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Research and Education

Management of Unhealthy Alcohol Use: From Research to Practice

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Opportunities to talk about alcohol

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- 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

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- 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

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- 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

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Case

A 43 year old man presents with epigastric discomfort and vomiting for 1 day.

Breath alcohol is 210 mg/dL (0.21 g/100mL).

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Case (continued)

He fell in the kitchen and bumped his head.

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.

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Case (continued)

T 98, RR 20, HR 110 (regular), BP 110/82 standing, 96, 140/70 lying down.

Unable to visualize fundi, EOMI, supple neck, mild epigastric tenderness, no tremor, frontal ecchymosis.

He is awake, alert and oriented to place, time and person. Speech is fluent. Gait normal. Sensorimotor exam non-focal.

Initial laboratory studies are pending.

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Intoxication

- Is he intoxicated (legal versus medical)?
- There is a differential

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Intoxication (DSM-IV)

- Reversible, substance-specific, recent ingestion
- Significant behavioral or psychological changes due to CNS effect during or shortly after use

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Case (continued)

Four hours later (15-20 mg/dL/hr [1 drink] elimination), the patient becomes tremulous, anxious, and continues to have nausea. BP 134/84, HR 90, ethanol level 146 mg/dl.

- What is the diagnosis?
- What is appropriate management?

Alcohol Withdrawal (DSM-IV)

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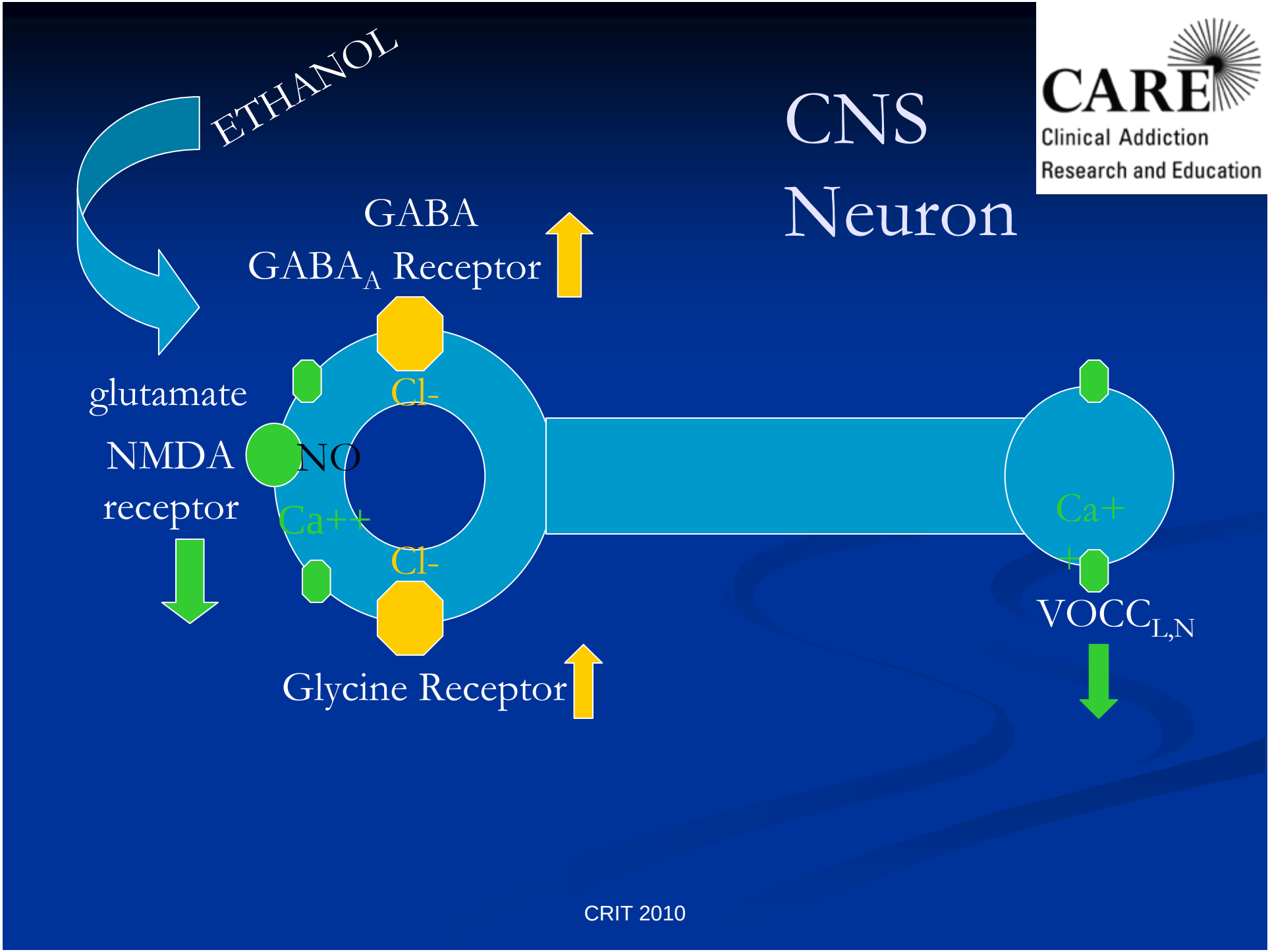
- Cessation or reduction in alcohol use that has been heavy and prolonged
- Two or more of the following, developing in hours to days, causing distress or impairment, not due to other condition
  - Autonomic hyperactivity (sweating, tachycardia)
  - Increased hand tremor
  - Insomnia
  - Nausea or vomiting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


ETHANOL
CNS
Neuron
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GABA
GABA$_A$ Receptor
glutamate
NMDA
receptor
Cl-
NO
Ca++
Cl-
Ca+
+
VOCC$_{L,N}$
Glycine Receptor

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Benzodiazepines vs. Placebo

Outcome: 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

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Benzodiazepines vs. Placebo
Outcome: Delirium

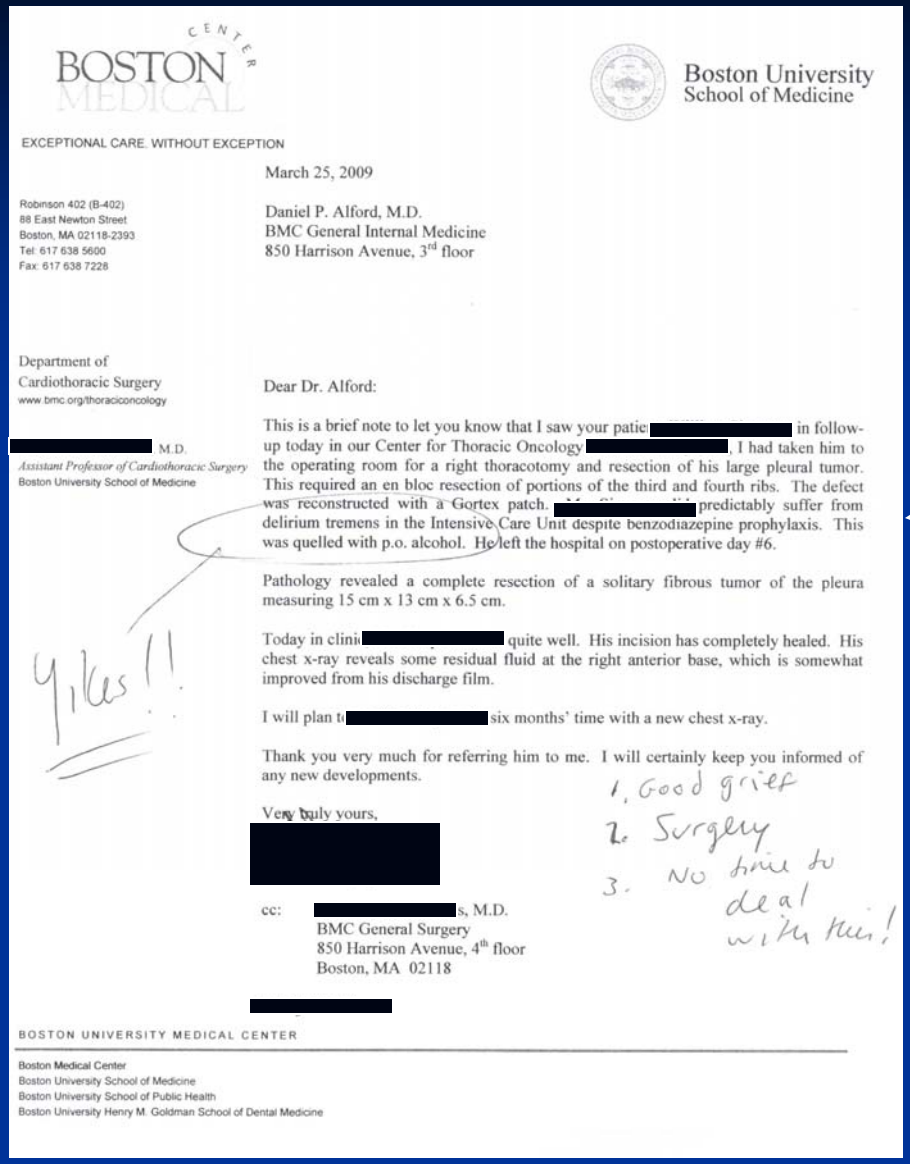
Chlordiazepoxide	3/172 (2%)
Placebo	11/186 (6%)

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

Alcohol Withdrawal
Alcohol

- Pros
  - The perfect cross-tolerant drug
  - The alcoholic's drug of choice
- Cons
  - Two controlled trials: in one (Gower 1980), more DTs and seizures c/w chlordiazepoxide; in the only *R*CT (Spies 1995) no diff c/w benzo+haloperidol or clonidine
  - Narrow toxic to therapeutic index
  - Many toxicities (hepatitis, gastritis, pancreatitis, marrow suppression...)
  - Need to monitor and adjust levels
  - Reinforces acceptability and continued use



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EXCEPTIONAL CARE. WITHOUT EXCEPTION

March 25, 2009

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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]

1. Good grief
2. Surgery
3. No time to deal with this!

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

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

ASAM Practice Guidelines
Treatment approaches

- **Monitor** q 4-8 hrs until symptoms improved
- **Symptom-triggered** (q 1 when CIWA≥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
Saitz and O'Malley Med Clin N A 1997;81:881-907

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Case (continued)

The patient is seen having a generalized tonic-clonic convulsion.

- What is the most likely etiology?
- What is the appropriate work-up?

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Alcohol Withdrawal

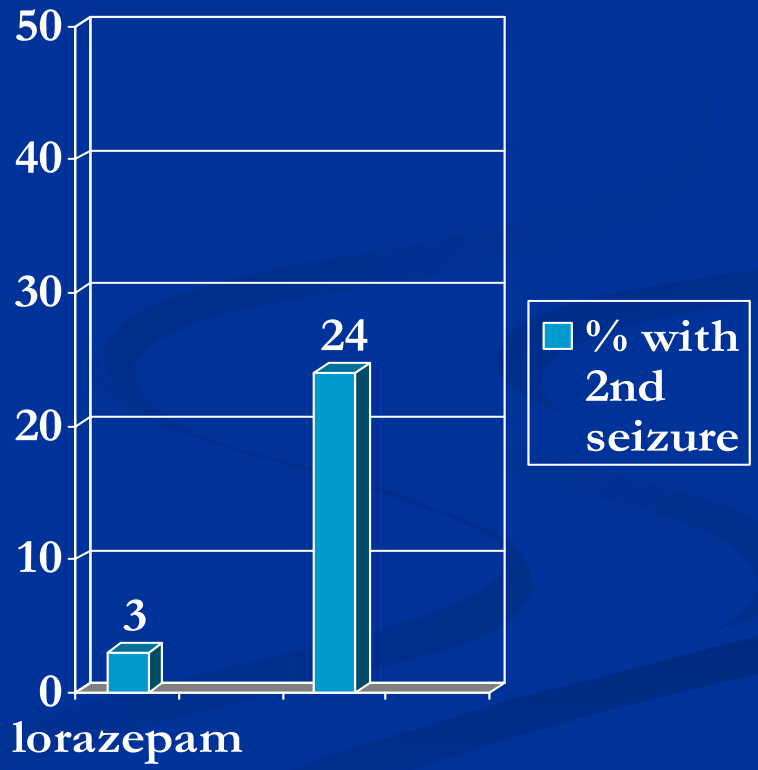
Seizures: Diagnosis

- 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

Victor & Brausch. Epilepsia 1967;8:1, Feussner et al. Ann Int Med 1981;94:519, Lechtenberg 1990

Seizure Recurrence

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



D'Onofrio G et al. N Engl J Med 1999;340:915-919.

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Case (continued)

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?

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Alcohol Withdrawal
DTs: Treatment

- 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

Thompson, Maddrey, Osler Medical Housestaff. Ann Int Med 1978;82:175

Alcohol Withdrawal Settings

- 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

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Management of Unhealthy Alcohol Use

- Detoxification is not treatment
- **Brief Intervention**
- Treatment
  - Counseling
  - **Pharmacotherapy**
- Self and mutual help

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Ingredients of Successful Brief Interventions

- What?
  - -10-15 minutes
  - -Feedback
  - -Advice
  - -Goal Setting
  - -Follow-up
- How?
  - -Empathy
  - -Self-efficacy
  - -Menu

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Efficacy of Brief Intervention

- Proportion of drinkers of risky amounts decreased from 69% (942/1374) to 57% (810/1410)
- Consumption decreased 15% (by 38 grams [about 3 standard drinks] per week)(n=5639)

Beich et al. BMJ 2003;327:536
Bertholet et al. Arch Intern Med. 2005;165:986

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Treatment in Medical Settings:
Project TrEAT

- RCT, 17 practices, 64 physicians
- N=774
  - Men >14 drinks/wk
  - Women >11 drinks/wk
- 93% 12 month follow-up
- Control: health booklet
- Intervention: health booklet + 2 10-15" physician discussions and a follow-up nurse phone call

Fleming MF, Lawton Barry K, et al. JAMA 1997;277:1039

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Project TrEAT Results

	Control before/after	Intervention before/after
Drinks/7d*	19/16 (-18%)	19/12 (-40%)
Binges/30d*	5/4 (-21%)	6/3 (-46%)
Hosp days*	42/146 (+248%)	93/91 (-1%)

*p<0.001

Fleming MF, Lawton Barry K, et al. JAMA 1997;277:1039

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Efficacy and Cost of Advice

TrEAT Long-term Follow-up

At 4 years…	Control	Intervention
Hospital Days (p<0.05)	663	420
ED Visits (p<0.08)	376	302
Risky Drinking* (p<0.001)	35%	23%

Cost of intervention: $166 per patient
(includes patient costs)

Net benefit: $546 in medical costs,
$7780 if societal costs included (mainly motor vehicle)

**36 months. >20 drinks (men), >13 drinks (women) per week*

Fleming MF et al. Alcohol Clin Exp Res. 2002;26(1):36-43.

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The Malmö Study

- Population-based cohort of middle-aged men identified by screening with upper decile GGT as isolated abnormality and at least 20 g alcohol daily
- Randomized to
  - GGT + RN q mo, MD q 3 mo
  - letter—GGT is high, restrict alcohol, F/U in 2 years
- 78% follow-up (4 years)

Kristenson H, et al. Alcohol Clin Exp Res 1983;7:203

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The Malmö Study

- 5-year hospital **utilization** decreased by 50% in 5 years (total approx. 1600 vs 800 days, mainly alcohol-related)
- **Sick days** decreased in intervention group
- **GGT** decreased in both groups (4 yrs)
- 16-year **mortality** decreased in intervention group
  - Total mortality: 10% vs. 14% (NS)
  - Alcohol-related (48% of all deaths): 4% vs. 7% (p=0.03)

Kristenson H, et al. Alcohol Clin Exp Res 1983;7:203

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Brief intervention in inpatients

- Systematic review: 11 studies, 5 in general medical settings, 2441 patients, 3 studies assessed drinking outcomes
- Weekly consumption: no differences 6 (n=2) and 12 mo (n=3)
- Decrease in weekly consumption at 12 mo (n=2)
- No studies found differences between BI patients and controls for laboratory markers, heavy drinking episodes, driving offenses, or death.

McQueen J, et al. *Cochrane Database Syst Rev.* 2009;(3):CD005191.

BRIEF INTERVENTION: EFFICACY, DRUGS

- 5 controlled studies in people *identified by screening*
  - DeMicheli et al, adolescents, primary care (Brazil)
  - Bernstein et al, in adult outpatients (US)
  - Humeniuk R et al, WHO ASSIST trial (international, multi-site)
  - Zahradnik A et al, hospitalized adults (Germany)
  - Bernstein et al, in pediatric emergency department patients

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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."

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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)

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

Patient Selection for Pharmacotherapy

- All people with alcohol dependence who are:
  - currently drinking
  - experiencing craving or at risk for return to drinking or heavy drinking
- Considerations
  - Specific medication contraindications
  - Willingness to engage in psychosocial support/therapy
  - Relationship/willingness to follow-up with health provider
  - Outpatient or inpatient clinical setting with prescriber, access to monitoring (e.g. visits, liver enzymes)

Disulfiram

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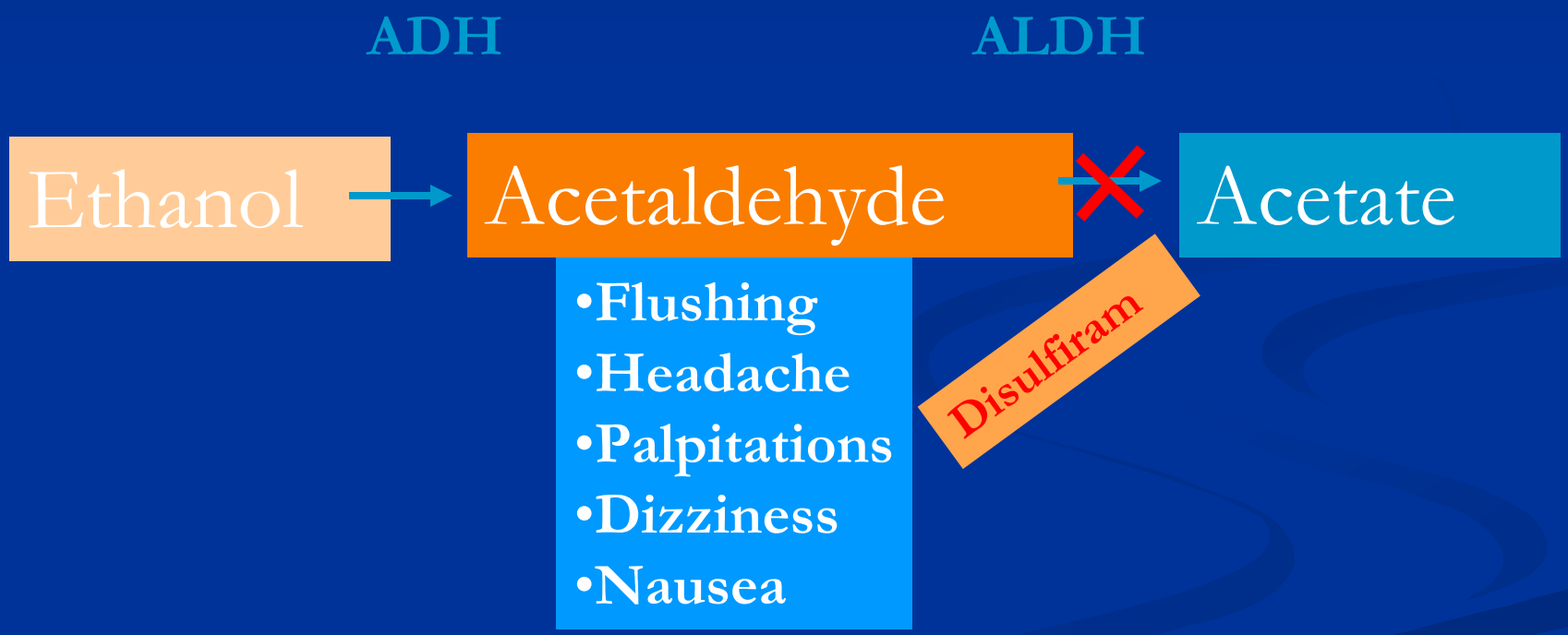

Fuller RK et al. JAMA 1986;256:1449

Monitored Disulfiram: Randomized studies

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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 was as follows: Gerrein 1973: 8 weeks; Azrin 1976: 2 years, Azrin 1982: 6 months; Liebson 1978: 6 months. * Thirty-day abstinence at 6 months

Length of follow-up was as follows: Gerrein 1973: 8 weeks; Azrin 1976: 2 years, Azrin 1982: 6 months; Liebson 1978: 6 months. * Thirty-day abstinence at 6 months

Prescribing

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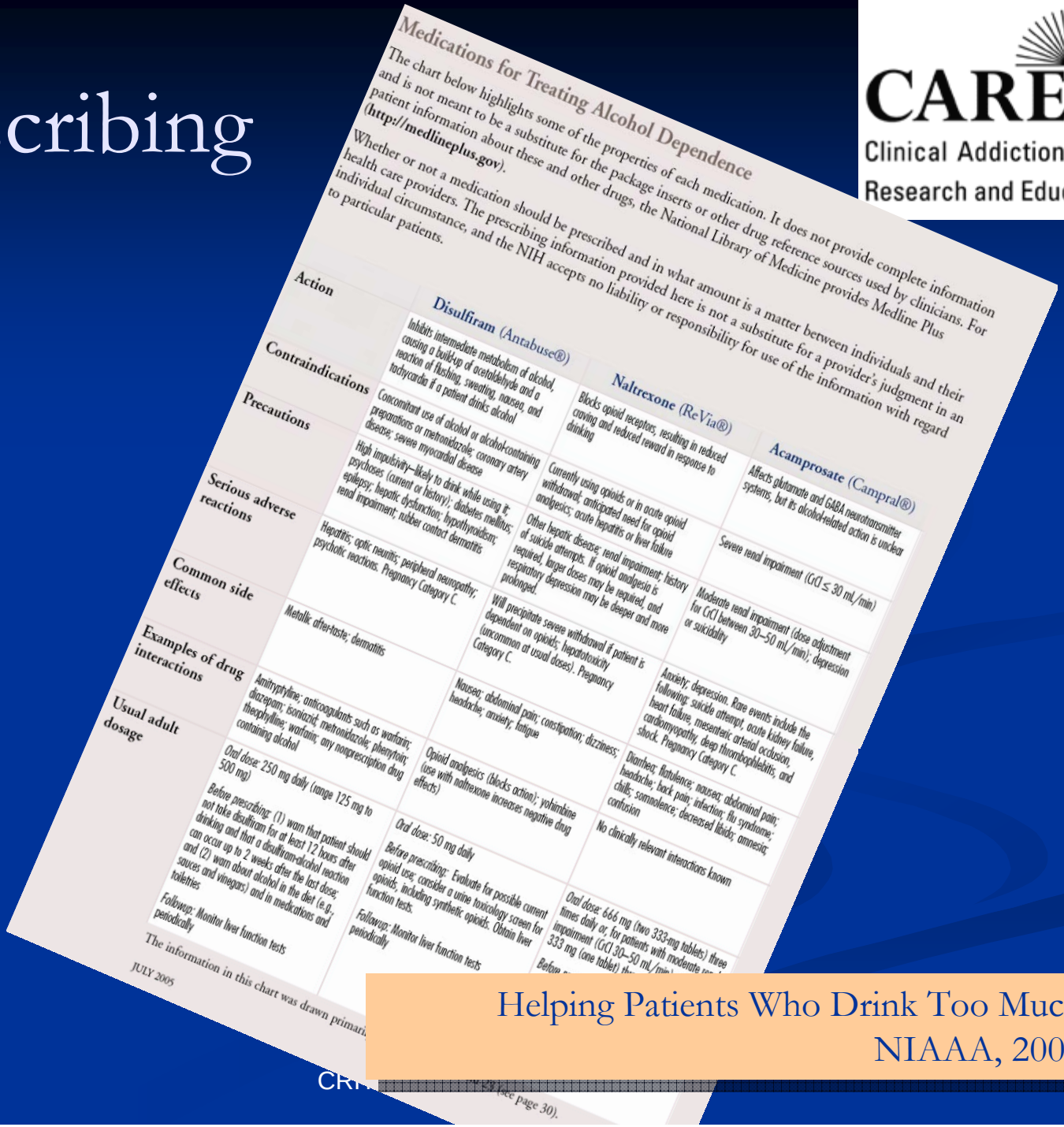

Medications for Treating Alcohol Dependence

The chart below highlights some of the properties of each medication. It does not provide complete information and is not meant to be a substitute for the package inserts or other drug reference sources used by clinicians. For patient information about these and other drugs, the National Library of Medicine provides Medline Plus (http://medlineplus.gov).

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

Action	Disulfiram (Antabuse®)	Naltrexone (ReVia®)	Acamprosate (Campral®)
Contraindications	Inhibits intermediate metabolism of alcohol, causing a build-up of acetaldehyde and a reaction of flushing, sweating, nausea, and tachycardia if a patient drinks alcohol	Blocks opioid receptors, resulting in reduced craving and reduced reward in response to drinking	Affects glutamate and GABA neurotransmitter systems, but its alcohol-related action is unclear
Precautions	Concomitant use of alcohol or alcohol-containing preparations or metronidazole; coronary artery disease; severe myocardial disease	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)
Serious adverse reactions	High impulsivity—likely to drink while using it; psychoses (current or history); diabetes mellitus; epilepsy; hepatic dysfunction; hypothyroidism; renal impairment; rubber contact dermatitis	Other hepatic disease; renal impairment; history of suicide attempts. If opioid analgesia is required, larger doses may be required, and respiratory depression may be deeper and more prolonged.	Moderate renal impairment (dose adjustment for CrCl between 30–50 mL/min); depression or suicidality
Common side effects	Hepatitis; optic neuritis; peripheral neuropathy; psychotic reactions. Pregnancy Category C.	Will precipitate severe withdrawal if patient is dependent on opioids; hepatotoxicity (uncommon at usual doses). Pregnancy Category C.	Anxiety; depression. Rare events include the following: suicide attempt, acute kidney failure, heart failure, mesenteric arterial occlusion, cardiomyopathy, deep thrombophlebitis, and shock. Pregnancy Category C.
Examples of drug interactions	Metallic after-taste; dermatitis	Nausea; abdominal pain; constipation; dizziness; headache; anxiety; fatigue	Diarrhea; flatulence; nausea; abdominal pain; headache; back pain; infection; flu syndrome; chills; somnolence; decreased libido; amnesia; confusion
Usual adult dosage	Amitriptyline; anticoagulants such as warfarin; diazepam; isoniazid; metronidazole; phenytoin; theophylline; warfarin; any nonprescription drug containing alcohol	Opioid analgesics (blocks action); yohimbine (use with naltrexone increases negative drug effects)	No clinically relevant interactions known
	Oral dose: 250 mg daily (range 125 mg to 500 mg) Before prescribing: (1) warn that patient should not 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) warn about alcohol in the diet (e.g., sauces and vinegars) and in medications and toiletries Followup: Monitor liver function tests periodically	Oral dose: 50 mg daily Before prescribing: Evaluate for possible current opioid use; consider a urine toxicology screen for opioids, including synthetic opioids. Obtain liver function tests. Followup: Monitor liver function tests periodically	Oral dose: 666 mg (two 333-mg tablets) three times daily or, for patients with moderate [illegible] impairment (CrCl 30–50 mL/min), 333 mg (one tablet) [illegible]

The information in this chart was drawn primari[illegible]

JULY 2005

[illegible] (see page 30).

Helping Patients Who Drink Too Much
NIAAA, 2007

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Prescribing Disulfiram

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

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

Acamprosate

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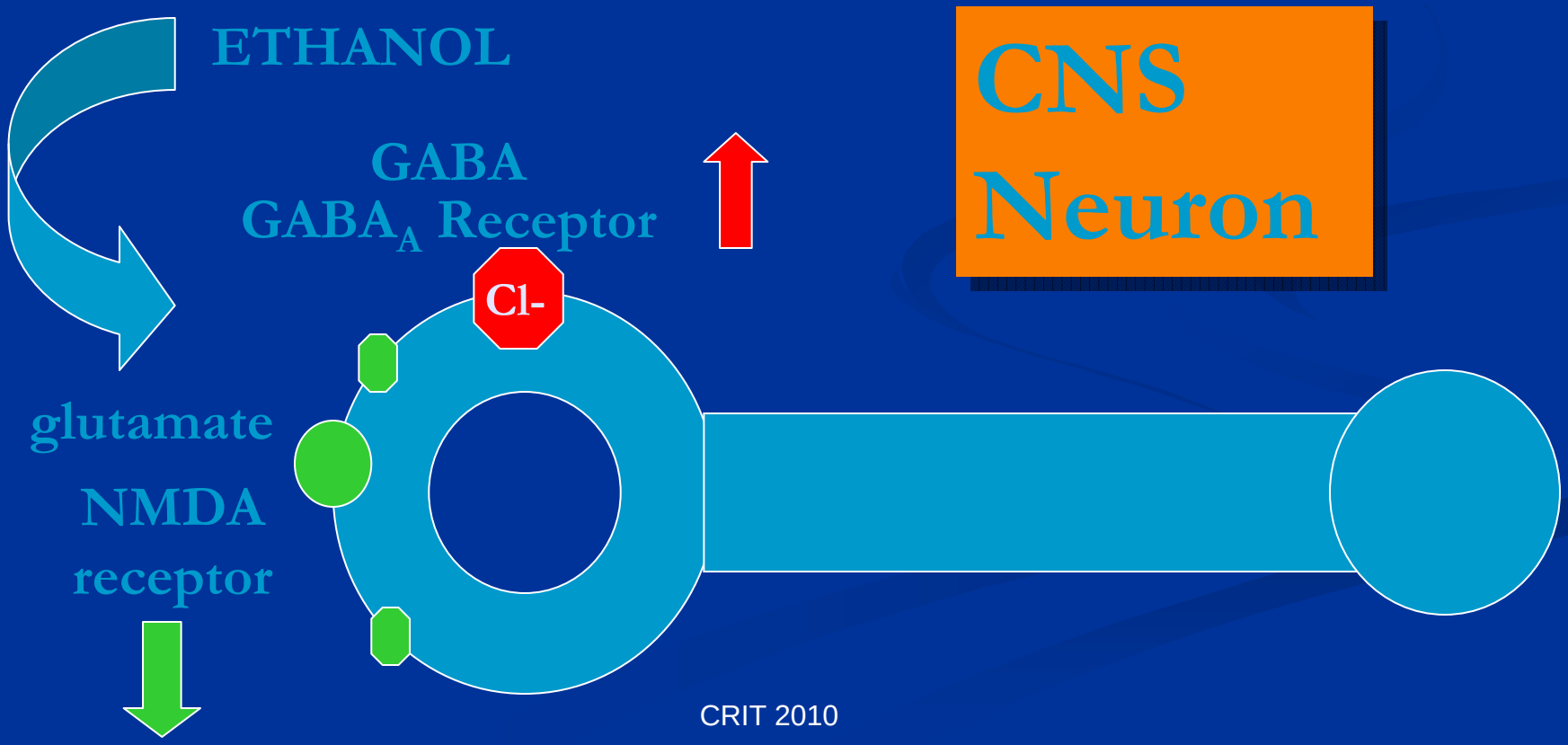
Stabilizes activity in the glutamate system



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Efficacy of Acamprosate

- Acamprosate vs. Placebo
- 7 studies, Treatment n=1195, Control n=1027
- Weighted mean difference favoring acamprosate (cumulative abstinence)
  - 27 days (95% CI 18 days, 36 days), p<0.00001
- Proportion of patients continuously abstinent for one year
  - Acamprosate 23%, Placebo 15%

Bouza C et al. Addiction 2004;99:811

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

Naltrexone

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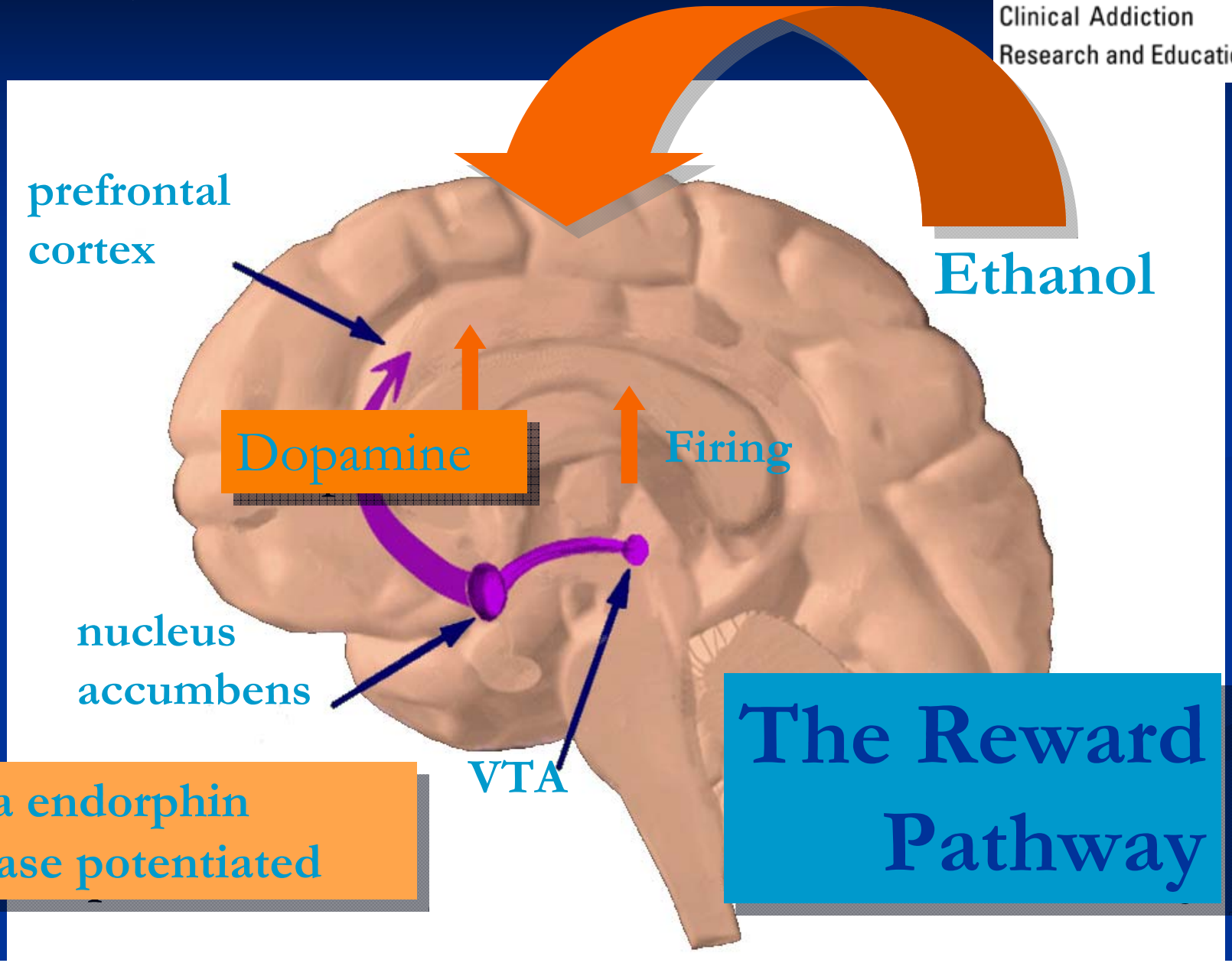

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Efficacy of Naltrexone

- 14 studies
- Relapse to heavy drinking
  - Naltrexone 428/1142 (37%), Control 445/930 (48%)
    - $p<0.00001$
- Odds Ratio (favoring naltrexone)
  - 0.62 (95% CI 0.52,0.75)

Bouza C et al. Addiction 2004;99:811

Bouza C et al. Addiction 2004;99:811

Injectable Naltrexone

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- 6-month RDBPCT, 180 mg, and 360 mg
- BRENDA every 2 weeks
- 92% abstinent for at least a week
- 43% abstinence goal
- RESULTS, 360 mg compared with placebo
  - 25% greater decrease in heavy drinking days
    - Median 3 vs. 6 heavy drinking days
      - Small subset abstinent @ baseline (n=36), 80% reduction
        - 41% vs. 17% complete abstinence, not stat. sig.

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Prescribing Naltrexone

Naltrexone 12.5 mg/d-->25 mg/d-->50 mg/d or 380 mg IM per month (VIP^3 program)

- Main contraindication:
  opiates, pregnancy
- Main side effects:
  nausea, dizziness

Pharmacotherapy Issues

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- Most subjects abstinent at study entry
- Modest effects

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Pharmacotherapy: other

- Topiramate
- Ondansetron
- Others
- Context: medical management

Topiramate, n=371, RCT

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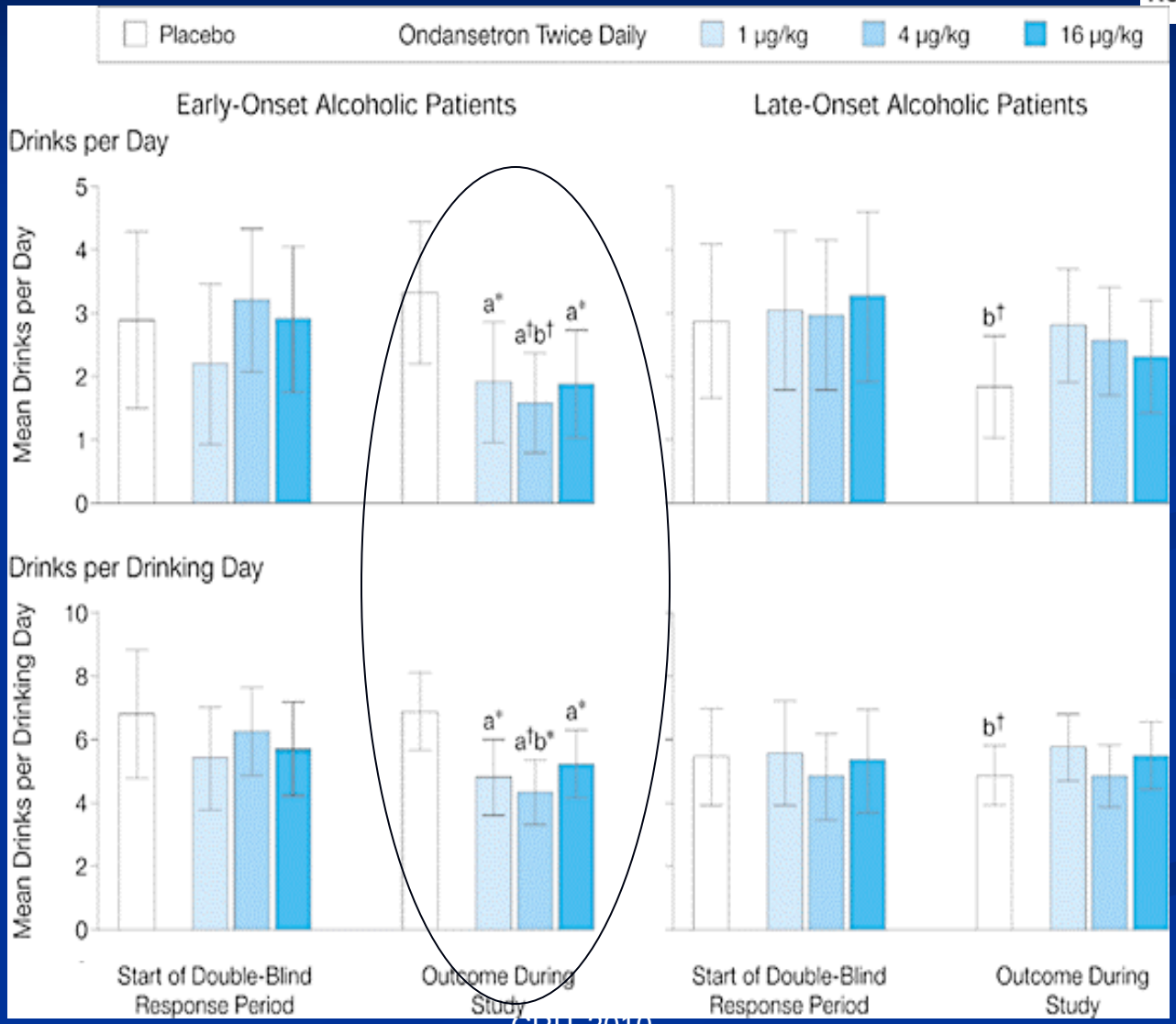
- Similar mechanism as acamprosate
- In analyses that considered all dropouts as having relapsed to baseline measures, topiramate recipients…
  - Had greater reductions in the percentage of drinking days (from a mean of 82% in both groups to **44%** among topiramate recipients, compared with **52%** for placebo recipients),
  - Had greater reductions in liver enzymes
  - Had greater increases in abstinent days (from a mean among topiramate recipients of 10% to **38%** compared with 9% to **29%** for placebo recipients)
  - Achieved ≥28 days of both continuous abstinence and continuous non-heavy drinking *sooner* than did placebo recipients

Johnson BA, et al. *JAMA*. 2007;298(14):1641–1651.

Ondansetron

- 5HT3 antagonist



Johnson BA et al. JAMA 2000;284:963-71

Good clinical outcome based on OPRM1 and medication group in those receiving medical management alone (no combined behavioral intervention) (test of genotype x medication interaction, P = .005)

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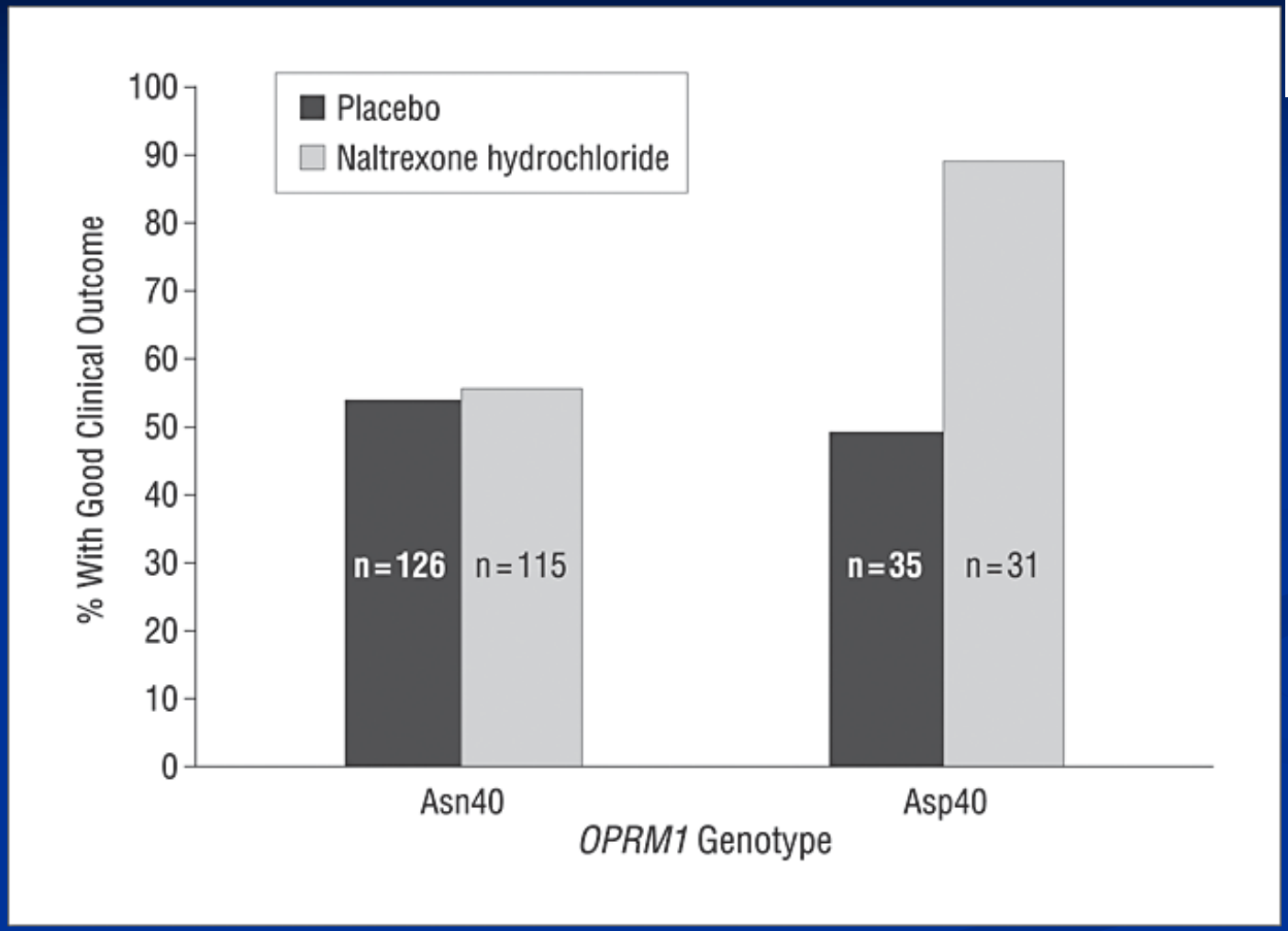


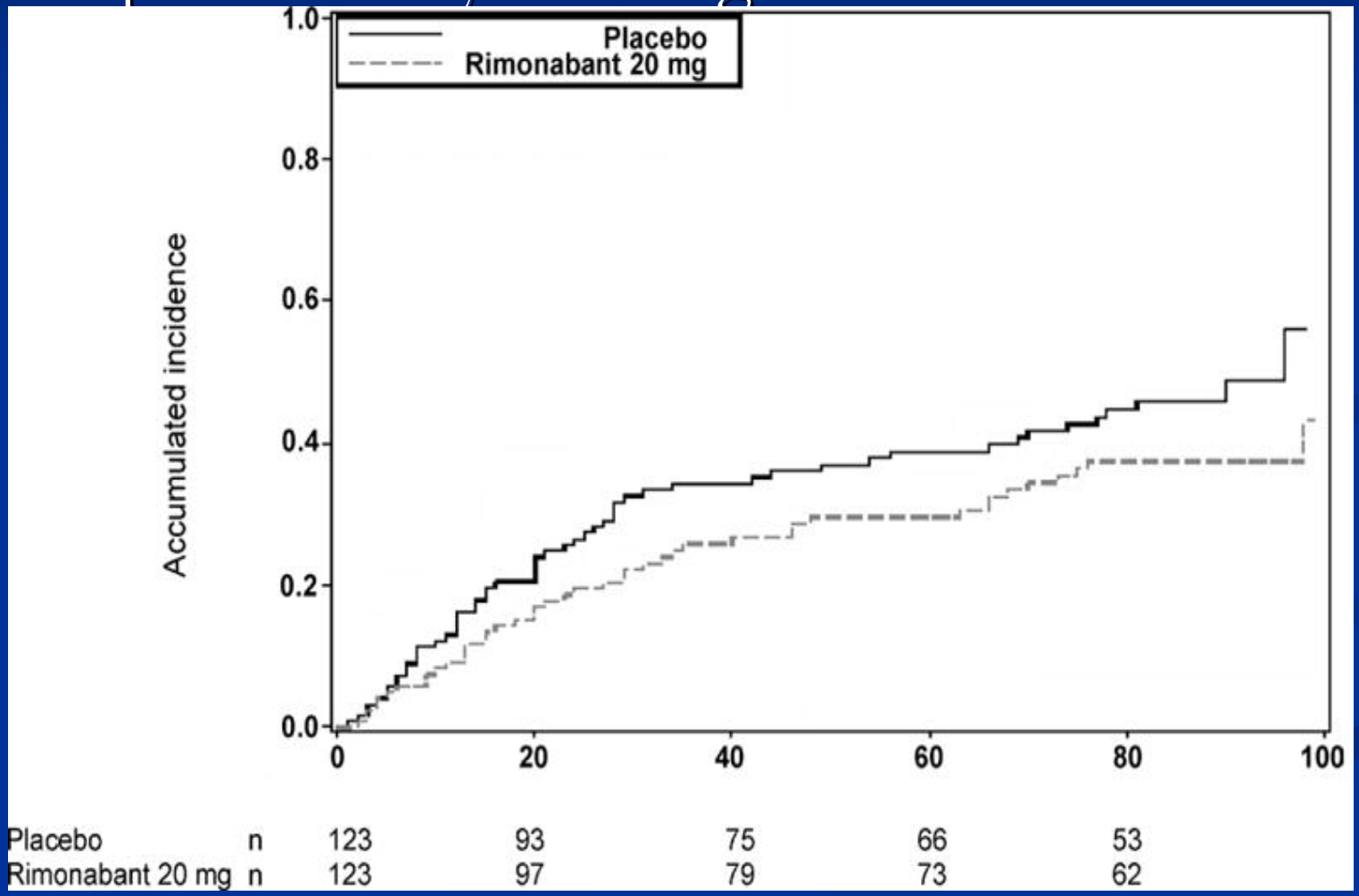
Anton, R. F. et al. Arch Gen Psychiatry 2008;65:135-144.

Asp40 allele coding for mu opioid receptor>> increase binding of β-endorphin and functional activity (though not risk factor for dependence)

ARCHIVES OF GENERAL PSYCHIATRY

Rimonabant

- CB-1 (cannabinoid receptor) blocker
- Relapse to heavy drinking



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

Baclofen

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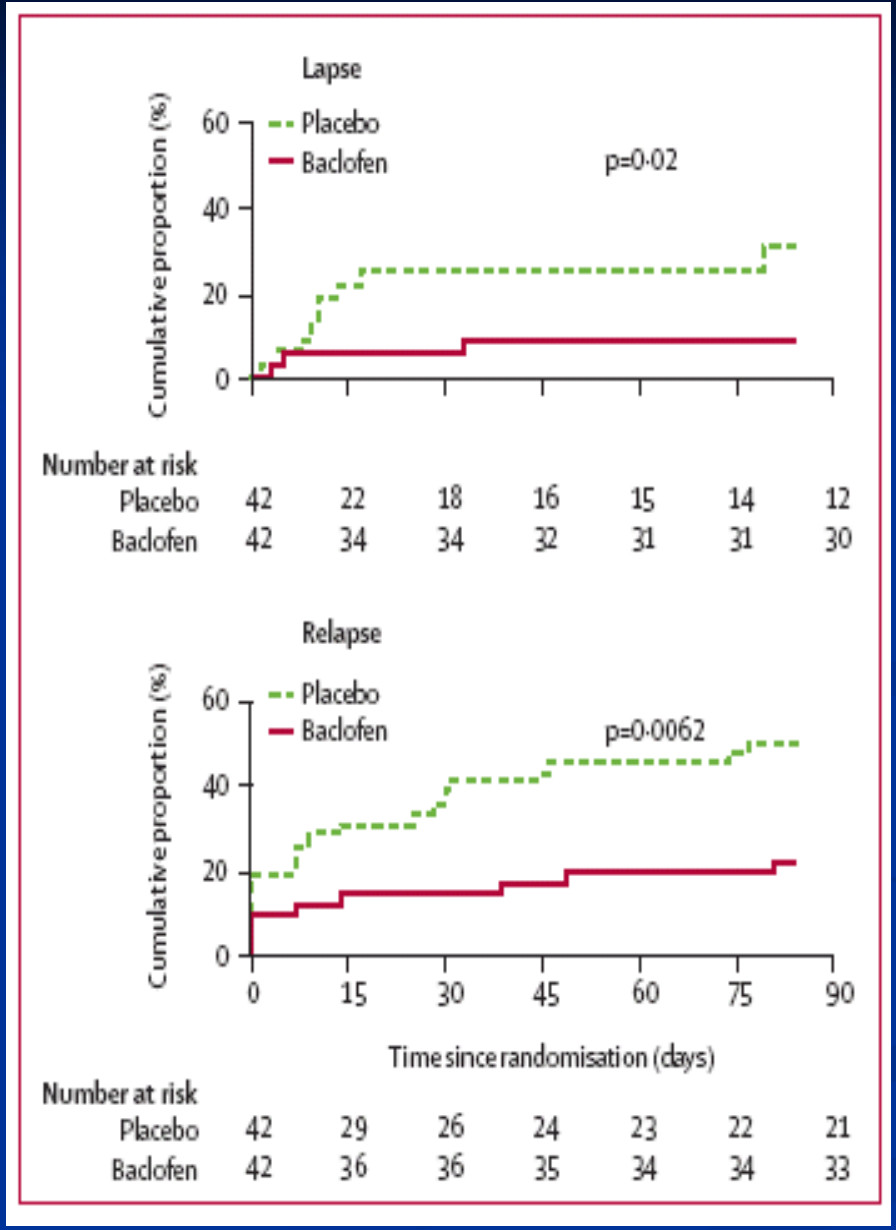
Cirrhosis and
alcohol dependence



Complete Abstinence:
71% vs. 29%

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

The COMBINE Study

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- 16-week randomized, multi-center trial
- 1383 men and women with alcohol dependence
- 9 arms
  - Naltrexone, acamprosate, both (v. placebo)
  - Combined behavioral intervention (CBI)
  - Medical management (all but CBI only [no pills] arm)
    - up to 9 visits focused on medication side effects and reinforcing abstinence

Anton RF et al. *JAMA* 2006 May 3;295:2003-17 (NCT00006206)

The COMBINE Study

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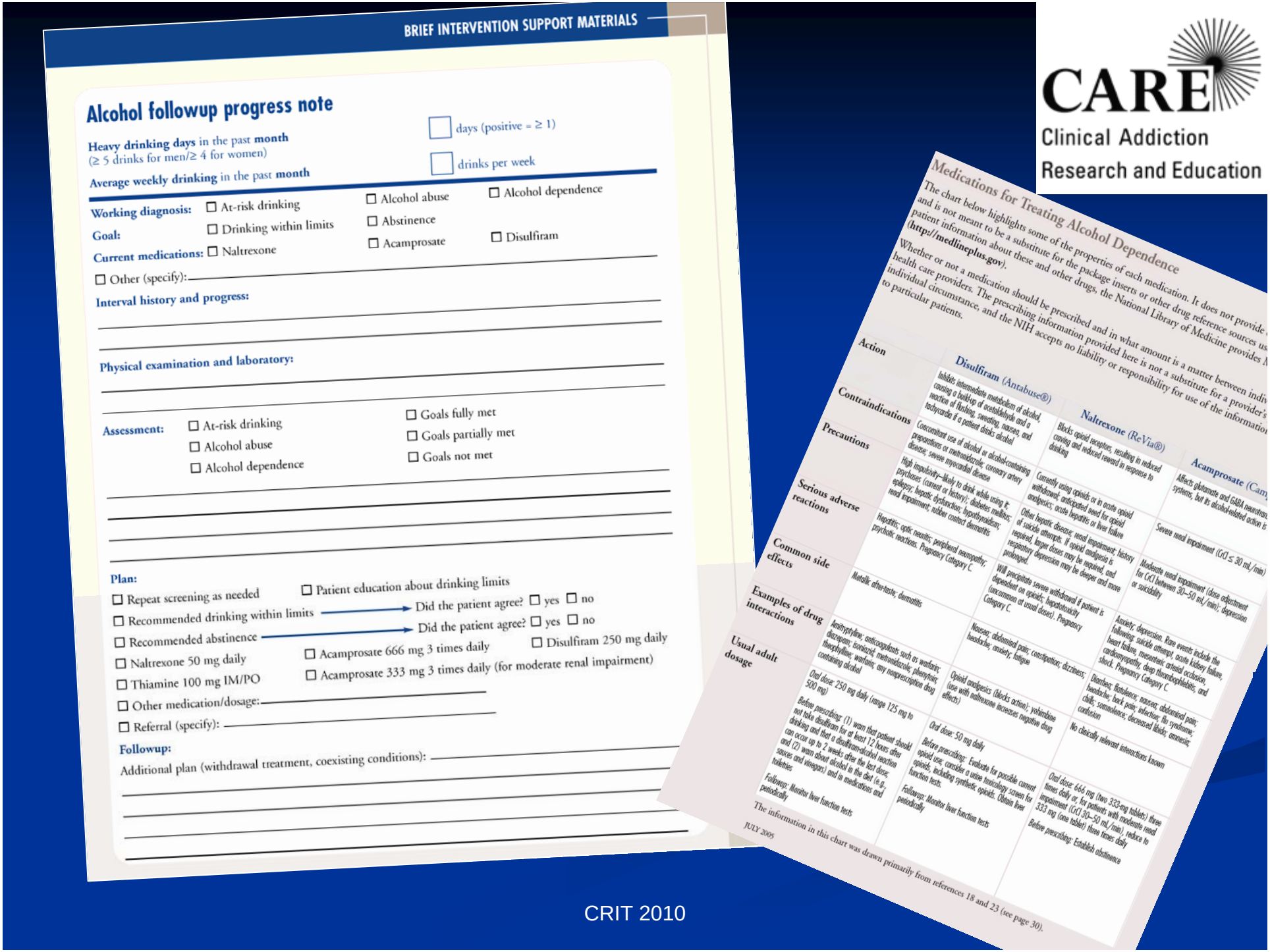
	Good Clinical Outcome %
Medical Management and Placebo	58
Medical Management and Placebo and **CBI**	71
Medical Management and **Naltrexone**	74

CBI=Combined Behavioral Intervention
Good Clinical Outcome=Abstinence or drinking moderate amounts without problems. P<0.025 (interaction p-value 0.02)



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The COMBINE Study

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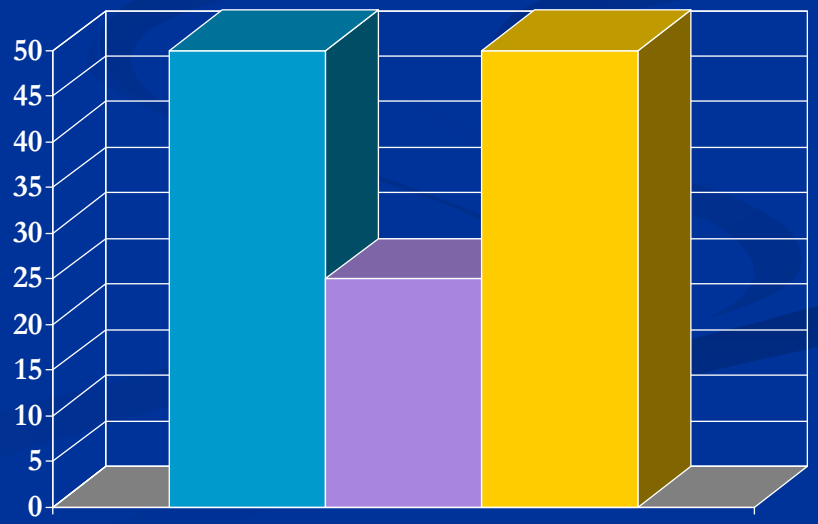
- One year after treatment ended, the groups did not differ significantly on drinking outcomes
  - Alcohol dependence is an illness that, like other chronic diseases, requires ongoing care



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Medications Usually given with Psychosocial Therapy

- Naltrexone & primary care management (PCM) vs. naltrexone & cognitive behavioral therapy (CBT)
  - Comparable results for initial 10 weeks, results favored PCM thereafter (2003)
- Naltrexone (vs. placebo) without obligatory therapy was effective in treating alcohol dependence (2002)

O'Malley SS et al. *Arch Int Med* 2003;163:1695-1704
Latt NC, et al. *Medical Journal of Australia* 2002;176:530-534

Pharmacotherapy with medications for Mood and Anxiety Disorders

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- Insufficient evidence to suggest their use in patients without mood disorders
- Treatment of patients with anxiety (buspirone) and depression (e.g. fluoxetine) can decrease alcohol use

Nunes & Levin. JAMA 2004;291:1887
Garbutt JC et al. JAMA 1999;281:1318

Treatment

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- 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.

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Summary

- Intoxication
- Withdrawal
- Brief intervention
- Pharmacotherapy
- Other (we didn't discuss)
  - Relapse prevention
  - Referral for treatment, AA/mutual help

The Temperate and the Intemperate

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JAMA February 2, 2005

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Dresden Prayer Book, 1475

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Pharmacotherapy Summary

- Pharmacotherapy for alcohol dependence has efficacy and should be considered for all patients with alcohol dependence
- Pharmacotherapy has proven efficacy when prescribed along with psychosocial counseling
- There is no clear drug of choice for this indication
- Combinations of efficacious drugs and new drugs for this indication hold promise

Pharmacotherapy for heavy drinking

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- RPCT of 153 adults, >18(F), 24(M) drinks per week, not mod/severe alcohol dependence (most had mild)
  - Daily or targeted naltrexone 50 mg
  - Both reduced heavy drinking (by 19%) c/w placebo
- Similar recent findings among hazardous drinking smokers

Kranzler HR et al. J Clin Psychopharm 2003;23(3)294-304
O'Malley SS, Int J Neuropsychopharmacol 2008 Sep 17 epub

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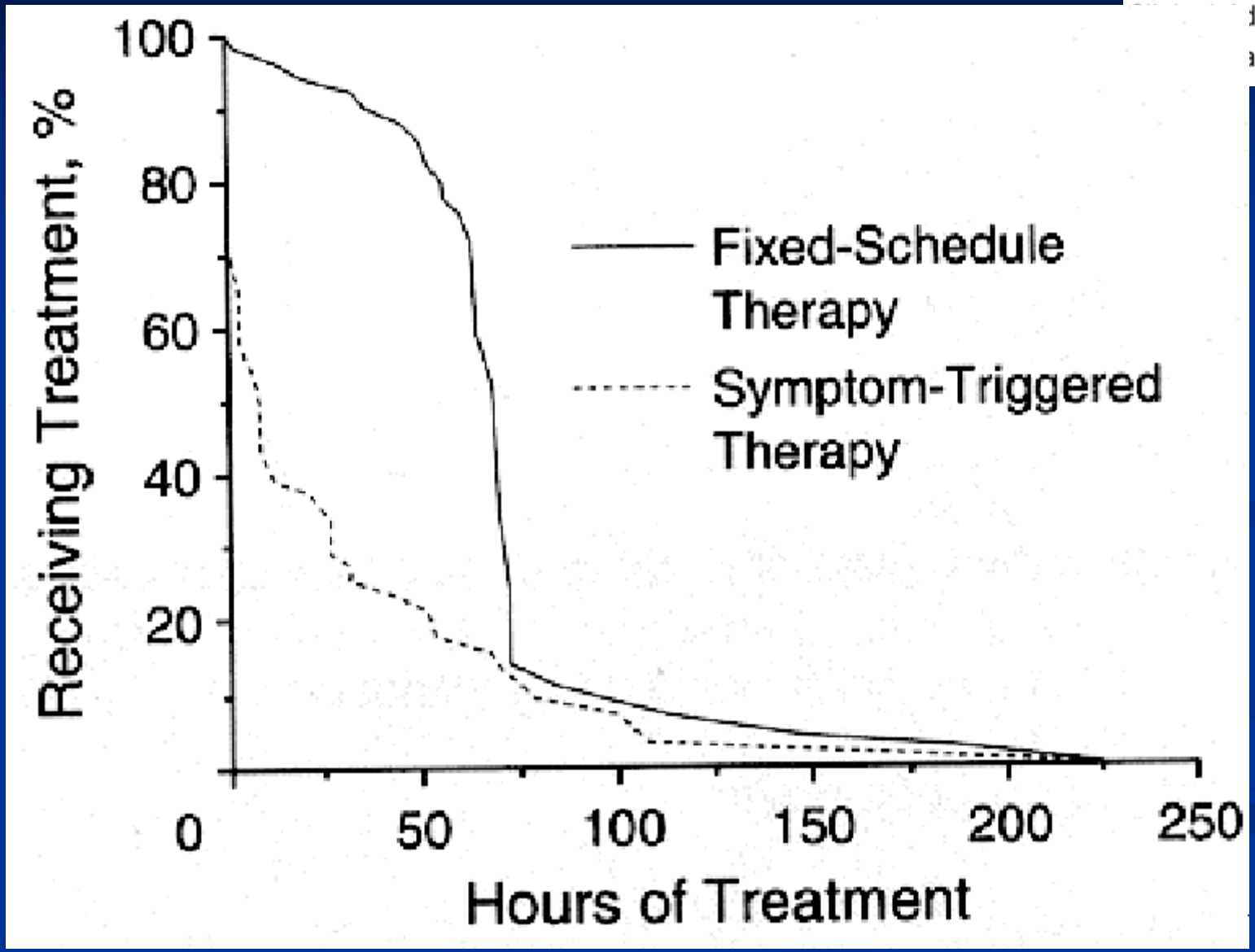
Symptom-triggered Therapy

- 101 adults with no past seizures hospitalized for alcohol withdrawal
- Placebo or Chlordiazepoxide 50 mg qid X4 then 25 mg qid X8 (double-blind)
- ALL: Chlordiazepoxide 25-100 mg q 1 hour as needed (objective scale: CIWA-Ar)

Saitz R et al JAMA 1994;272:519-23

Decreased Duration of Treatment



Saitz R et al JAMA 1994;272:519-23

Outpatient Detoxification

- RCT: Inpatient versus outpatient (med ctr)
- Inpatient
  - Meds, AA, and social, recreational counseling
- Outpatient
  - Daily evaluation, review of meds, counseling
- Both: oxazepam 30 mg qid and hs (all PRN) ('round the clock if seizure history)
  - until minimal symptoms, negative BAC, and ≤30 mg oxazepam/24 hrs

Hayashida et al. NEJM 1989;320:358

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RCT Outcomes

	OUT(N=87)	IN (N=77)
Completing treatment (%)*	72	95
Days of treatment (mean)*	4.5	9.2
Cost ($)*	175-388	3319-3665
Abstinence (1 month)(%)**	66	81
No Intoxication (1 month)(%)*	76	88
Abstinence (6 months)(%)	48	46
No Intoxication (6 mo)(%)	59	51

**p<0.001, **p<0.03*

Hayashida et al. NEJM 1989;320:358

BRIEF INTERVENTION: EFFICACY, DRUGS

- Randomized, controlled trial in 59 adolescents seeking medical care in an adolescent care setting (unknown number screened)
- Decreased ecstasy and marijuana use and drug problems

DeMicheli D et al. Rev Assoc Med Bras 2004; 50(3): 305-13

BRIEF INTERVENTION: EFFICACY, DRUGS

- 1,175 with risky heroin or cocaine use (DAST ≥3) outpatients (of 23660 screened) randomized to brief negotiated interview (BNI) or referral list/written advice
- 82% completed 6-month follow-up
- 6-month abstinence (hair)
  - Opiates: 40% of BNI, 31% of control (risk difference 9%)
  - Cocaine: 22% of BNI, 17% of control (risk difference 5%)
- About 38% of subjects in both randomized groups (no difference) reported a contact with drug treatment, virtually all of which was detoxification

Bernstein et al. Drug Alcohol Depend 2005;77:49

BRIEF INTERVENTION: EFFICACY, DRUGS

- 731 outpatients-Brazil, US, India, Australia (unknown number screened)
- Low and high risk scores excluded
- BI (vs. no BI) associated with a 3-point greater decrease in a substance use score (max score 336 points).
- Cannabis- and stimulant-specific scores decreased more for BI subjects (by about 2–3 points on scales with a maximum of 39 points); opioid scores did not differ by group
- US results not significant

Humeniuk R, et al. *Technical Report of Phase III Findings of the WHO ASSIST Randomized Controlled Trial.* Geneva, Switzerland: WHO. 2008. 122pp.

BRIEF INTERVENTION: EFFICACY, DRUGS

- 126 hospitalized patients (of 10,900 screened) abusing or using addictive prescription drugs on 60 of last 90 days
- After BI (2-MI sessions), no difference in daily dose or discontinuation
- At 3 months, greater proportion decreased use by 25% after BI than in control group (52% vs. 30%)
  - But, unclear if use was appropriate or not
  - No intervention effects at 12 months

Zahradnik A, et al. *Addiction.* 2009;104(1):109–117
Otto C, et al. *Drug Alcohol Depend* 2009;105:221-6.

BRIEF INTERVENTION: EFFICACY, DRUGS

- 210 emergency department patients age 14-21(of 7,804 screened)
  - Smoked MJ 3 or more times/month or reported risky behavior associated with MJ use (e.g. unprotected sex; driving) and had no risky alcohol use
  - 3 groups
    - Non-assessed control: written risks and resources
    - Assessed control: same, plus assessment battery
    - Intervention: same, 20-30” BI plus 10-day booster call (5-10”)
  - 71% 12-month follow-up (timeline follow-back self-report)
- 45% vs. 22% abstinent, 4.2 fewer days of use c/w control, no evidence of assessment effects
- No differences in risky behavior or consequences.

Bernstein E et al. Acad Emerg Med 2009; 16: 1174-85.

Why?

- Drug may be more complicated and varied than alcohol
- Drug may be more severe
- Should not be surprising that intervention that works for alcohol may or may not work for drug
- (PS no well-validated brief screening tool for primary care)
- There is no single treatment that works for all heart disease…

Pharmacogenomics

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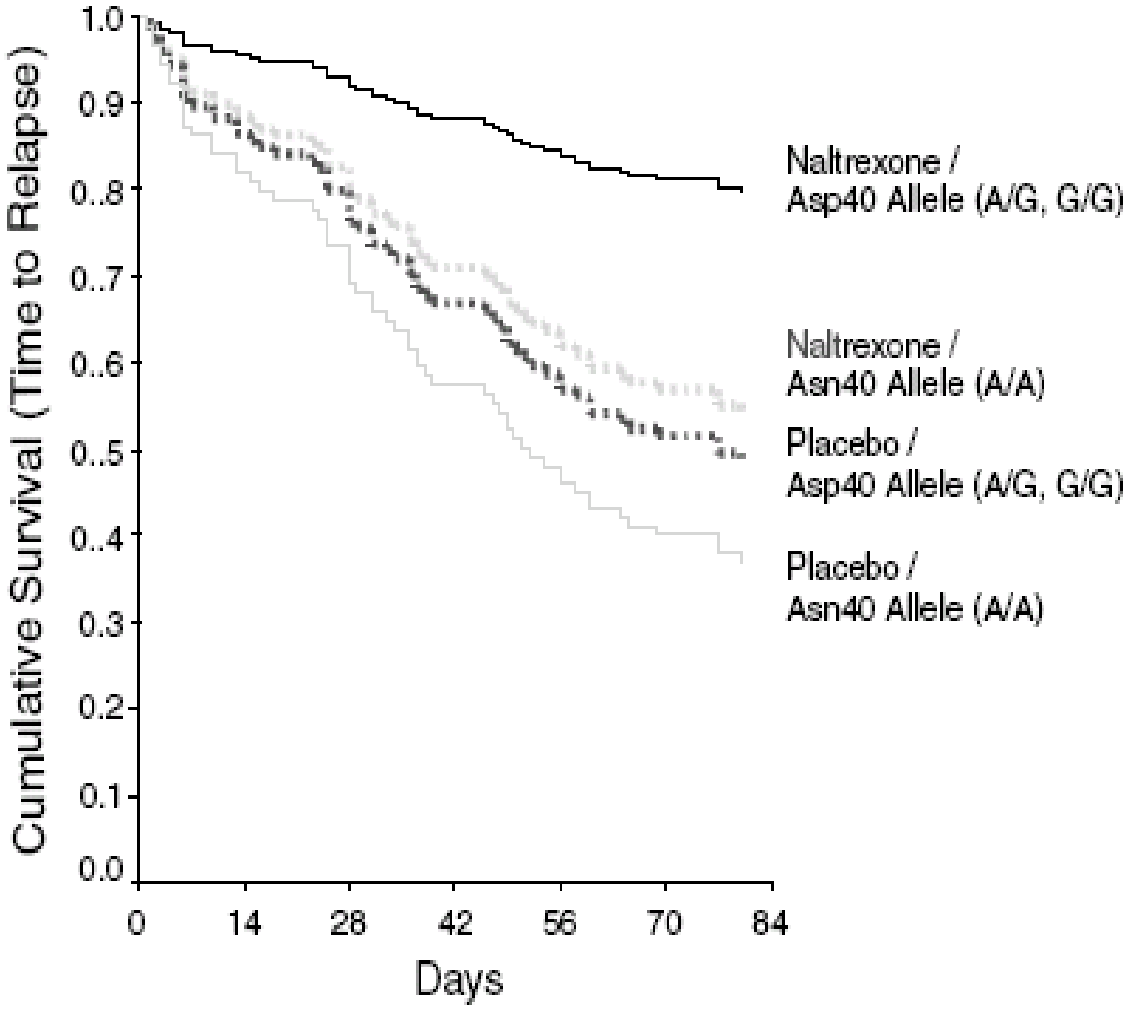

Oslin DW et al. Neuropsychopharmacology. 2003;28:1546

Buprenorphine: Dose-response

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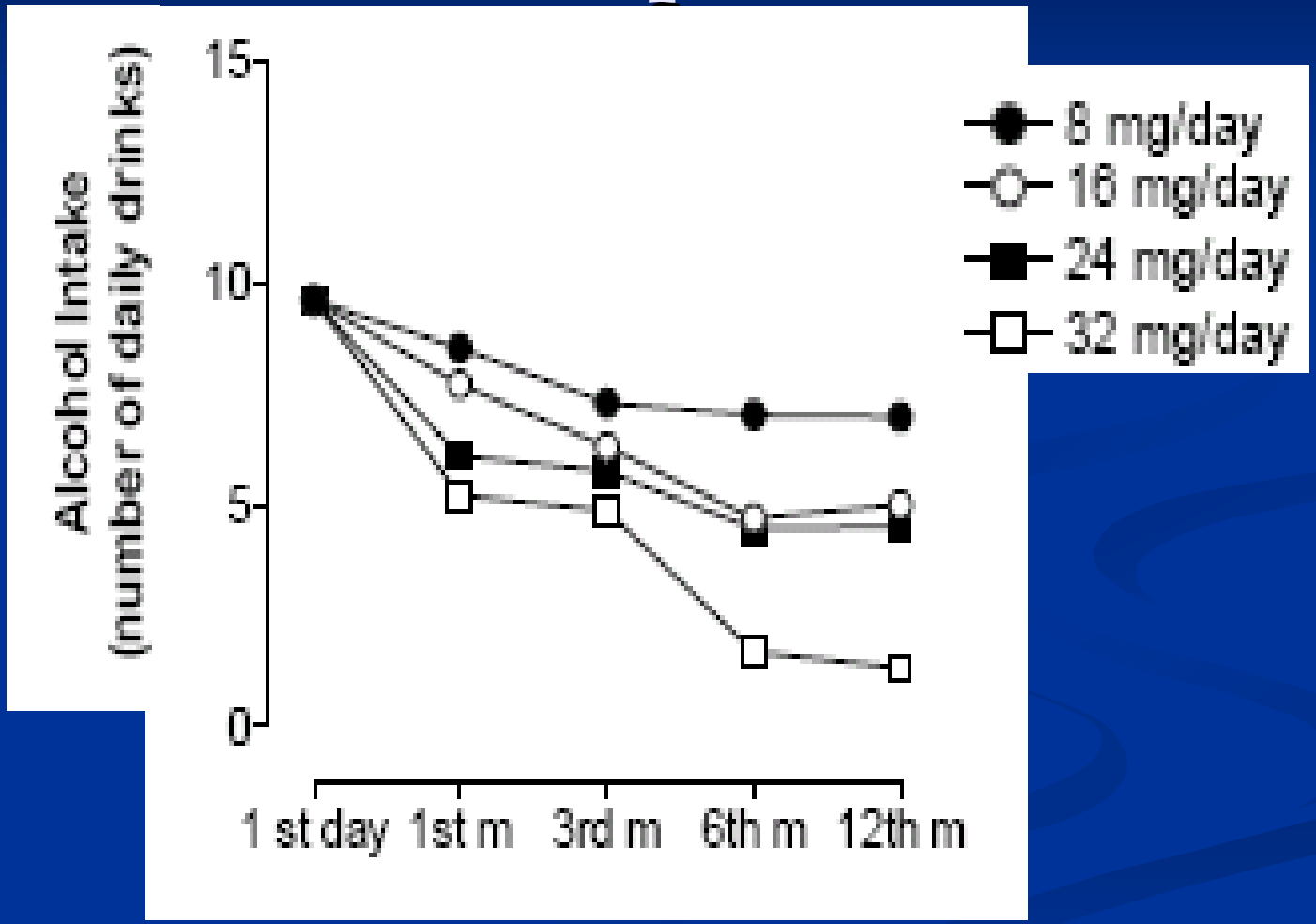

Nava et al. Progress in Neuropsychopharmacology & Biological Psychiatry 2008 *in press*.

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On the horizon

Efficacy of Topiramate

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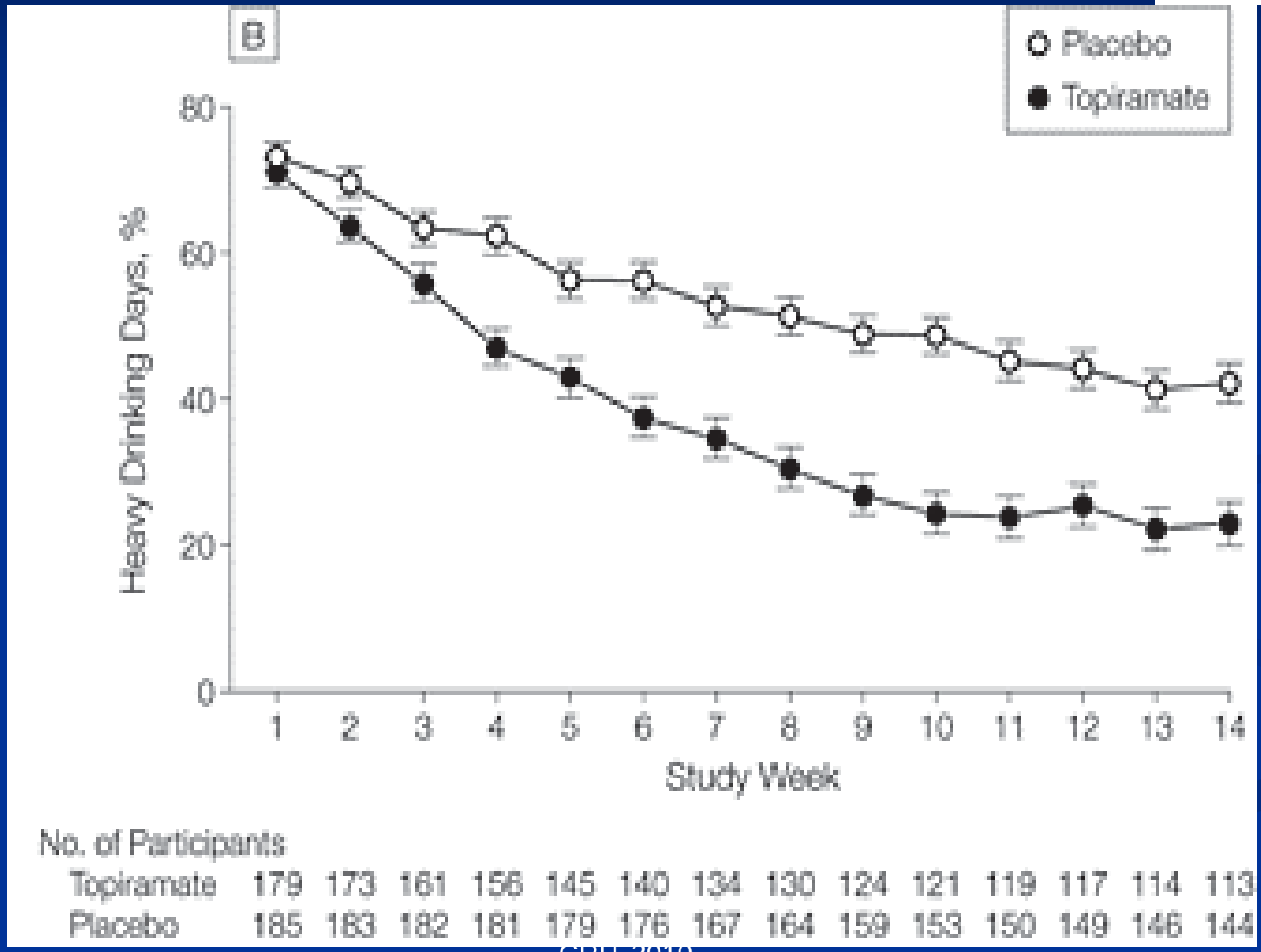

Johnson BA, et al. *JAMA*. 2007;298(14):1641–1651.

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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