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.

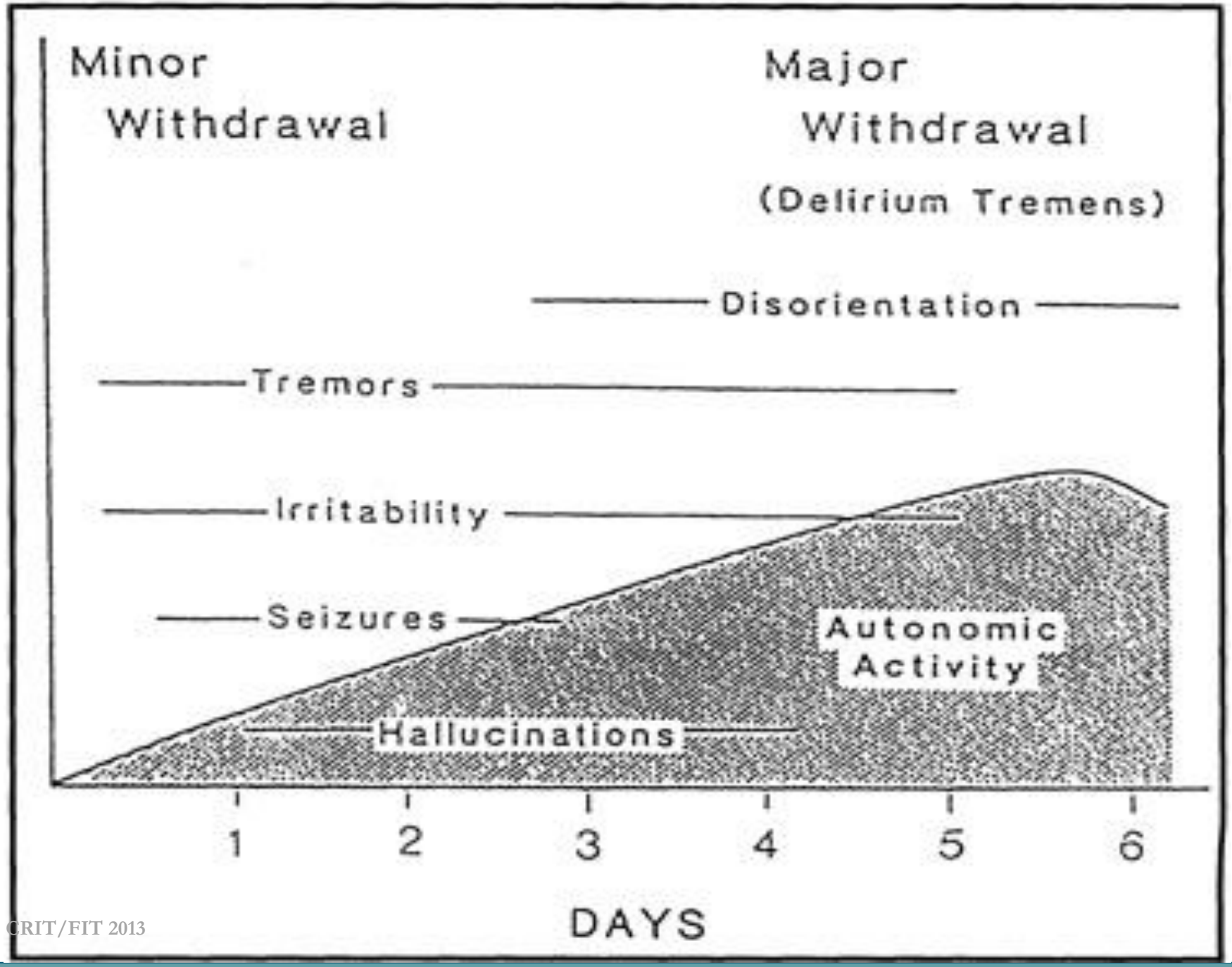
T 98, RR 18, HR 110 (regular), BP 136/82 standing, 100, 140/70 lying down.

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?

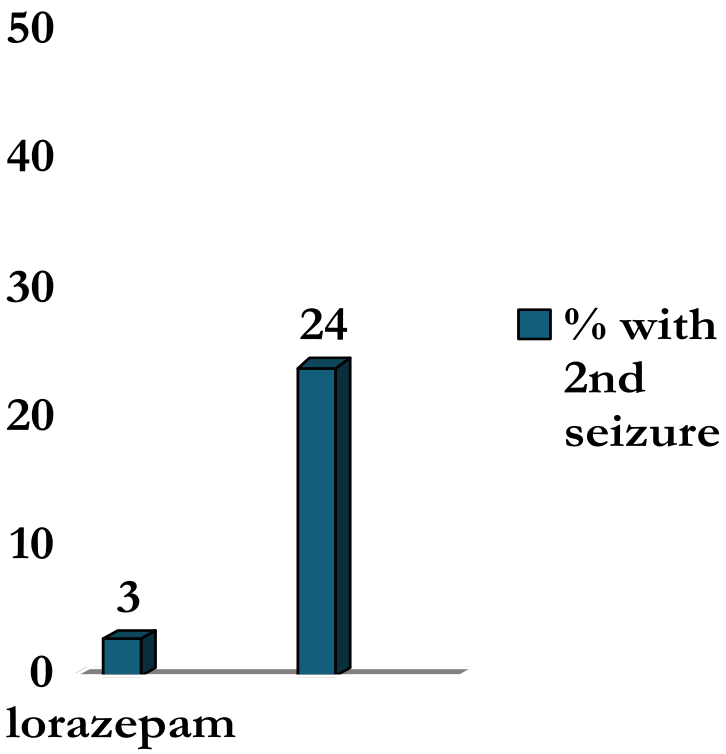

Minor
Withdrawal
Major
Withdrawal
(Delirium Tremens)
Disorientation
Tremors
Irritability
Seizures
Autonomic
Activity
Hallucinations
1
2
3
4
5
6
DAYS

ALCOHOL WITHDRAWAL SEIZURES

- Recurrent detox and prior seizure are risk factors
- 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



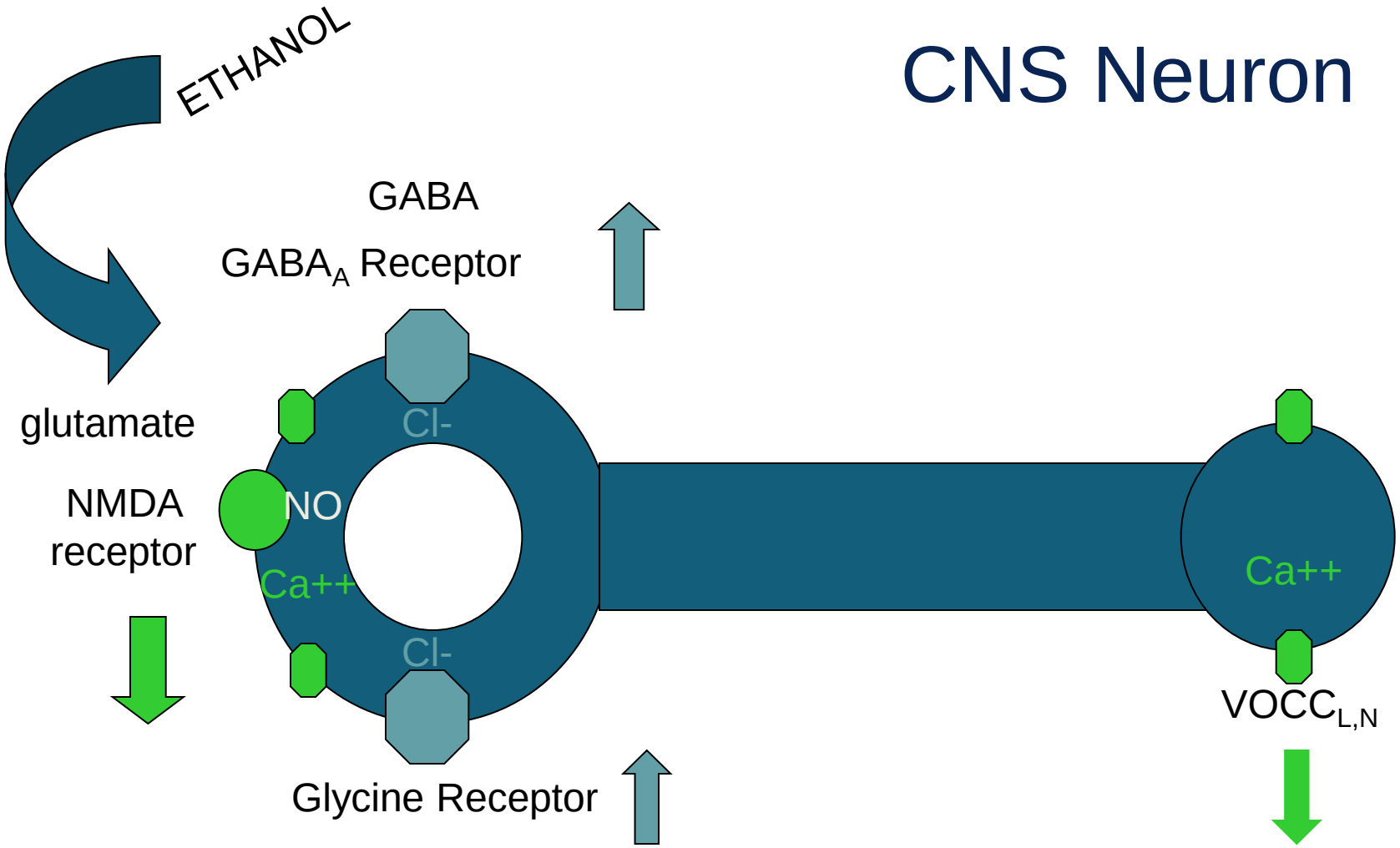
Four hours later (15-20 mg/dL/hr [1 drink] elimination), the patient becomes tremulous, anxious, and complains of nausea. BP 134/84, HR 90, ethanol level 146 mg/dl.

- 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

CNS Neuron



Benzodiazepines reduce seizures

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

RRR 93%, p<0.001

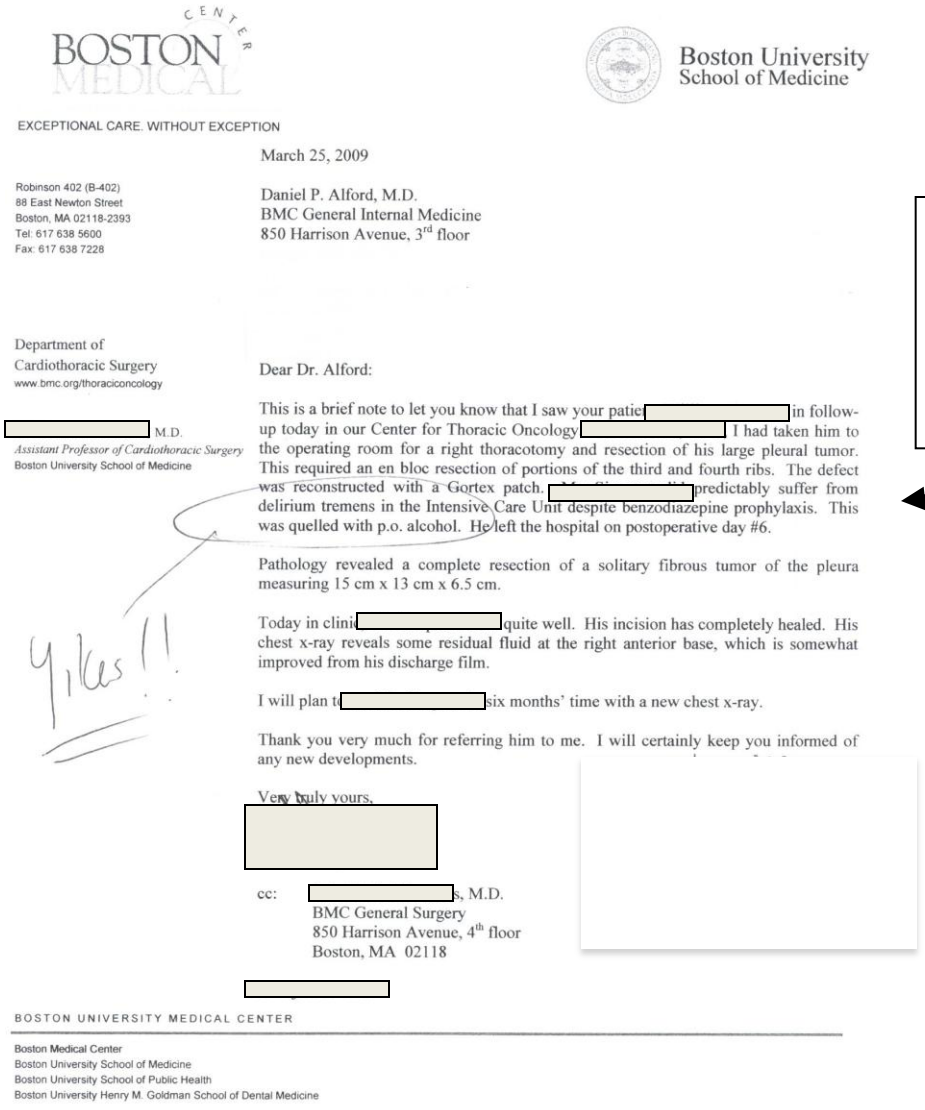
Sereny 1965, Kiam 1969, Zilm 1980, Sellers 1983, Naranjo 1983, summarized in Mayo-Smith MF & ASAM Working Group JAMA 1997;278:144-51

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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Assistant Professor of Cardiothoracic Surgery
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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. M[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 Medical Center
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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"

CARE Clinical Addiction Research and Education

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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).

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

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.

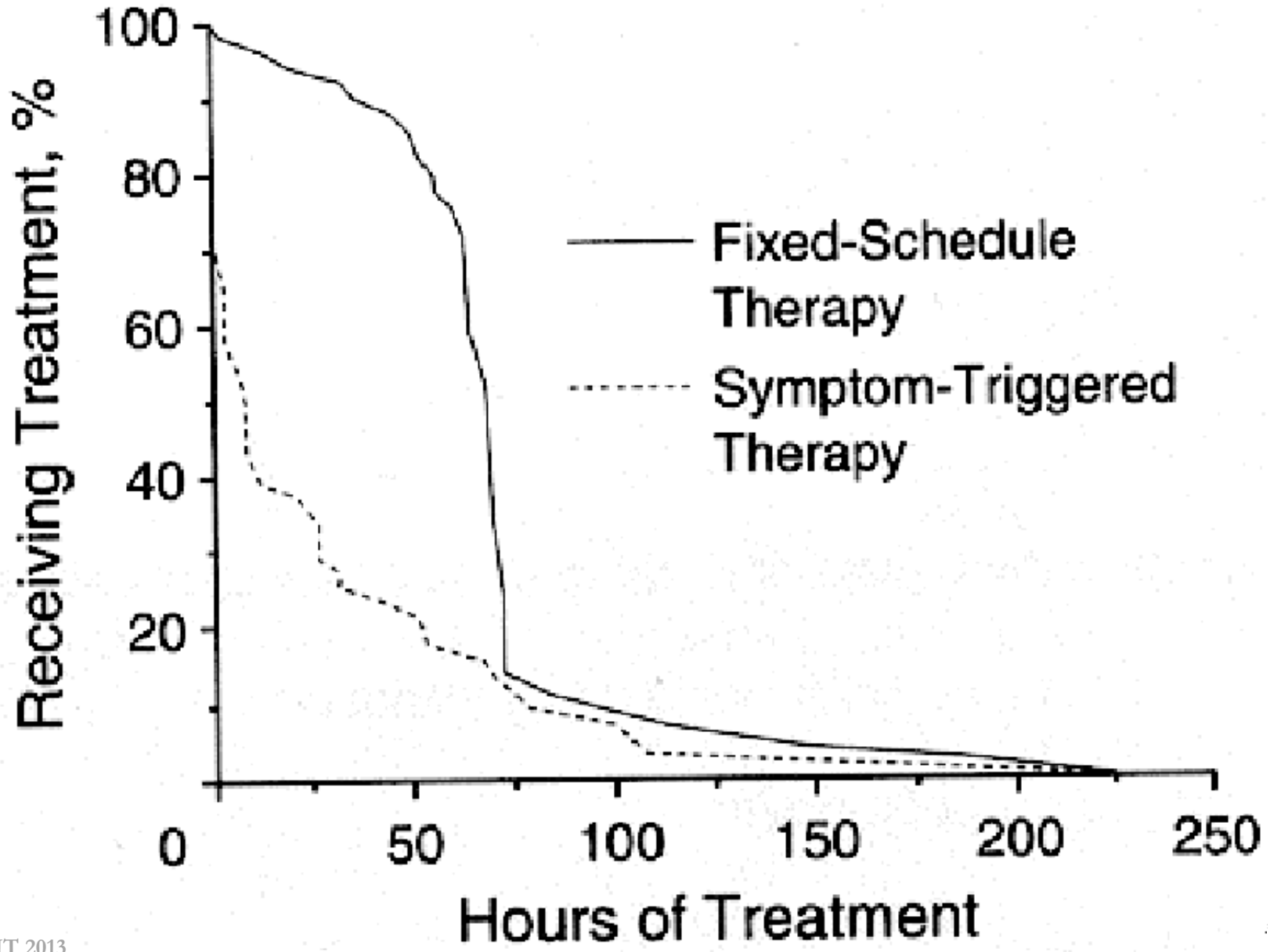
0—Not present
1—Very mild
2—Mild
3—Moderate
4—Moderately severe
5—Severe
6—Very severe
7—Extremely severe

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-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
Saitz and O'Malley Med Clin N A 1997;81:881-907

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

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

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

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

"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?"

Table 4. Brief Counseling and Referral.*

How to Advise or Refer Patients	Examples or Explanations
Elicit information about how the patient views the problem.	"What do you think about your drinking? Are you ready to make a change in your alcohol use? How confident are you that you could cut down if you wanted to?"
Express concern and provide clear advice regarding the ideal goal (abstinence or reduced consumption for those with nondependent alcohol use, achieved through brief counseling; abstinence for patients with alcohol dependence).†	"I am concerned about your drinking; my medical advice is that the healthiest choice for you is to cut down or abstain."
Provide specific feedback about alcohol consumption in comparison with population norms, and link existing problems to alcohol use when appropriate, to make information relevant to the patient.	"Ninety-three percent of adults drink less than the amounts you report drinking. You mentioned your heartburn is worse when you drink. Alcohol is probably causing your heartburn."
Express empathy, let the patient know you believe that change is possible, and acknowledge that it is the patient's responsibility to change.	"The fact you were able to quit before for a week tells me you can do it again. But it must be difficult. It is up to you to make these changes."
When the patient expresses interest or gives permission, provide information, including a menu of options, about how to change.	"Would you like information on how to cut down or abstain? Other people have found a range of options helpful, such as keeping a drinking diary, counseling, and mutual-help groups. What do you think about these?"
Anticipate and discuss situations in which the patient feels at risk for drinking excessively, and talk about strategies to avoid drinking excessively.	"What ways might help you avoid drinking excessively when you go out with friends who drink?" Have the patient keep a drinking diary (including the number of drinks consumed per day).
Schedule a follow-up session to assess drinking and changes in alcohol use.	"Please think about your drinking and the health risks we discussed; contact me if you decide you would like assistance in the future. Let's schedule a follow-up visit in a month to talk again." In the follow-up, review the drinking goal, the actual drinking history, and any consequences since the last visit. If the serum levels of γ-glutamyltransferase or carbohydrate-deficient transferrin were initially abnormal, monitor levels.
For patients who are not ready to change their alcohol use, advice about changing their habits or getting help is counterproductive because the patient will enumerate the reasons against change; avoid confrontation and argument.	
Elicit the patient's own reasons for drinking, reasons for not drinking, and concerns about changing.	"What do you like about drinking? What do you like to drink? What are some problems you have noticed when or after you drink? What would it be like not to drink?"
For patients with alcohol dependence, provide brief counseling with the goal of increasing motivation to change; the recommended change is abstinence and linkage with any or all known effective interventions (mutual-help groups, pharmacotherapy, and counseling).‡	Consider referral to a specialist (a physician who specializes in addiction medicine or an alcoholism-treatment provider) for evaluation and confirmation of the diagnosis, even if the patient is not ready to begin treatment.
Know local referral options, such as health plan referral services, public treatment resources, physicians, other counselors, employee-assistance programs, and national resources (in the United States, http://findtreatment.samhsa.gov); know what patients can expect when they seek assistance.§	Help the patient take the first step (e.g., make an appointment); follow up on treatment entry and engagement.
For patients in recovery, address plans for what to do in the event of relapse.¶	"What would you do if you felt your drinking was out of control?"

* Data are from the Department of Health and Human Services[3] and the U.S. Preventive Services Task Force.[5] This model includes a recommended structure for effective discussions about changing health behavior (elicit–provide–elicit).[23] The elements of brief interventions with proven efficacy include feedback, responsibility, advice, a menu of options, empathy, and support of self-efficacy.

† Patients may need additional assistance if their goal is not achieved. Patients who are pregnant or trying to conceive, who have a medical condition that would be worsened by drinking, or who are taking a medication that interacts with alcohol should be advised to abstain. Discus-

Saitz R. N Engl J Med 2005;352:596-607.

www.wordle.net

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))

*Jonas DE et al. Ann Intern Med 2012;157:645-54.
Kaner et al. Drug and Alcohol Review 2009;28:301–23
**Beich et al. BMJ 2003;327:536
***Bertholet et al. Arch Intern Med. 2005;165:986
Kristenson H, et al. Alcohol Clin Exp Res 1983;7:203 (mortality)
Fleming MF et al. Alcohol Clin Exp Res. 2002;26(1):36-43 (cost)
Cuijpers et al. *Addiction* 2004;99: 839–845 (mortality)

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 —Feb. 12, 2002, Department of Defense news briefing transcript http://dod.gov The Poetry of D.H. Rumsfeld, http://www.slate.com/id/2081042/

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)

Beurden, Anderson et al. Addiction 2012 epub ahead of print DOI: 10.1111/j.1360-0443.2012.03868.x .
Hilbink et al JABFM 2012;25:712-22.
Kaner et al. BMJ 2013;346:e8501 doi: 10.1136/bmj.e8501 (2013)
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
Saitz et al. Ann Intern Med 2007;146:167-76
Freyer-Adam J et al. Drug Alcohol Depend 2008
Bischoff G et al. Drug Alcohol Depend 2008
Bischof et al. Int J Pub Health 2010
Saitz et al. Int J Pub Health 2010

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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 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."

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
- 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)

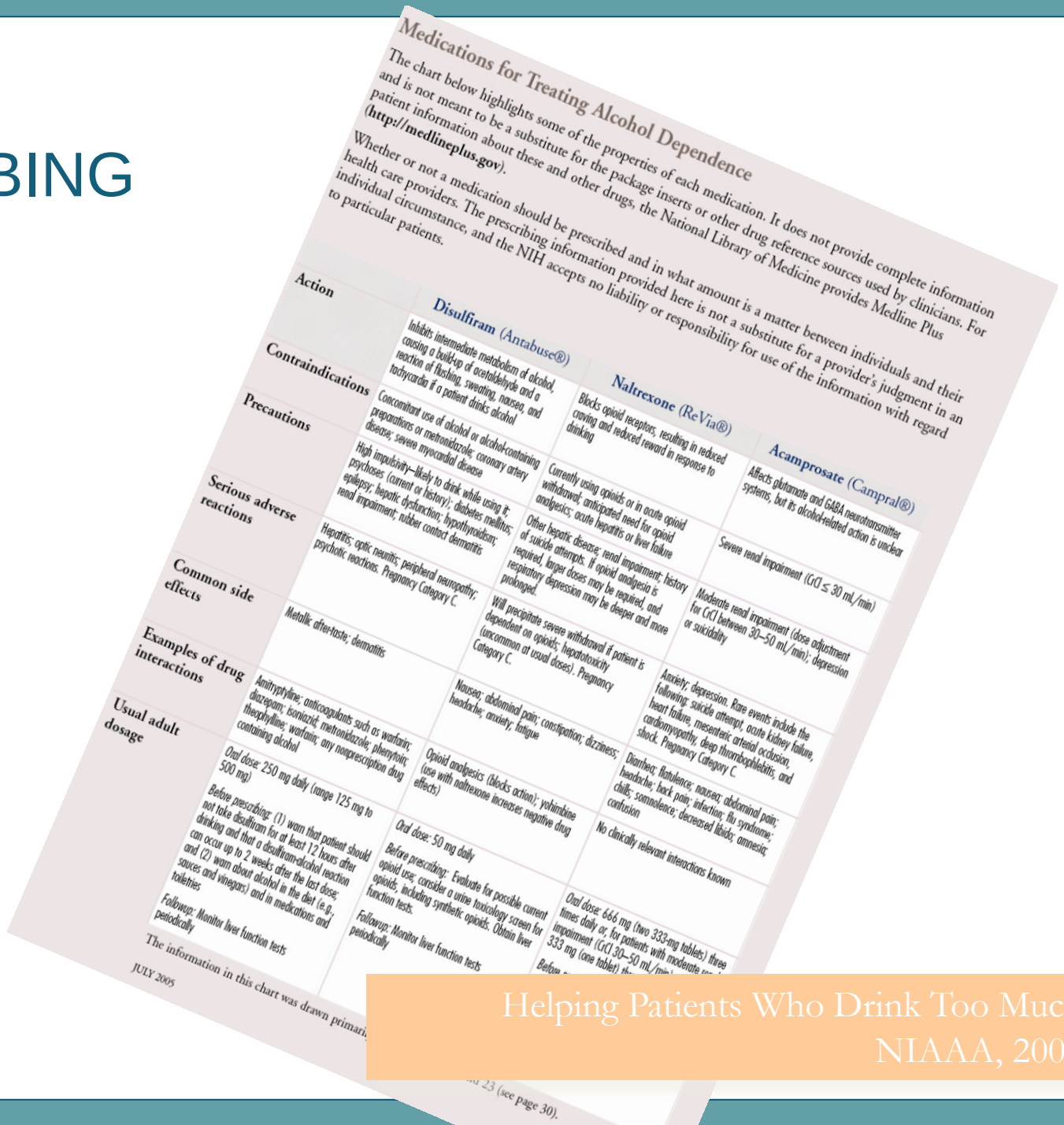
*O'Malley SS et al. *Arch Int Med* 2003;163:1695-1704.
*Anton RF et al. *JAMA* 2006 May 3;295:2003-17.
**Latt NC, et al. *Med J Australia* 2002;176:530-534.
RCT: naltrexone effective without obligatory therapy

Medication-Assisted Treatment

Medication-Assisted Treatment

Counseling-Assisted Pharmacotherapy

PRESCRIBING



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.

	Disulfiram (Antabuse®)	Naltrexone (ReVia®)	Acamprosate (Campral®)
Action	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
Contraindications	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)
Precautions	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
Serious adverse reactions	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.
Common side effects	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
Examples of drug interactions	Amitryptyline; 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
Usual adult dosage	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] 23 (see page 30).

Helping Patients Who Drink Too Much
NIAAA, 2007

Alcohol followup progress note

Heavy drinking days in the past **month** (≥ 5 drinks for men/≥ 4 for women) ☐ days (positive = ≥ 1)

Average weekly drinking in the past **month** ☐ drinks per week

Working diagnosis: ☐ At-risk drinking ☐ Alcohol abuse ☐ Alcohol dependence

Goal: ☐ Drinking within limits ☐ Abstinence

Current medications: ☐ Naltrexone ☐ Acamprosate ☐ Disulfiram

☐ Other (specify):

Interval history and progress:

Physical examination and laboratory:

Assessment: ☐ At-risk drinking ☐ Alcohol abuse ☐ Alcohol dependence ☐ Goals fully met ☐ Goals partially met ☐ Goals not met

Plan:

☐ Repeat screening as needed ☐ Patient education about drinking limits

☐ Recommended drinking within limits → Did the patient agree? ☐ yes ☐ no

☐ Recommended abstinence → Did the patient agree? ☐ yes ☐ no

☐ Naltrexone 50 mg daily ☐ Acamprosate 666 mg 3 times daily ☐ Disulfiram 250 mg daily

☐ Thiamine 100 mg IM/PO ☐ Acamprosate 333 mg 3 times daily (for moderate renal impairment)

☐ Other medication/dosage:

☐ Referral (specify):

Followup:

Additional plan (withdrawal treatment, coexisting conditions):

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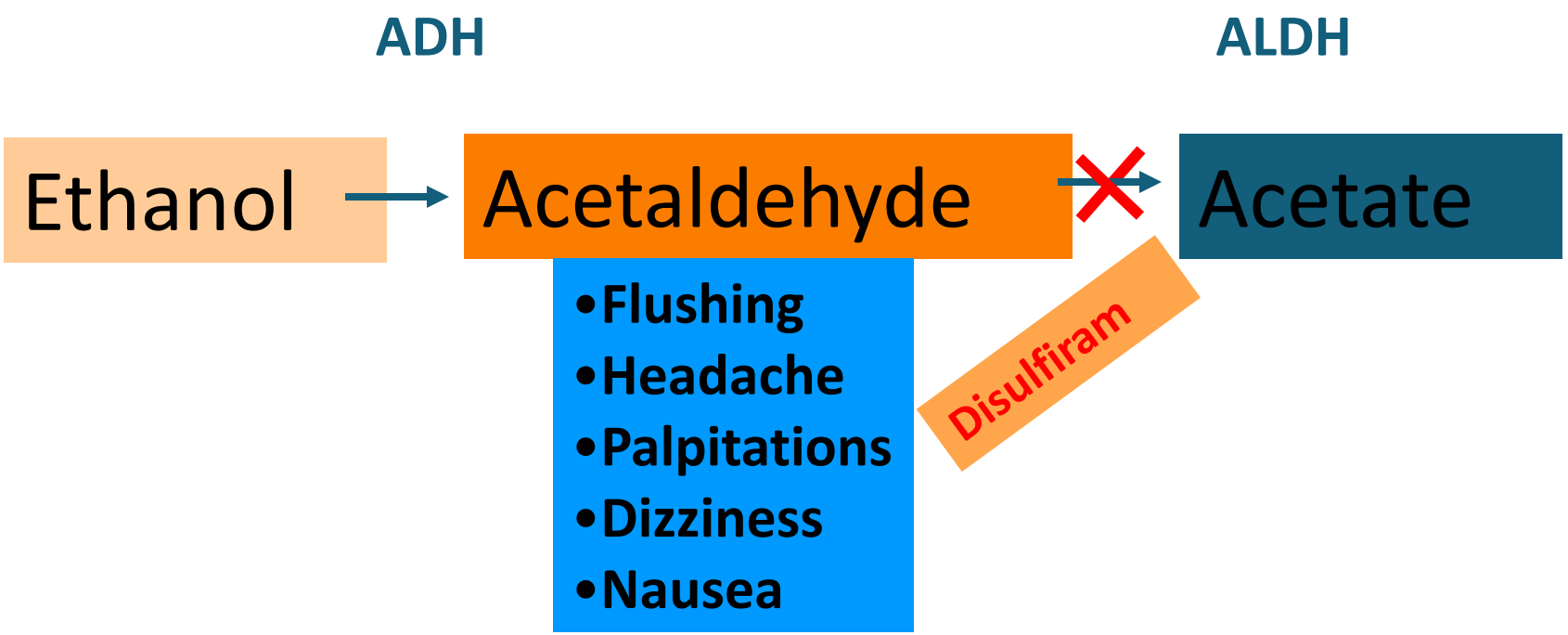
Disulfiram



Fuller RK et al. JAMA 1986;256:1449

Monitored Disulfiram: 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.

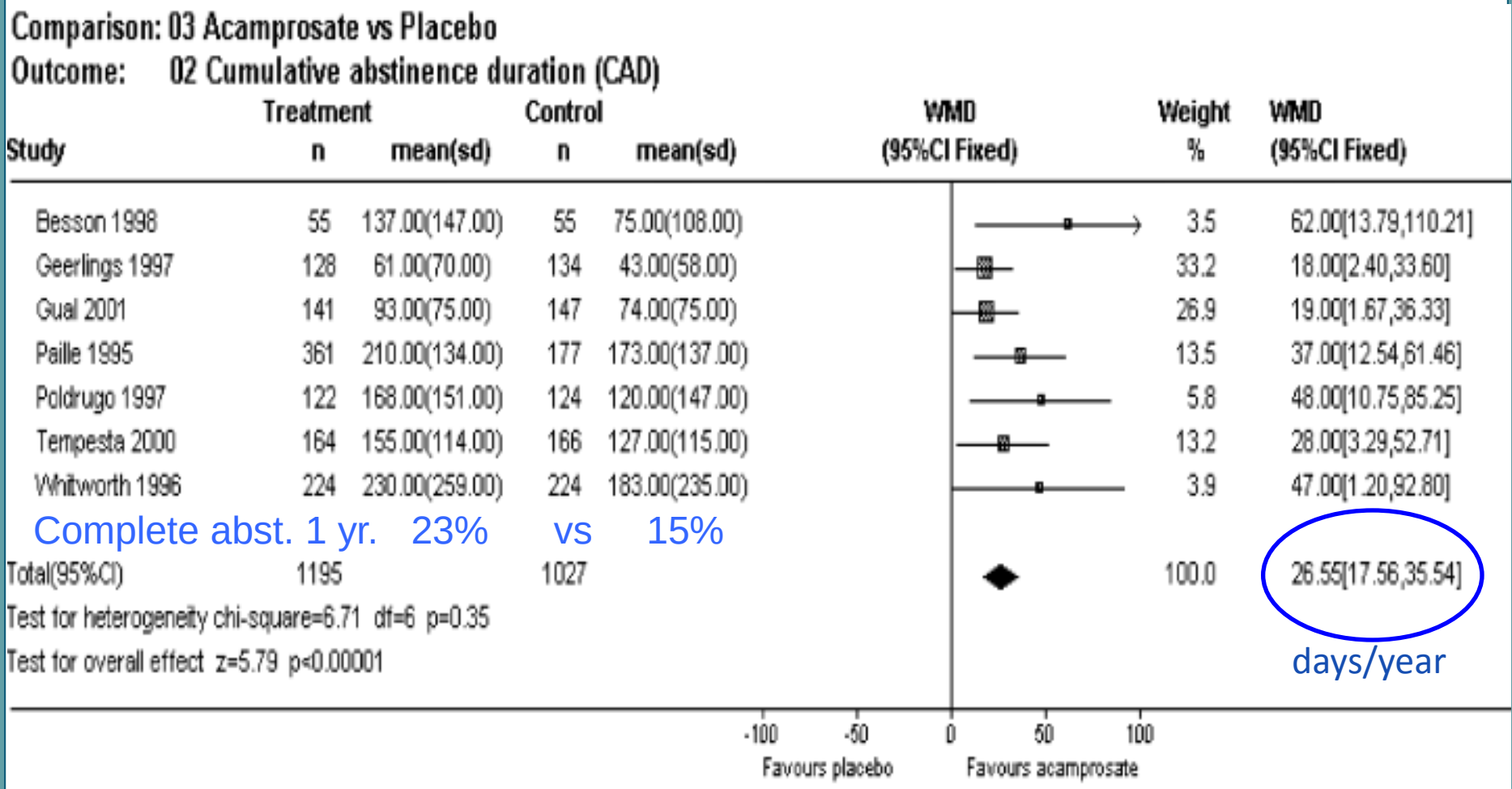
*Thirty-day abstinence at 6 months.

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"



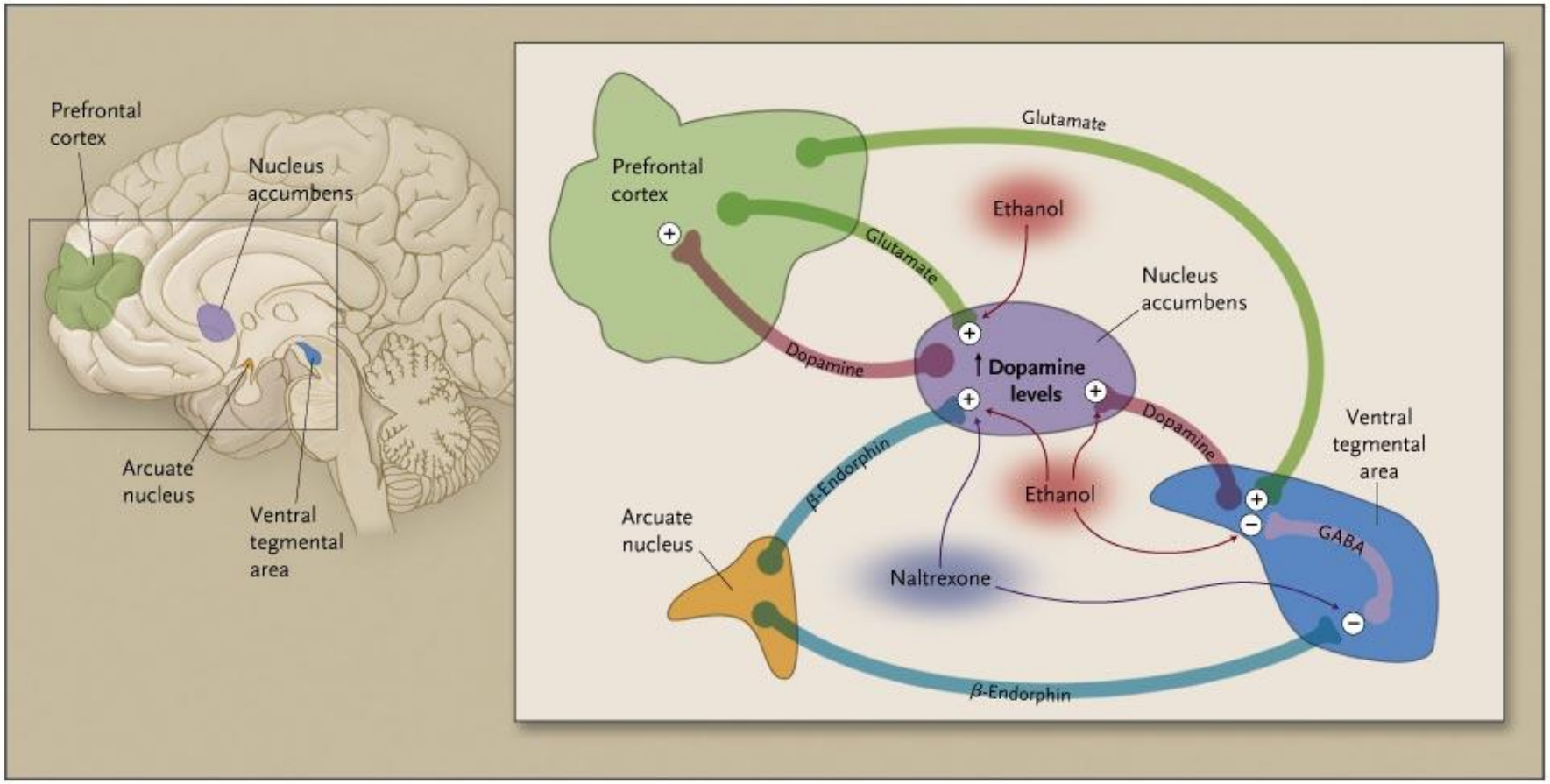
Bouza C et al. Addiction 2004;99:811

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



The NEW ENGLAND JOURNAL of MEDICINE

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

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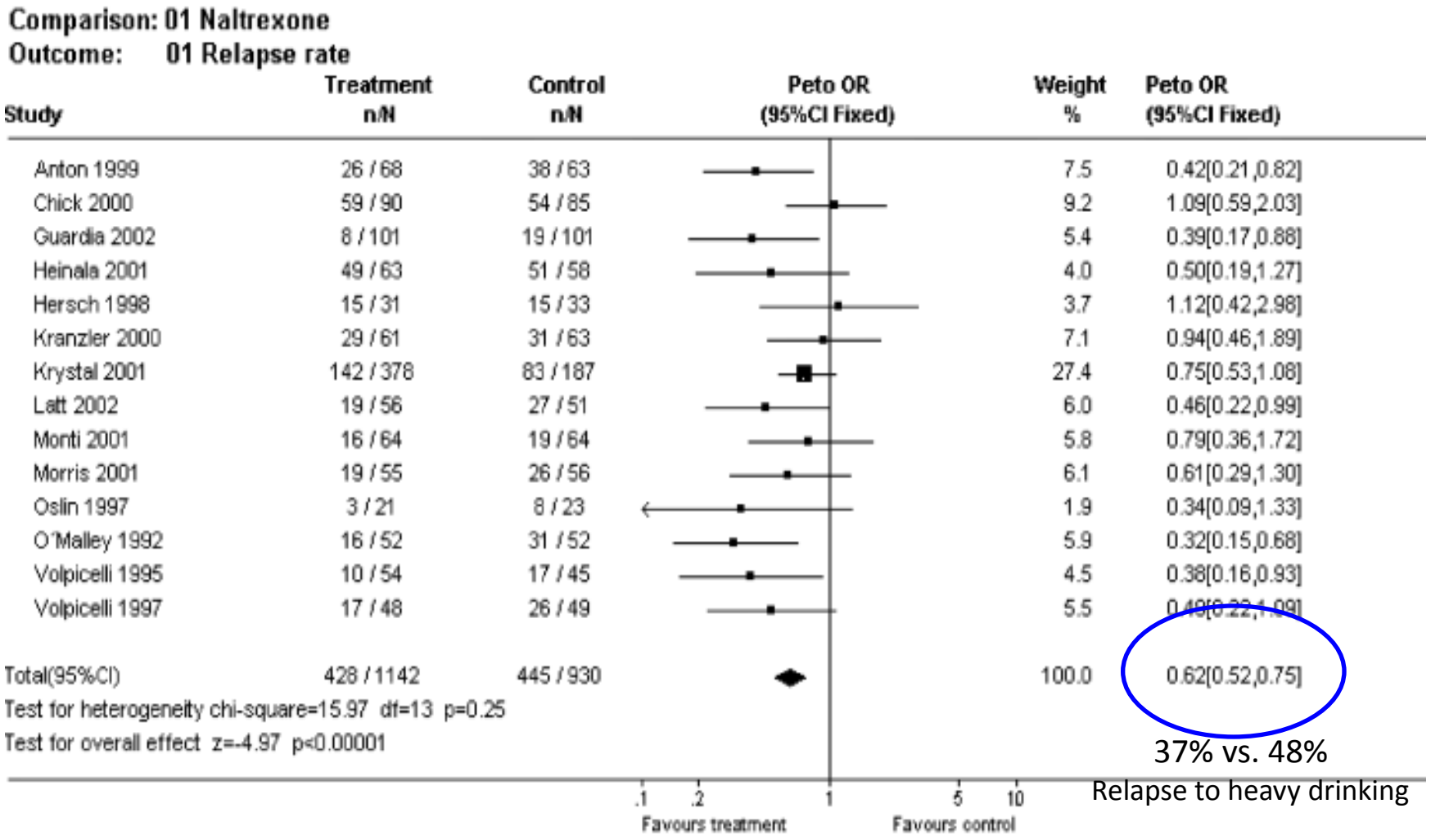
Efficacy of Naltrexone



37% vs. 48%

Relapse to heavy drinking

Bouza C et al. Addiction 2004;99:811

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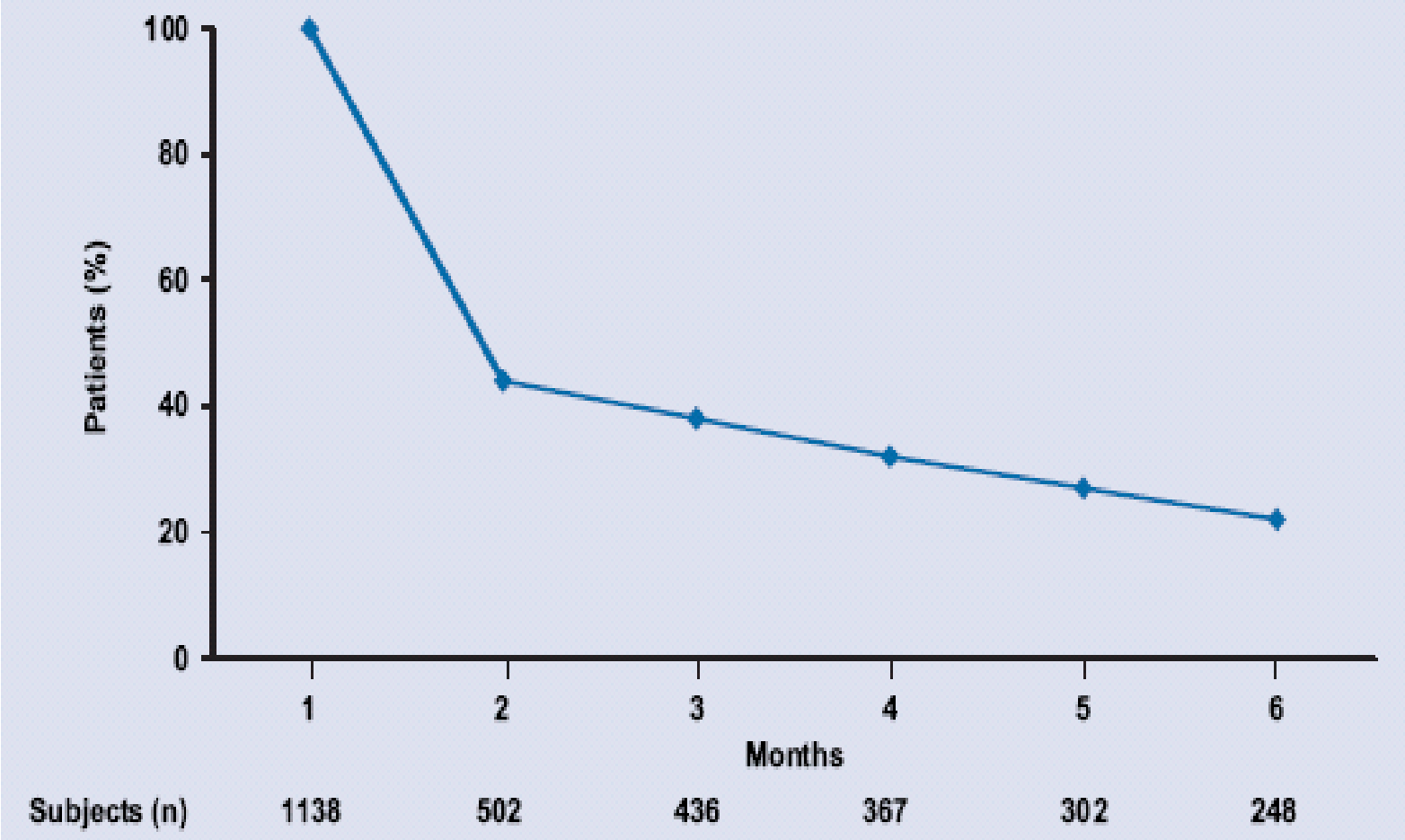
Receipt of Naltrexone

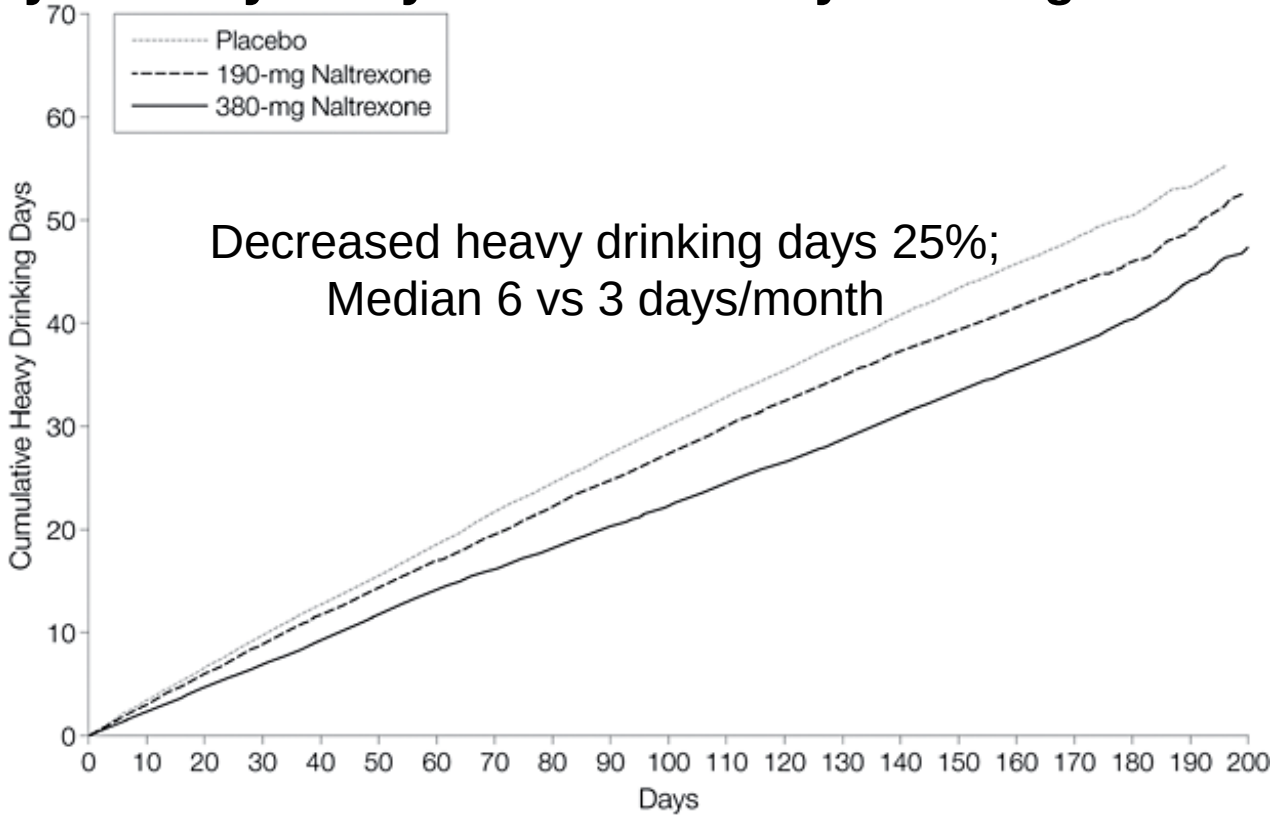
14% got 80% of a 6-mo course



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

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

The COMBINE Study

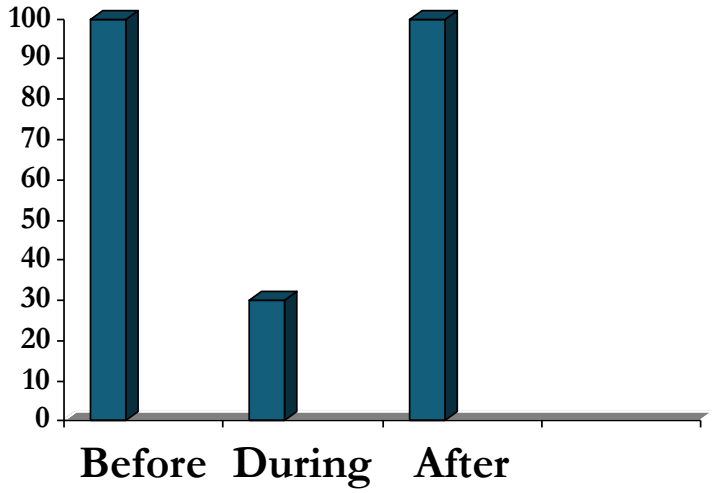
N=1383, 16 wk trial	Good Clinical Outcome %
Medical Management and Placebo	58
Medical Management and Placebo and **CBI**	71
Medical Management and **Naltrexone**	74

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

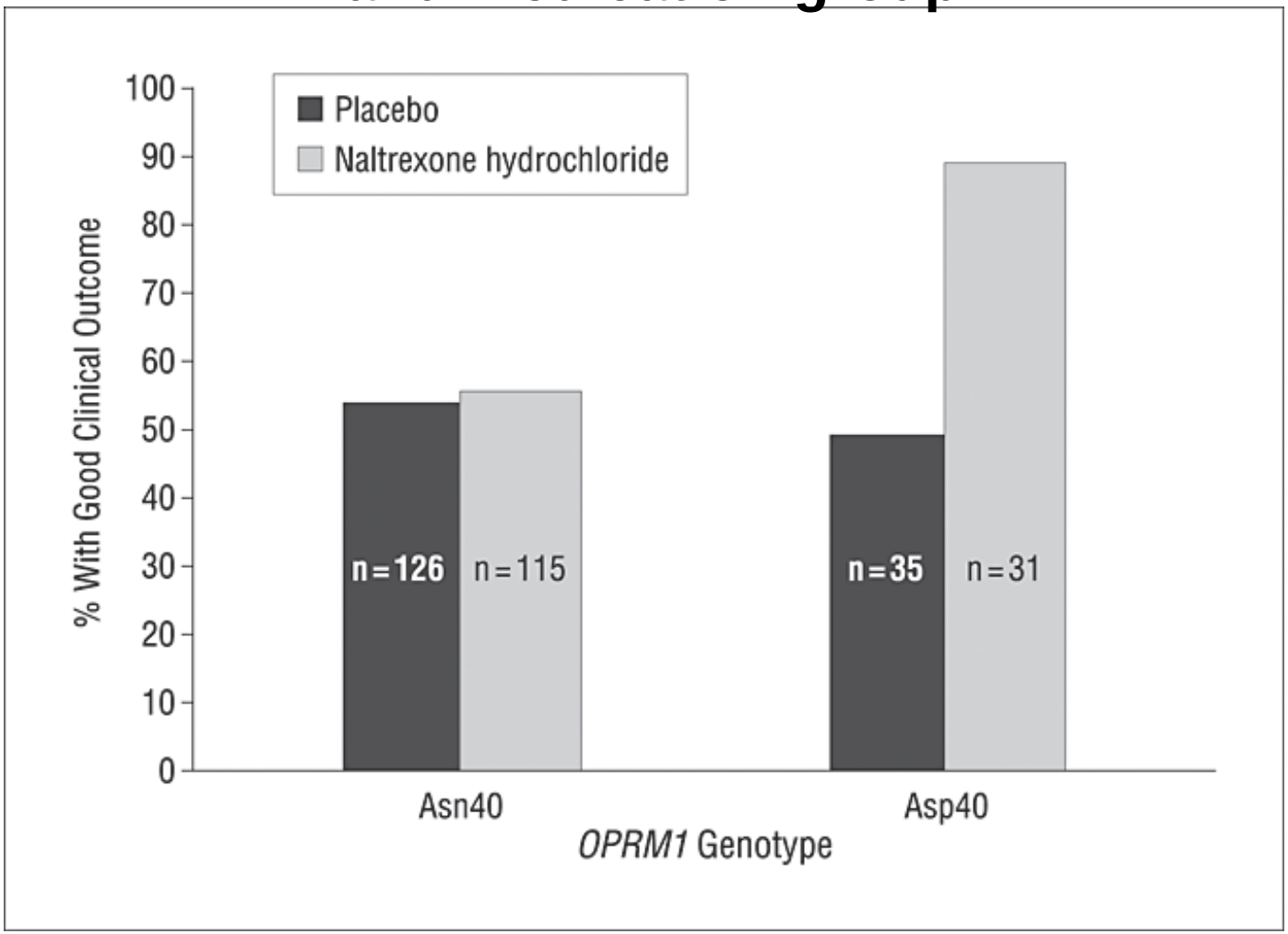
Anton RF et al. *JAMA* 2006 May 3;295:2003-17
(NCT00006206)

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



Good clinical outcome based on OPRM1 and medication group



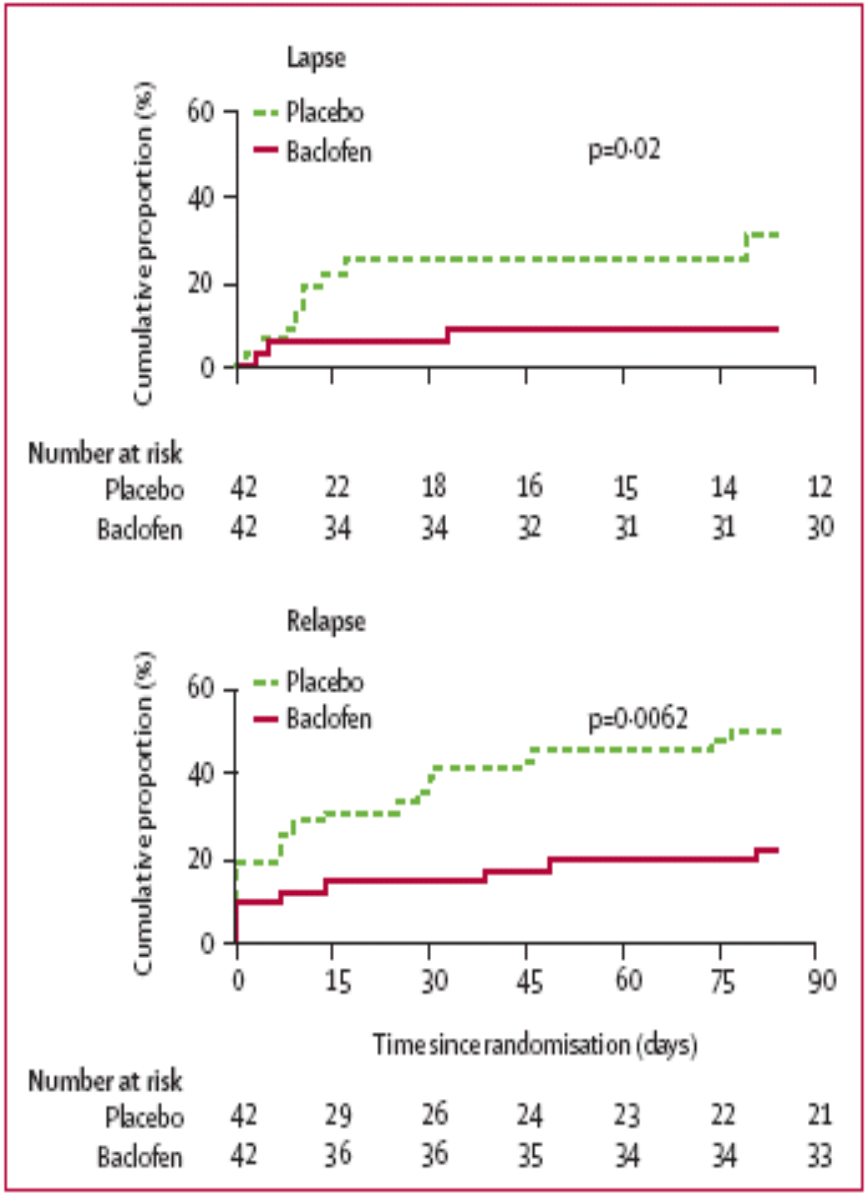
Medical management alone (no CBI). Genotype vs. medication interaction p=0.005
Anton, R. F. et al. Arch Gen Psychiatry 2008;65:135-144.

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

Baclofen



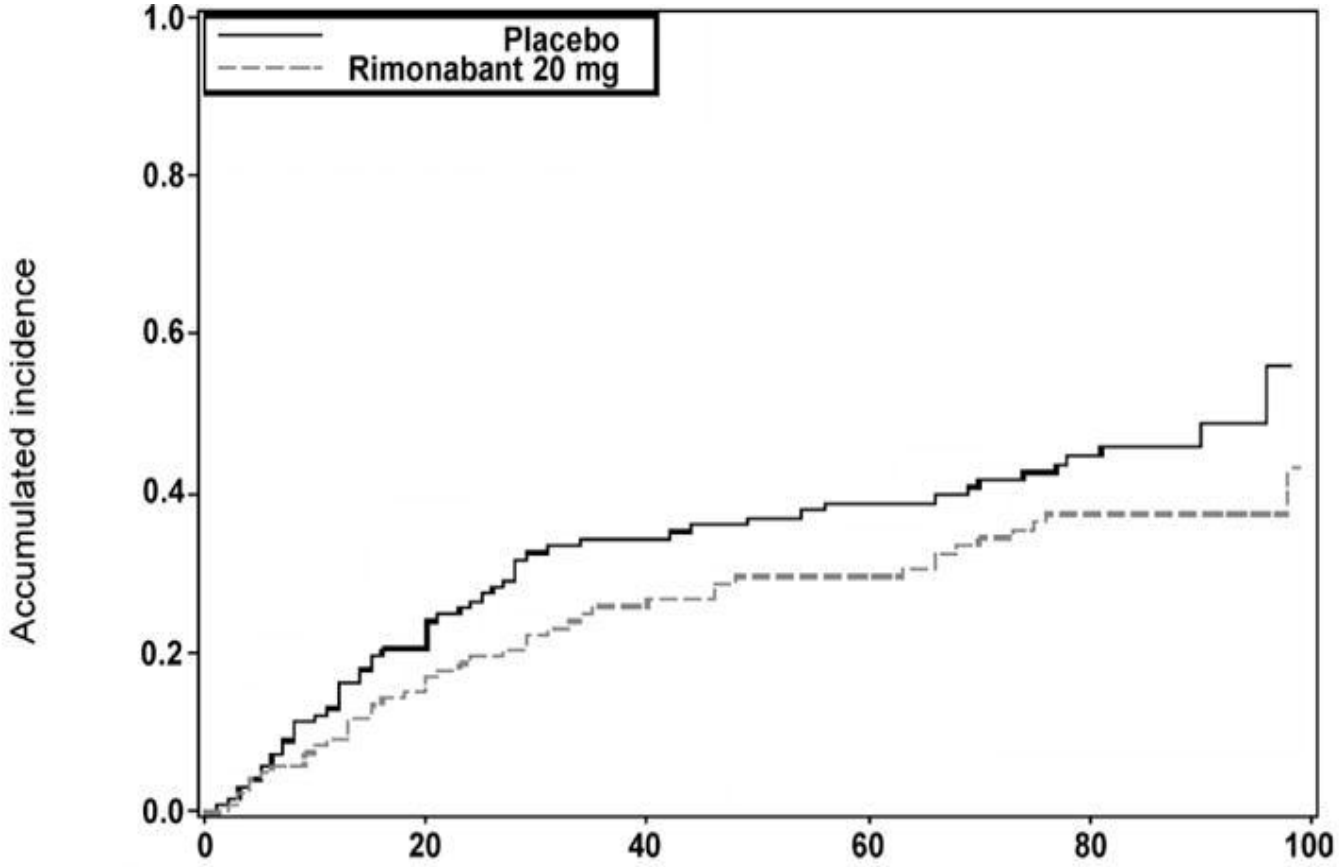
Complete Abstinence: 71% vs. 29%

Not replicated

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

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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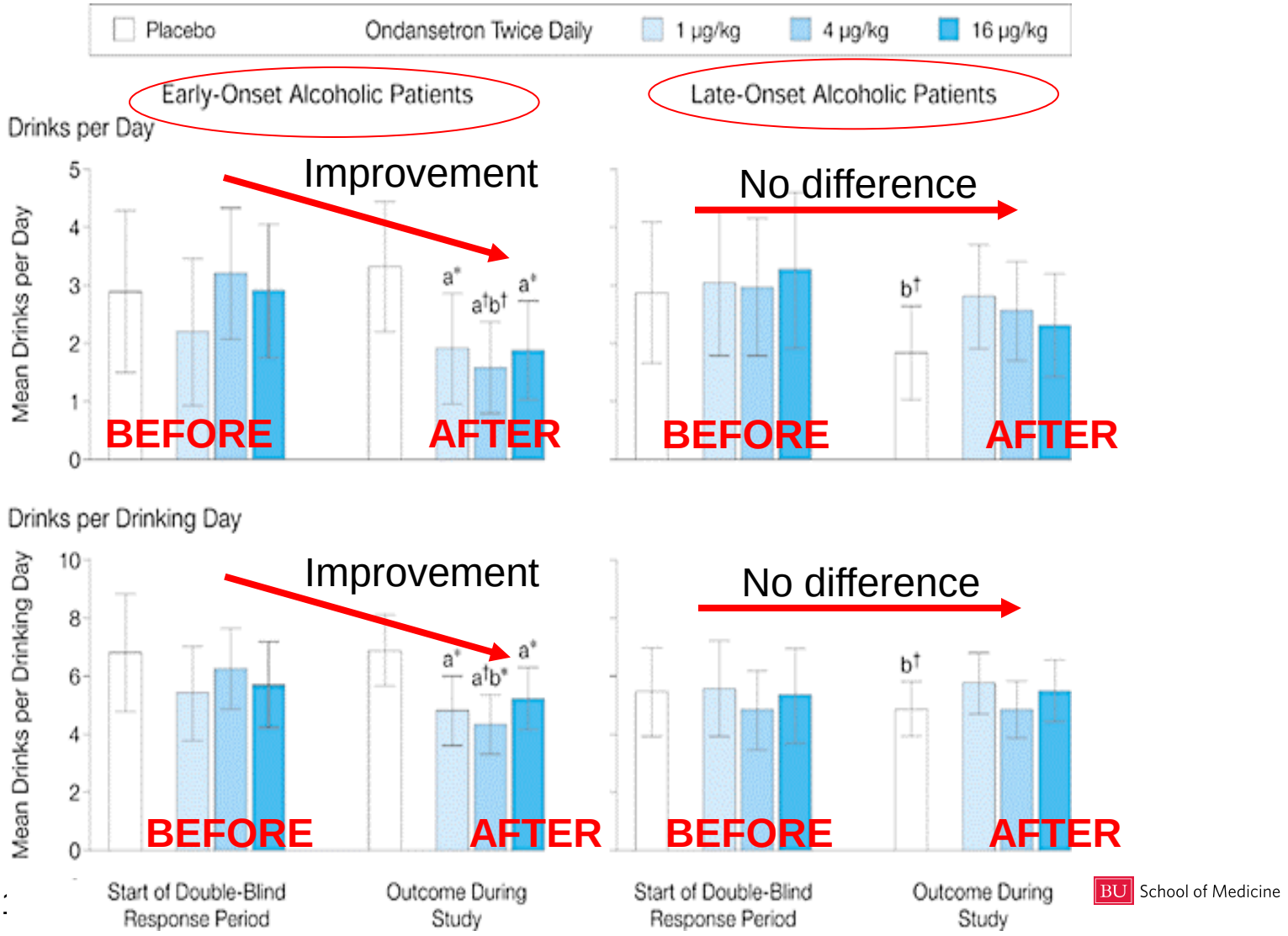
Ondansetron

- 5HT3 antagonist



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

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

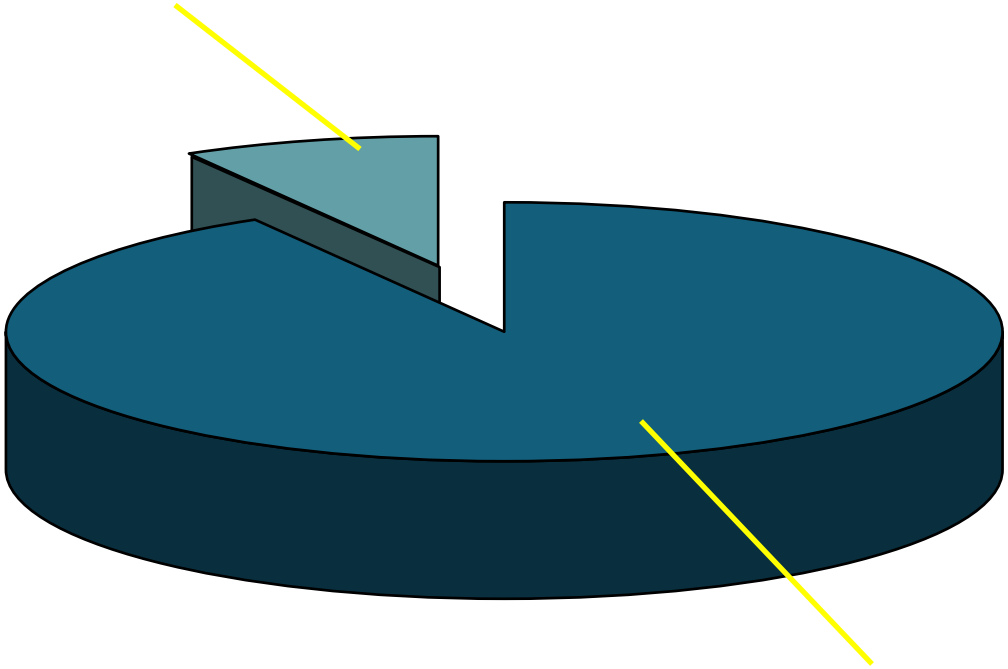
TREATMENT EFFECTIVENESS

- At one year, 2/3^{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.

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
McGlynn E et al. N Engl J Med 2003;348:2635-2645

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

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

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

Author(s)	N	Difference	Comment
Richmond et al. (VB)	378	-	Nonrandom
WHO (VB)	1559	+ B & VB	NS for women
Anderson & Scott	154	+	Men
Nilssen	338	+	
Senft et al.	516	Borderline	
Maisto et al.	301	-	Outside clinic
Scott & Anderson	72	-	Women

RED=no diff
GREEN= + study

Brief multi-contact

Author(s)	N	Difference	Comment
Maisto et al.	301	-	Decrease but NS
Curry et al.	307	+	Good quality
Fleming et al.	774	+	Good quality
Fleming et al.	158	+	Good quality; Elderly
Nilssen	338	+	
Ockene	530	+	Good quality
Wallace	909	+	Good quality

Example intervention (Fleming)
health booklet +
2 10-15” physician discussions
And follow-up nurse phone call

Whitlock et al. Ann Intern Med 2004; 140:557-68