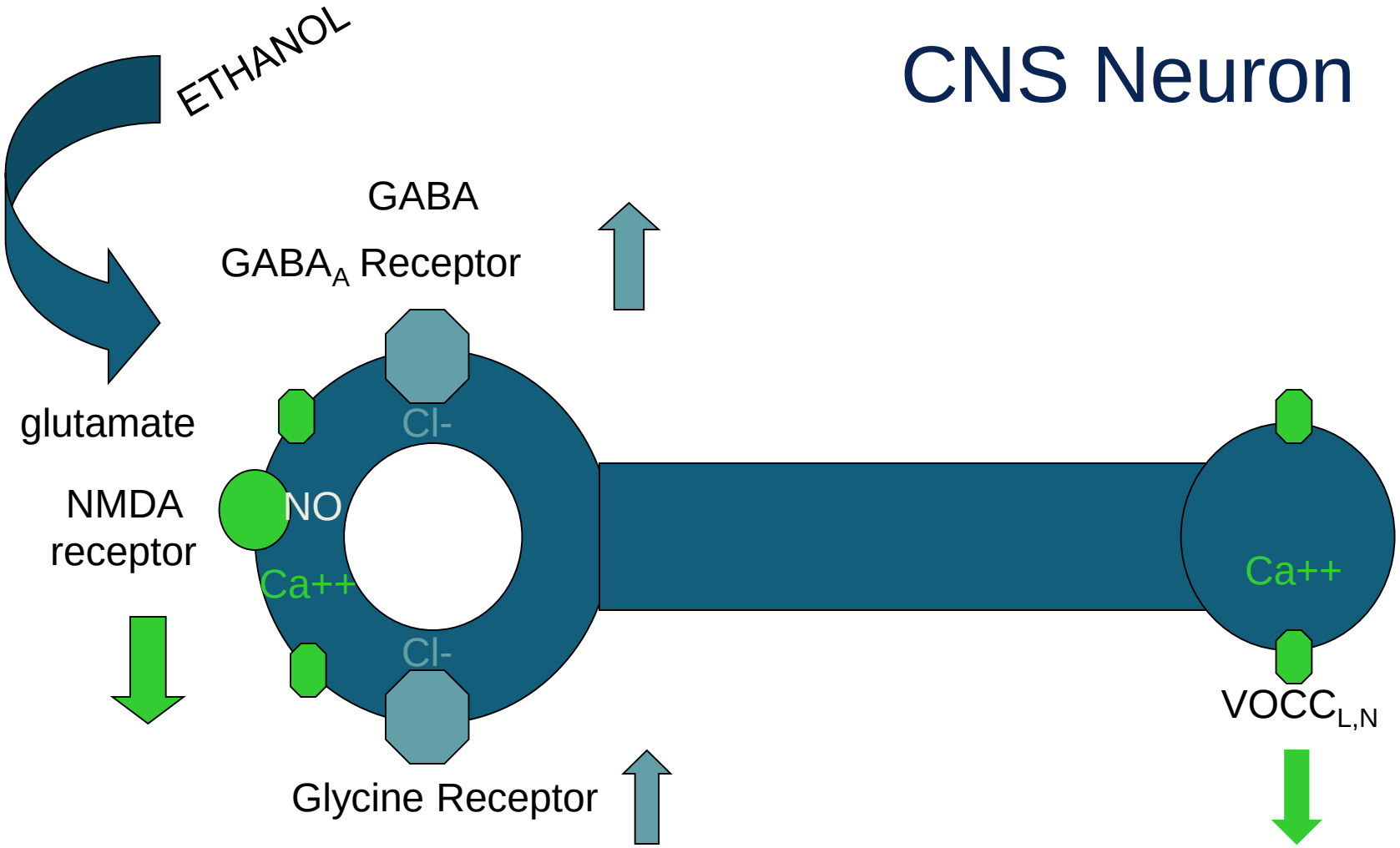
SUMMARY

- Benzodiazepines for withdrawal; individualize
- Pharmacotherapy

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

EXTRA SLIDES

CNS Neuron



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)

Pletcher et al. J Qual Pat Safety 2005;31:148-57
Hecksel et al. Mayo Clin Proc 2008;83:274-9

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

NSSATS 2002, D'Aunno 2004 & McClellan AT et al. J Subst Abuse Treat 2003

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).

E. Cobham Brewer 1810–1897. Dictionary of Phrase and Fable. 1898.

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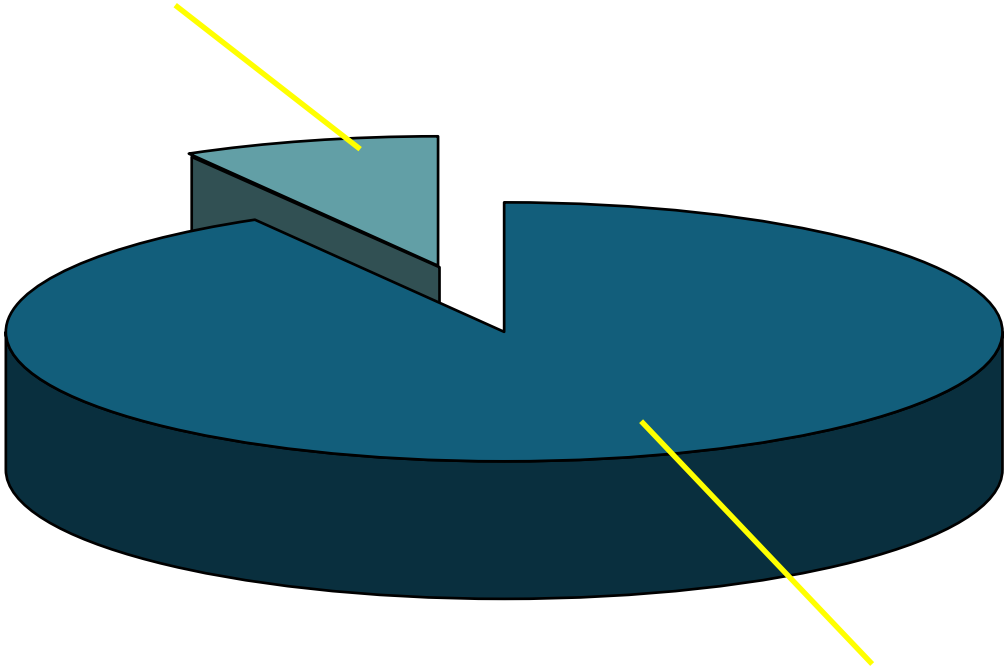
Alcohol Use Disorder: Treatment Gap

1,600,000 (8%) received treatment



17,900,000 (92%) did not

OAS, CSAT, SAMHSA NSDUH 2006
Green-Hennessey 2002; NSDUH 2009; NAMCS 2008

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Prescriptions for the 4 FDA approved Rxs

	Disulfiram	Naltrexone	Acamprosate	Injectable naltrexone
Prescriptions	179,000	221,000	306,000	15,000
Cost per rx	$78	$100	$114	$489

- 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
Harris KM et al. Psychiatr Serv 2004;55(3):221

Table 3. Difference Between Topiramate and Placebo on Physical and Psychosocial Measures of Health by the Primary (Mixed Model) Analytic Approach[a]

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

Johnson BA et al. Arch Intern Med 2008;168(11):1188-99