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Management of Unhealthy Alcohol Use: From Research to Practice

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Outline

- Withdrawal
- Treatment

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Case

43 year old man, epigastric discomfort and vomiting. Fell, bumped head.

Lives alone, drinking all day-disabled (back pain).

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

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

Unable to visualize fundi, mild epigastric tenderness, no tremor, frontal ecchymosis. Awake, alert, oriented. Speech is fluent. Gait normal. Sensorimotor exam non-focal.

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Case (continued)

Four hours later (15-20 mg/dL/hr [1 drink] elimination)—tremor, anxiety, nausea.

BP 134/84, HR 90, ethanol level 146 mg/dl.

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

Alcohol Withdrawal (DSM-IV)

- 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/illusions
  - Psychomotor agitation
  - Anxiety
  - Grand mal seizures

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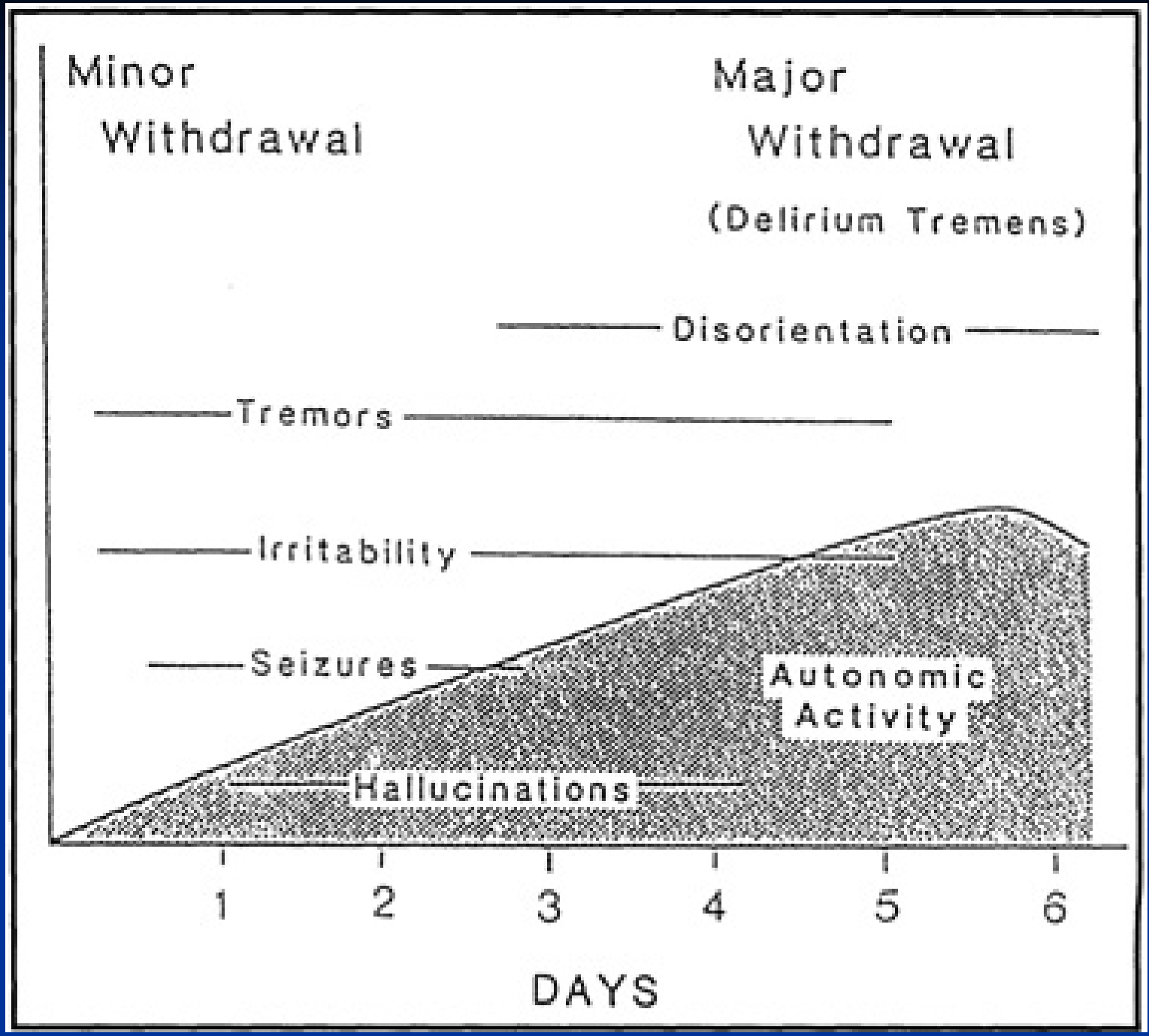

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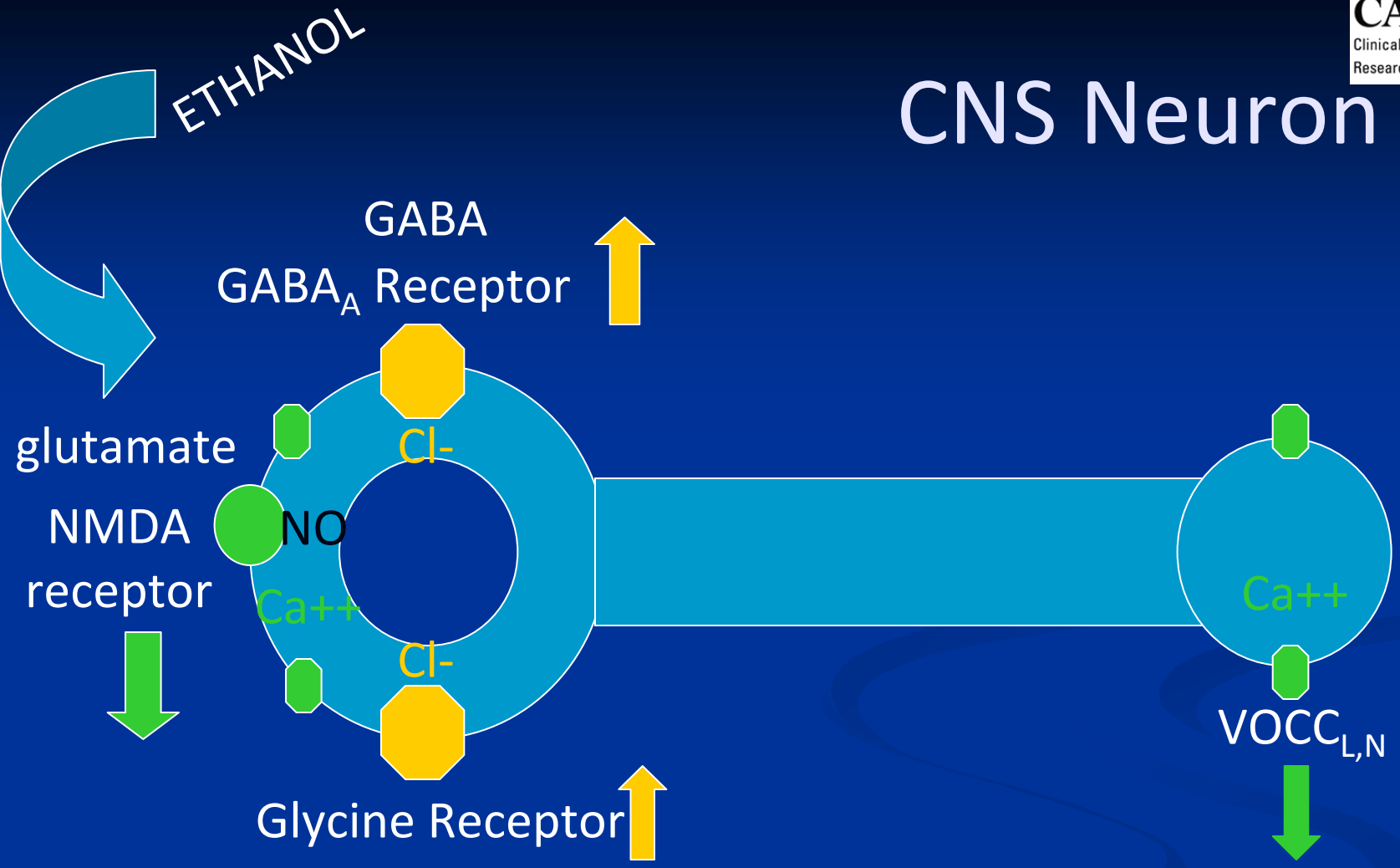
CNS Neuron



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Benzodiazepines vs. Placebo

Outcome: Seizures

ANY1/188 (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

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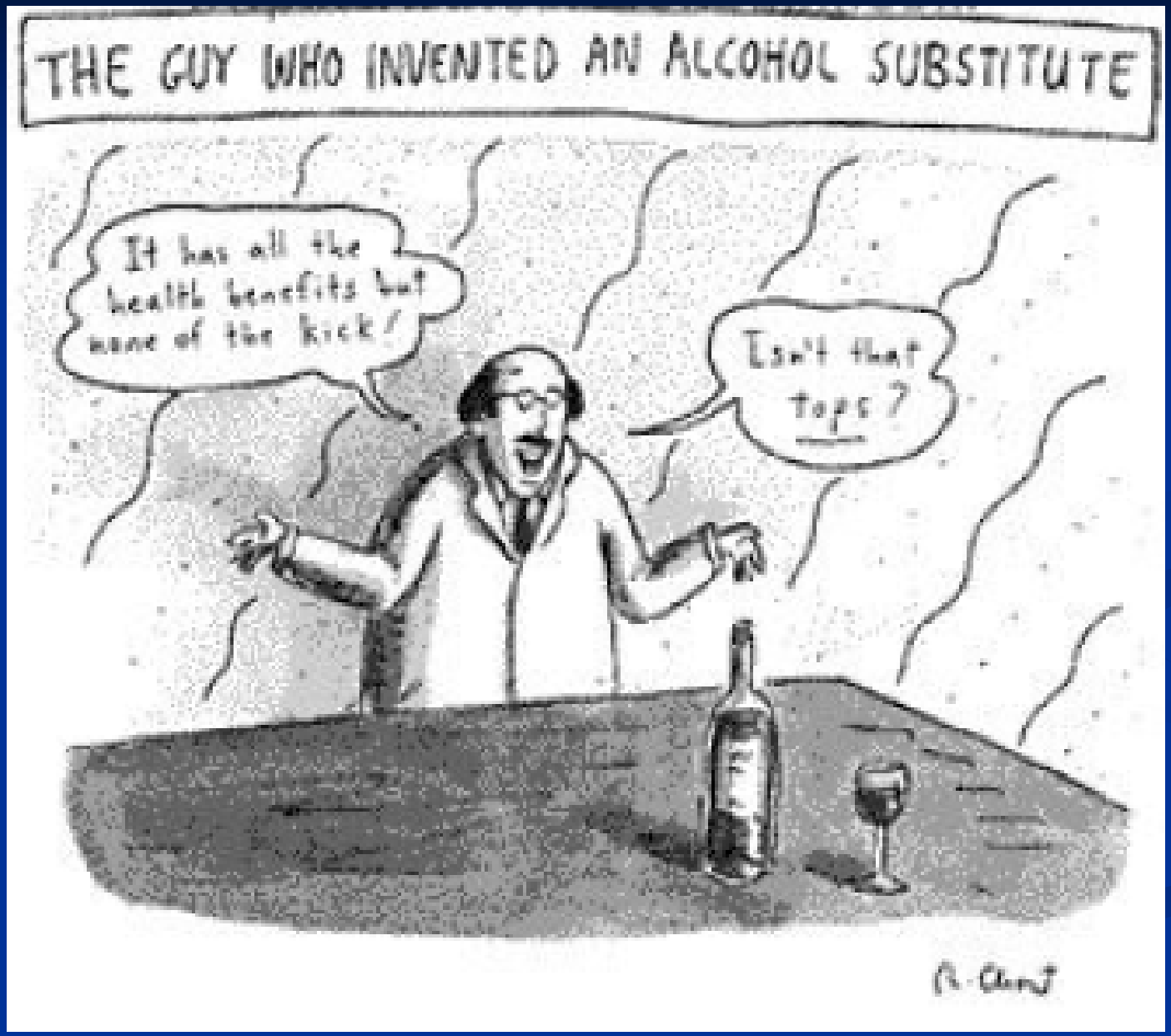

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Alcohol: Not for withdrawal

- Pros
  - The perfect cross-tolerant drug
  - The alcoholic's drug of choice
- Cons
  - Two controlled trials:
    - Gower 1980: more DTs and seizures vs. chlordiazepoxide
    - Spies 1995 (RCT): no diff vs. benzo+haloperidol or clonidine
  - 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)

Decreased Duration of Treatment

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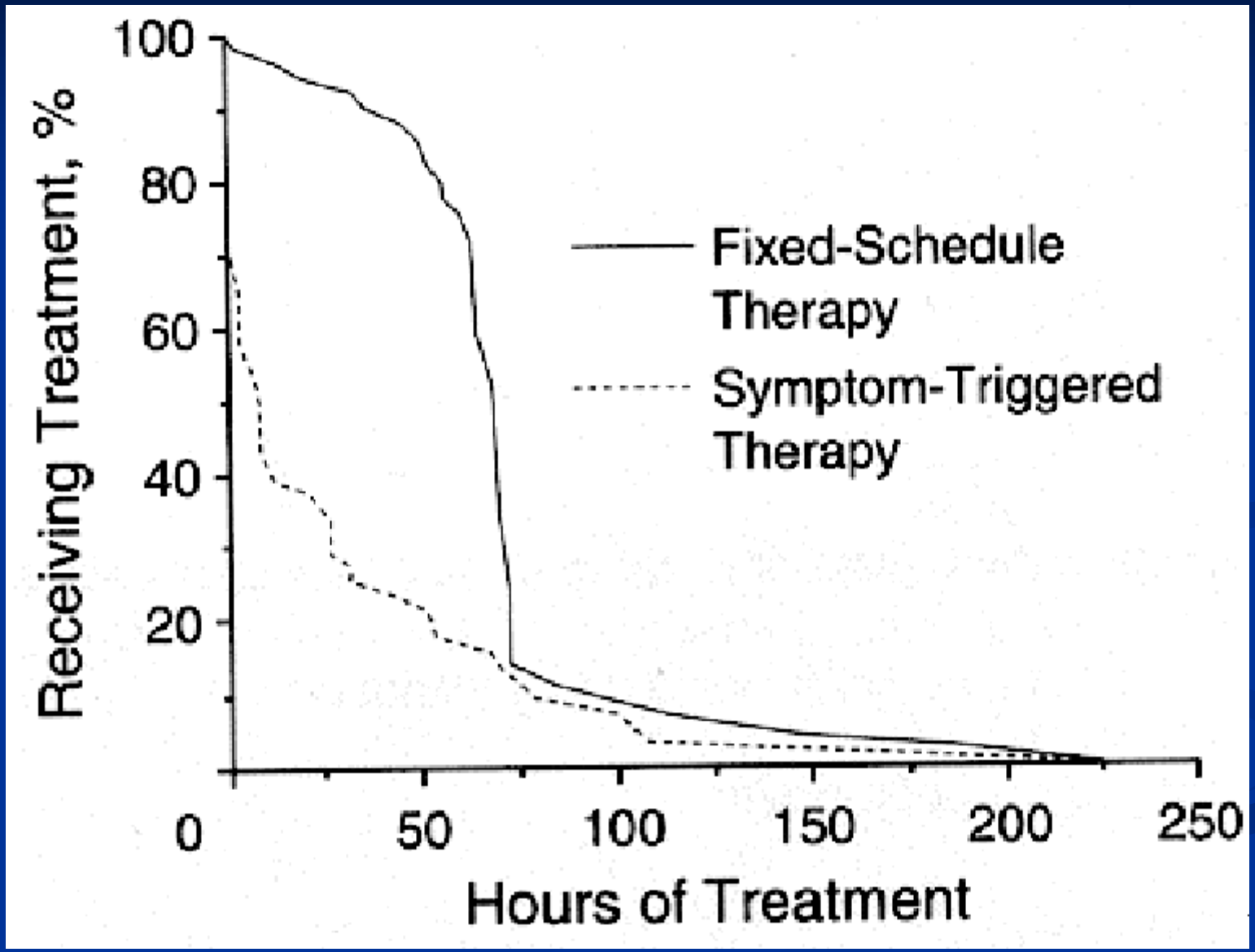

Saitz R et al JAMA 1994;272:519-23

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

Total score: _____ (maximum = 67) Rater's initials _____

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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

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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

- Risk factors: recurrent detoxification, prior seizure
- Occur 24-48 hrs after abstinence or decrease
- Often prior to autonomic hyperactivity
- Generalized, 79% <3, <3% status), 86%/1st 6 hrs
- Consider other diagnoses: fever, delirium, focal exam, head trauma, focal or multiple, 1st seizure, or status
- CT scanning unhelpful if clinical picture consistent

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

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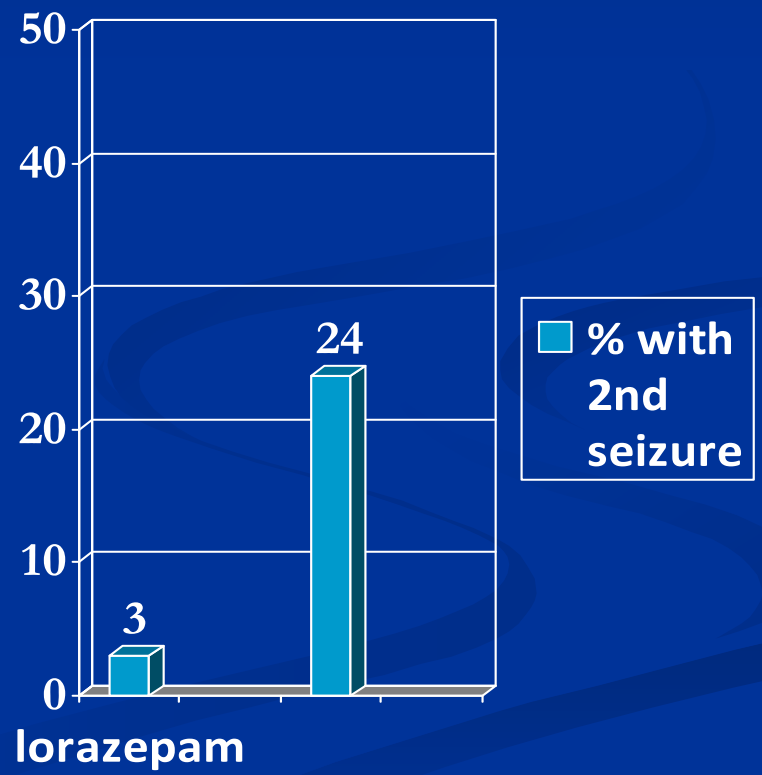
Treat to prevent the second one

- 186 subjects
- RPCDBT
- 2 mg lorazepam IV
- Decreased hospital admission



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

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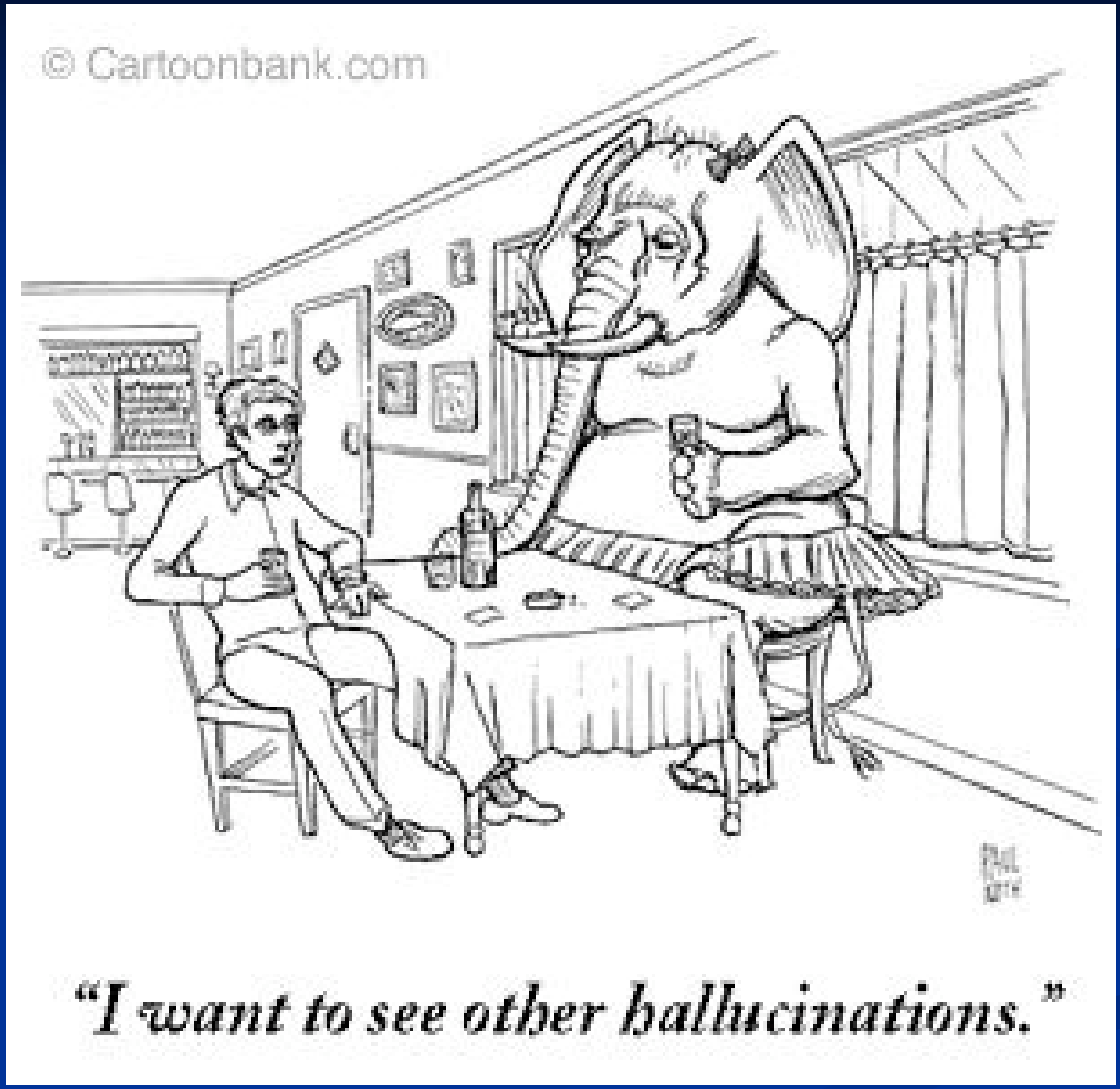

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Case (continued)

The patient tells you he is at the racetrack with his friends, BP 170/100, HR 110, T 99

- What is the diagnosis?
- What if he were febrile?

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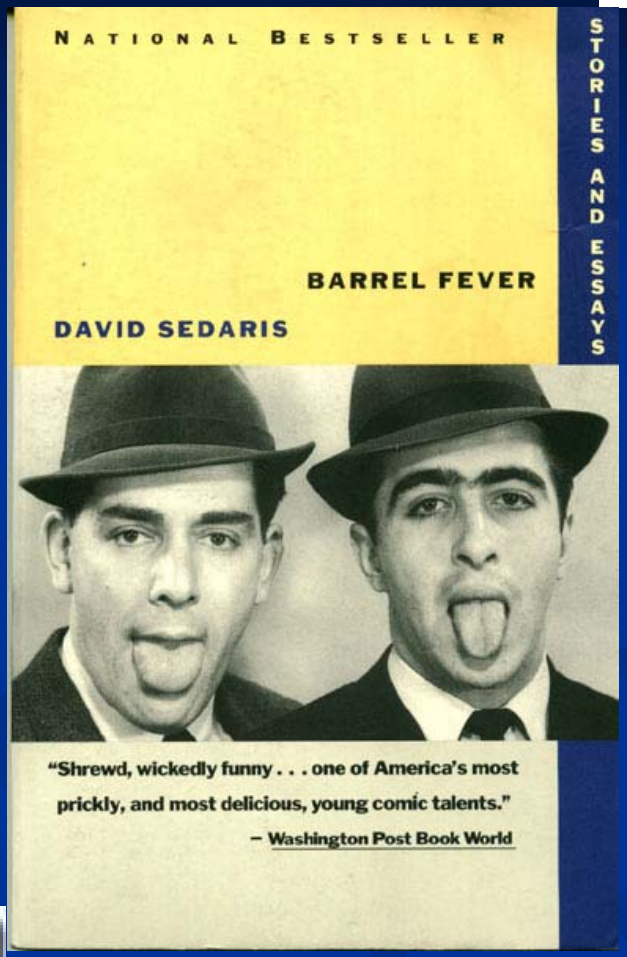

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Alcohol Withdrawal
DTs: Treatment time to light somnolence/adequate control

- 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

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

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- 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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Treatment of Unhealthy Alcohol Use

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


LESS CHOLESTEROL
REGULAR CHECKUPS
NO NICOTINE
NO ALCOHOL
LOW SODIUM
MODERATE EXERCISE
NO SUGAR

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Ingredients of Successful Brief Interventions

- What?
  - -10-15 minutes, multiple
  - -Components:
    1. Feedback
    2. Advice
    3. Goal Setting
- How?
  - -Empathy
  - -Self-efficacy
  - -Menu

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Efficacy of Brief Intervention Among those with Non-dependent Unhealthy Alcohol Use Identified by Screening in Primary Care: Meta-analyses of Randomized Trials

- BI decreased the proportion of drinkers of risky amounts from 69% (942/1374) to 57% (810/1410) at 12 mo
- BI decreased consumption 15% (by 38 grams [about 3 standard drinks] per week)(n=5639)
- No diff. between longer BI or efficacy vs. effectiveness study designs

Beich et al. BMJ 2003;327:536
Bertholet et al. Arch Intern Med. 2005;165:986
Kaner EF et al. Drug Alcohol Rev. 2009; 28(3):301–323

Two trials of note

- Fleming: Men and women with unhealthy use in primary care, 2 10-15 minute visits plus RN phone call
  - BI decreased hospital days, emergency department visits (p=0.08), and cost (medical cost/benefit=$166/$546 ($7780 societal) over 4 years
- Kristenson: Middle aged men with high GGT and heavy drinking, q mo visits with RN and q 3 mo with MD for BI and GGT
  - BI decreased 16-year **mortality**
    - Total mortality: 10% vs. 14% (NS)
    - Alcohol-related (48% of all deaths): 4% vs. 7% (p=0.03)

Fleming MF, Lawton Barry K, et al. JAMA 1997;277:1039
Fleming MF et al. Alcohol Clin Exp Res. 2002;26(1):36-43.
Kristenson H, et al. Alcohol Clin Exp Res 1983;7:203

Hospital and Trauma Patients

- Systematic reviews: mixed results
  - No differences
  - Effects on drinking but not problems
  - Effects on problems but not drinking
  - No effects on heavy drinking episodes
- Recent large study found effect on drinking (Taiwanese men)
- Issues: Severity, comorbidity, self-change

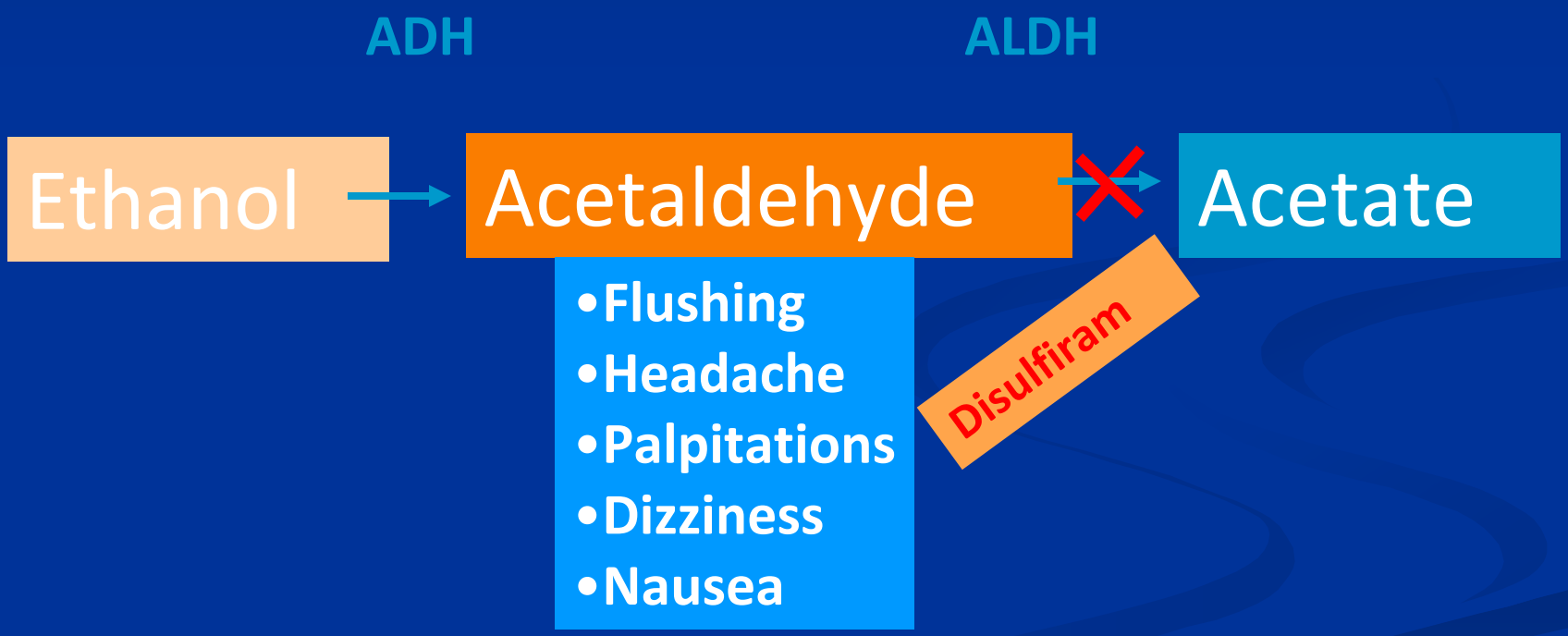
Emmen MJ et al. BMJ, doi:10.1136/bmj.37956.562130.EE, 16 Jan 2004
McQueen J et al. Cochrane Database Syst Rev. 2009;3:CD005191
Liu S-I et al. Addiction 2011;106:928–940

Treatment of Dependence

- Treatment
  - Counseling (not generic)
  - Address psychiatric conditions
  - **Pharmacotherapy**
- Self and mutual help

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

Disulfiram



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

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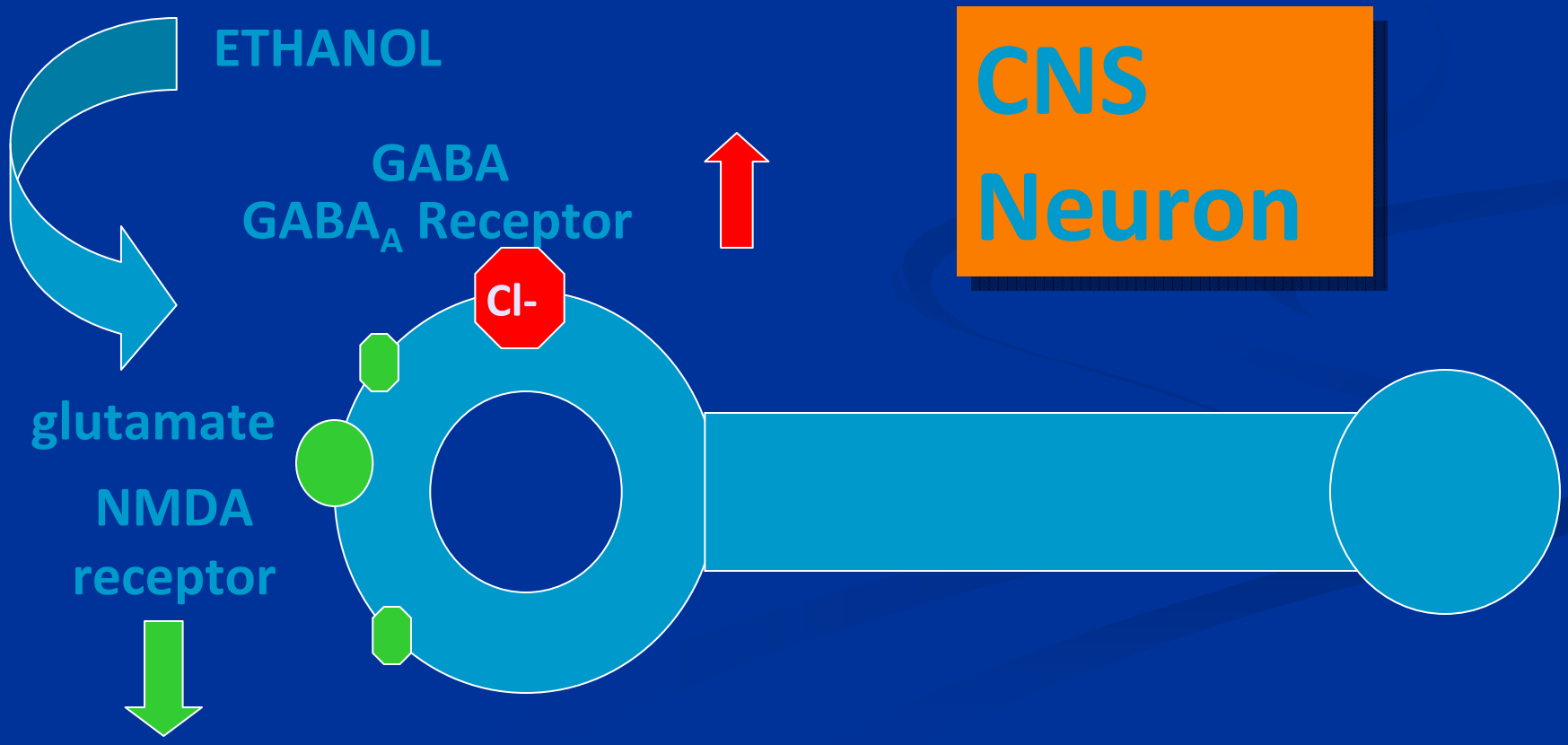
Prescribing Disulfiram

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

Acamprosate

Stabilizes activity in the glutamate system



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Efficacy of Acamprosate

- Acamprosate (n=1195) vs. placebo (n=1027), 7 trials
- More days abstinent
  - 27 days (95% CI 18 days, 36 days)
- Greater proportion of patients continuously abstinent (1 year)
  - 23% vs. 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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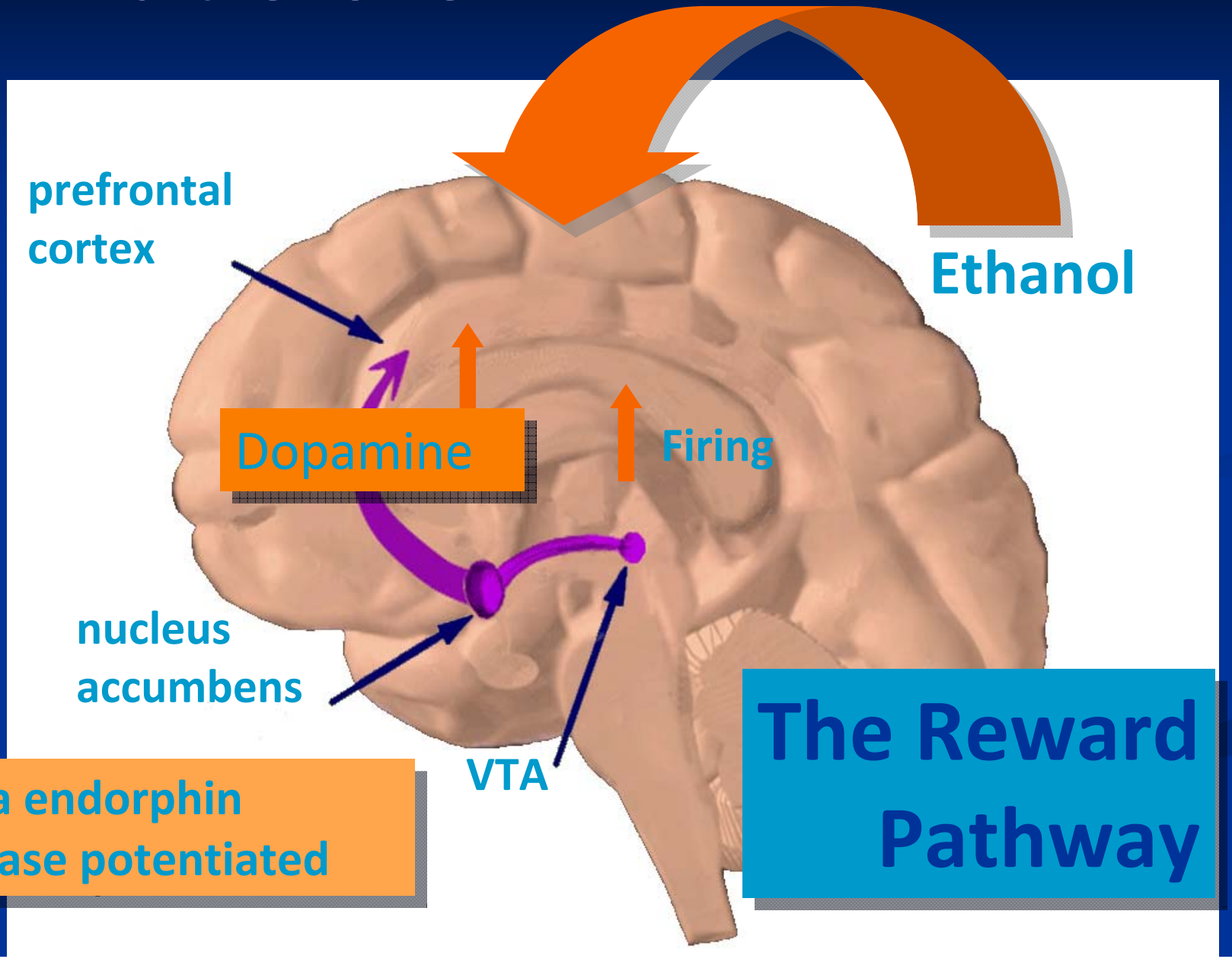

Efficacy of Naltrexone

- Naltrexone (n=1142) vs. placebo (n=930), 14 trials
- Smaller proportion relapse to heavy drinking (37% vs. 48%, OR 0.62 (95% CI 0.52,0.75))

Bouza C et al. Addiction 2004;99:811

Injectable Naltrexone

- 6-month RDBPCT, 180 mg, and 360 mg, n=627
  - 91% drank within a week of study entry
  - 43% abstinence goal (didn't predict outcome)
- 360 mg compared with placebo
  - 25% greater decrease in heavy drinking days
    - Median 3 vs. 6 heavy drinking days per month
      - 8% subset abstinent 7d. @ baseline (n=36), 80% reduction in heavy drinking days, and more complete abstinence (41% vs. 17%, NS)

Garbutt JC et al. JAMA 2005;293(13):1617-1625. doi:10.1001/jama.293.13.1617

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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

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Medications Under Study

- Topiramate (Topamax)
- Ondansetron (Zofran)
- Baclofen
- Rimonabant
- Buprenorphine??
- Combinations
- For people with alcohol “problems,” but not dependence
  - Targeted use

The COMBINE Study

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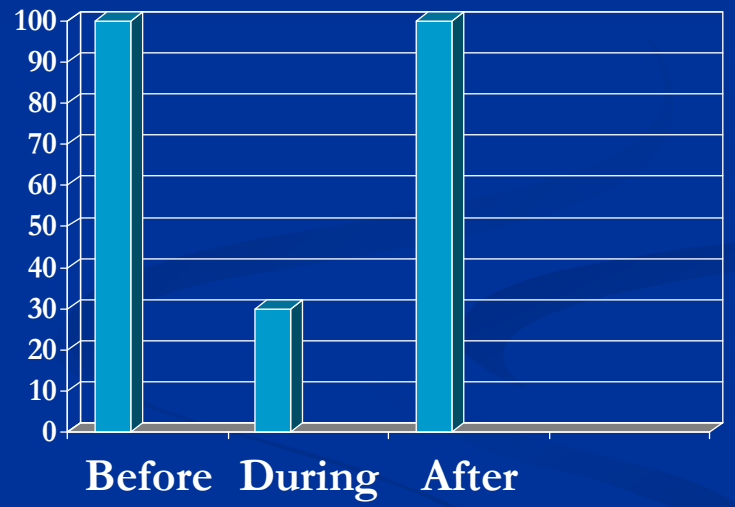
N=1383, 16 wk trial	Good Clinical Outcome %
Medical Management and Placebo	58
Medical Management and Placebo and **CBI**	71
Medical Management and **Naltrexone**	74

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

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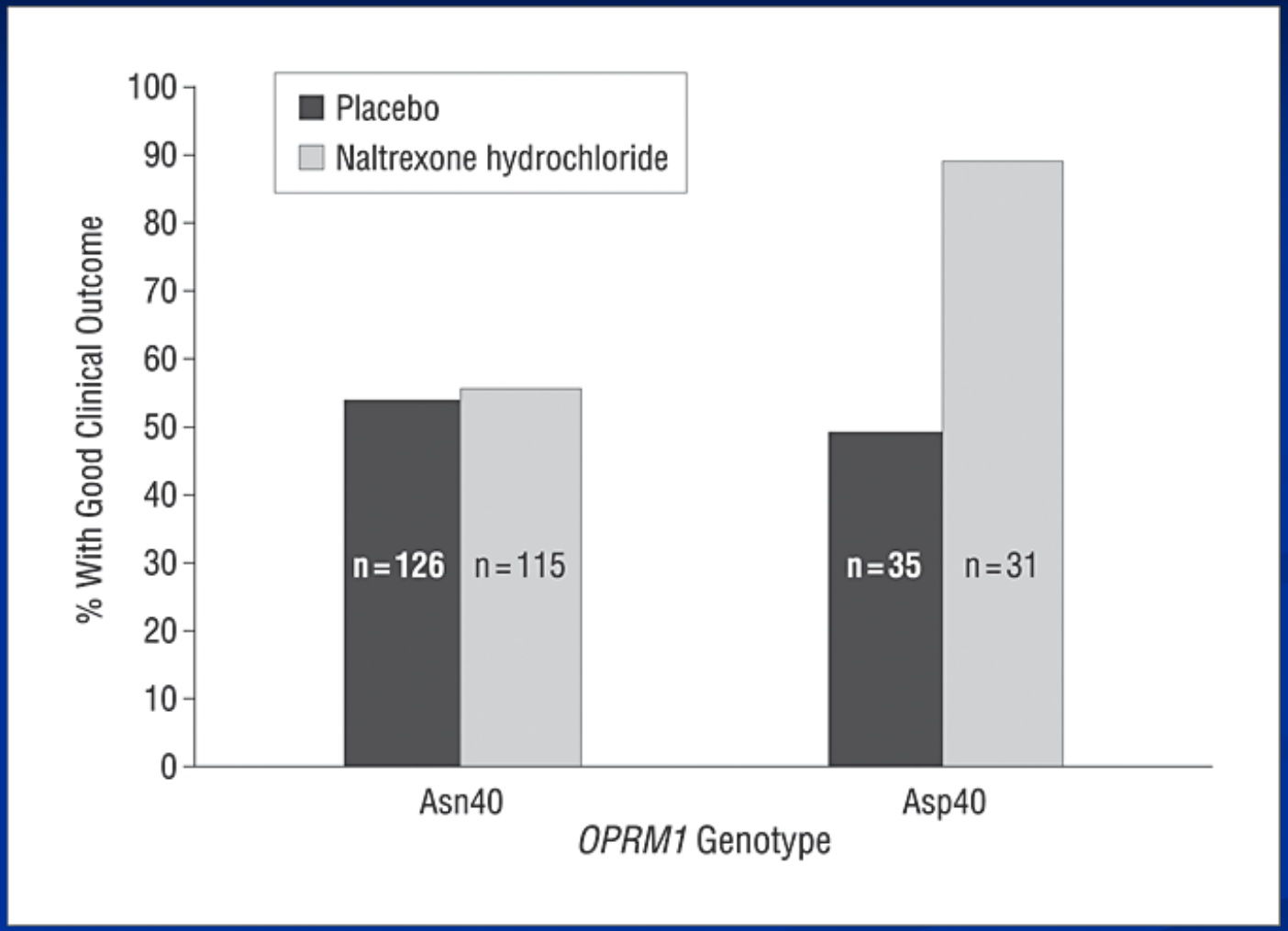

Medical management alone (no CBI). Genotype vs. medication interaction p=0.005
Anton, R. F. et al. Arch Gen Psychiatry 2008;65:135-144.

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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 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

Specialty Treatment

- 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

- Manage withdrawal according to the evidence
  - Benzodiazepines as needed
- Brief intervention*—to decrease use and link with treatment
- Manage dependence
  - Referral for counseling and mutual help groups*
  - Address psychiatric comorbidity
  - Pharmacotherapy

*stay tuned re how…