Pharmacotherapy of Alcohol Use Disorders

Roger D. Weiss, MD
Professor of Psychiatry, Harvard Medical School
Chief, Division of Alcohol and Drug Abuse
McLean Hospital
rweiss@mclean.harvard.edu

Disclosure Statement

- Consultant
  - Reckitt Benckiser

Prescribing Medication

vs.

Taking Medication

What Parameters Are Used to Determine Treatment Efficacy for Alcohol Dependence?

- Percent days abstinent
- Percent days heavy drinking
- Likelihood of any drinking (abstinence rate)
- Likelihood of heavy drinking
- Drinks per drinking day
- Time to first drink/relapse
- Consequences of drinking
- Biological markers

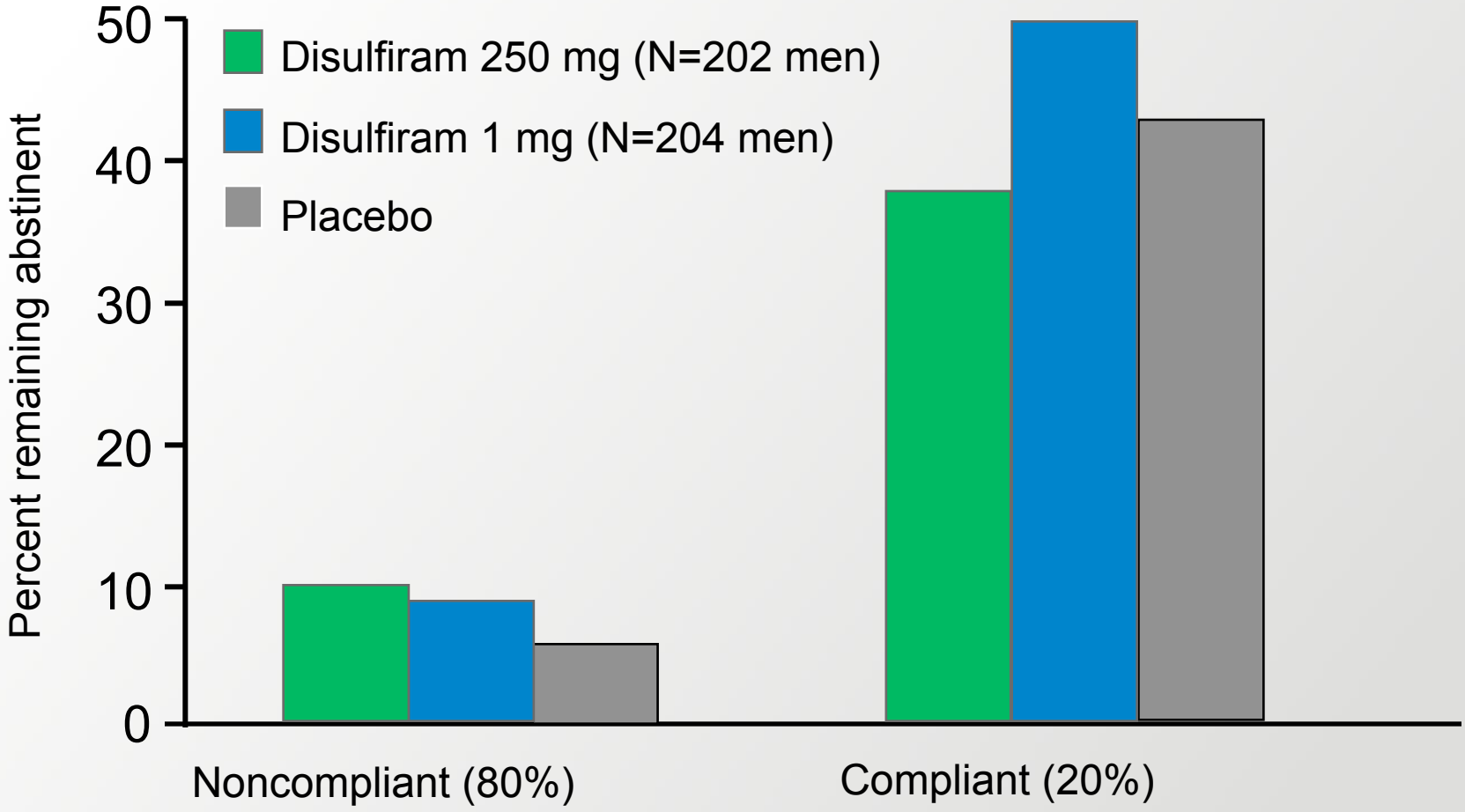
FDA-Approved Medications for Alcohol Dependence

- Disulfiram
- Naltrexone
- Acamprosate

Disulfiram

- Mechanism of action: inhibits aldehyde dehydrogenase, an enzyme in the metabolism of alcohol
- Leads to acetaldehyde poisoning when alcohol is ingested
- Reaction occurs 10-15 min. after drinking
- Reaction can be quite severe, occasionally fatal; severity is related to dose and individual characteristics

Disulfiram and Abstinence Rates



Fuller RK et al., *JAMA*. 1986(Sept);256(11):1449-1455.

Disulfiram: Dosing

- Can prescribe 125-500 mg/day
- Since disulfiram works via the FEAR of its effects, low doses can be as effective as higher doses to start
- Dilemma: what to do if someone drinks on a lower dose?

Disulfiram: Contraindications

- Alcohol-containing products or paraldehyde within 14 days of discontinuing disulfiram
- Recent use of metronidazole
- Severe coronary occlusion or myocardial disease
- Hypersensitivity to disulfiram or other thiuram derivatives used in pesticides and rubber vulcanization
- Psychosis

Disulfiram: Precautions

- Significant illness such as diabetes, cirrhosis, cerebral damage, seizure disorder, hypothyroidism, serious kidney disease

Disulfiram: Side Effects

- Most common: dermatitis, garlicky or metallic taste

<u>More serious side effects</u>

- **Hepatic:** hepatitis
- **Neurologic:** peripheral neuropathy
- **Ophthalmic:** optic neuritis
- **Psychiatric:** psychotic disorder or exacerbation

Disulfiram: Monitoring

- Do baseline and follow-up LFTs
- No generally accepted guidelines about what level is acceptable to start or unacceptable to continue
- Severe hepatotoxicity frequently occurs early, so getting LFTs more often early in the course of treatment is a good idea

Disulfiram: Advantages

- Built-in impulse control due to long elimination time (up to 2 weeks)
- May indirectly reduce desire to drink
- Best used in careful, impulsive, situational drinkers
- May be used PRN later
- Importance of adherence strategies

Disulfiram: Disadvantages

- Side effects, including the 2 side effects of greatest concern
  1. Liver toxicity
  2. Risk of unintentional or intentional alcohol reaction
- Other disadvantage is possible overreliance on disulfiram, underreliance on other supports

Naltrexone for Alcohol Dependence

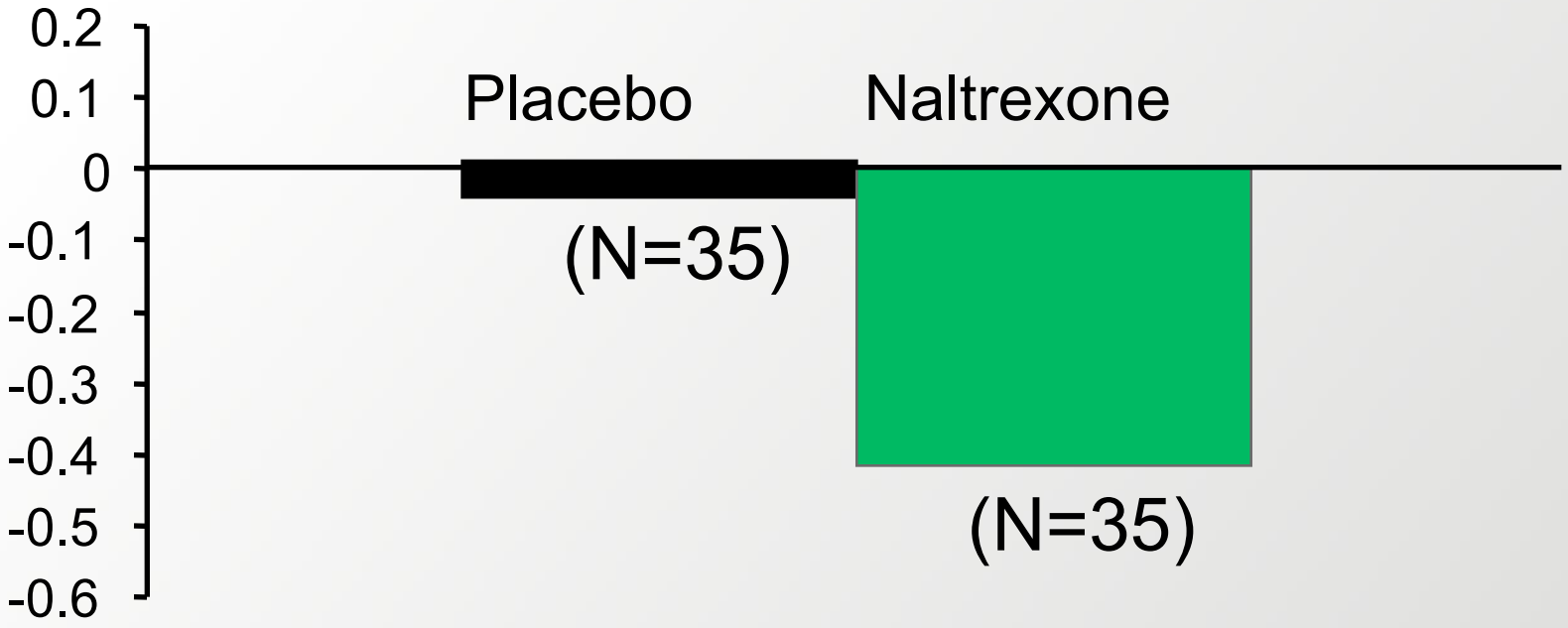
- 70 VA patients, all men with alcohol dependence
- 12-week double-blind, placebo-controlled
- Naltrexone 50 mg/day
- Day treatment (6 hrs/d) for 1 month, then twice/week group therapy for 2 months
- Major psychiatric illness excluded
- 23% of NTX Ss vs. 54% placebo Ss **relapsed**; similar rate of **drinking**

Volpicelli et al., (1992).

Naltrexone for Alcohol Dependence: Mechanism of Action

- May reduce alcohol-induced craving
- May reduce craving independent of drinking
- Differences in the experience of a slip
- Does not make someone a controlled drinker
- Helps a patient get back to abstinence faster
- Mostly positive studies, but some negative

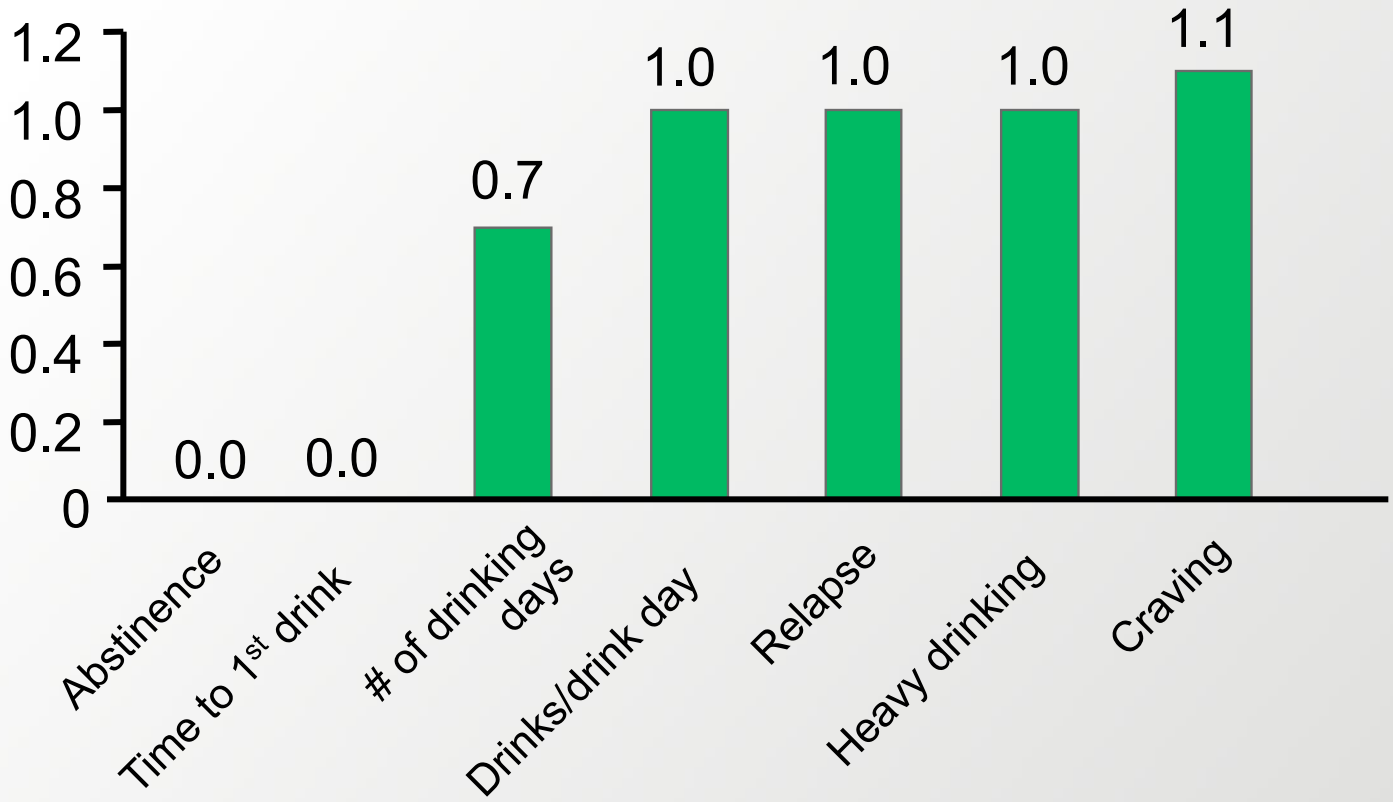
Subjective “High” Produced by Alcohol



+1 = Increased high
0 = No change in high
-1 = Decreased high

p<0.006; Volpicelli JR et al., *Am J Psychiatry*. 1995(April);152(4):613-615.

NTX Outcome Measures



NTX score measures the strength of evidence favoring naltrexone, represented by averaging efficacy scores for all RCTs that measured the particular outcome. Points were assigned as: 0 (NS), 1 (+), and 2 (++). Score of 1 or above represents statistically significant advantage of NTX over placebo

Leavitt SB. Addiction Treatment Forum. 2002(March):1-8.

Naltrexone for Alcohol Dependence: Dosing

- 50 mg/day is typical dose
- Some patients respond to 25 mg
- Starting with lower doses may reduce side effects
- COMBINE study used 100 mg/day, but 50 mg/day is more typical

Naltrexone for Alcohol Dependence: Contraindications

1. Concomitant or recent use of opioids
2. Hypersensitivity to naltrexone
3. Liver failure or acute hepatitis
4. Naloxone challenge test failure
5. Black box warning about hepatocellular injury with higher doses

Naltrexone for Alcohol Dependence: Precautions

- Hepatic impairment
- History of suicide attempts

Naltrexone Side Effects

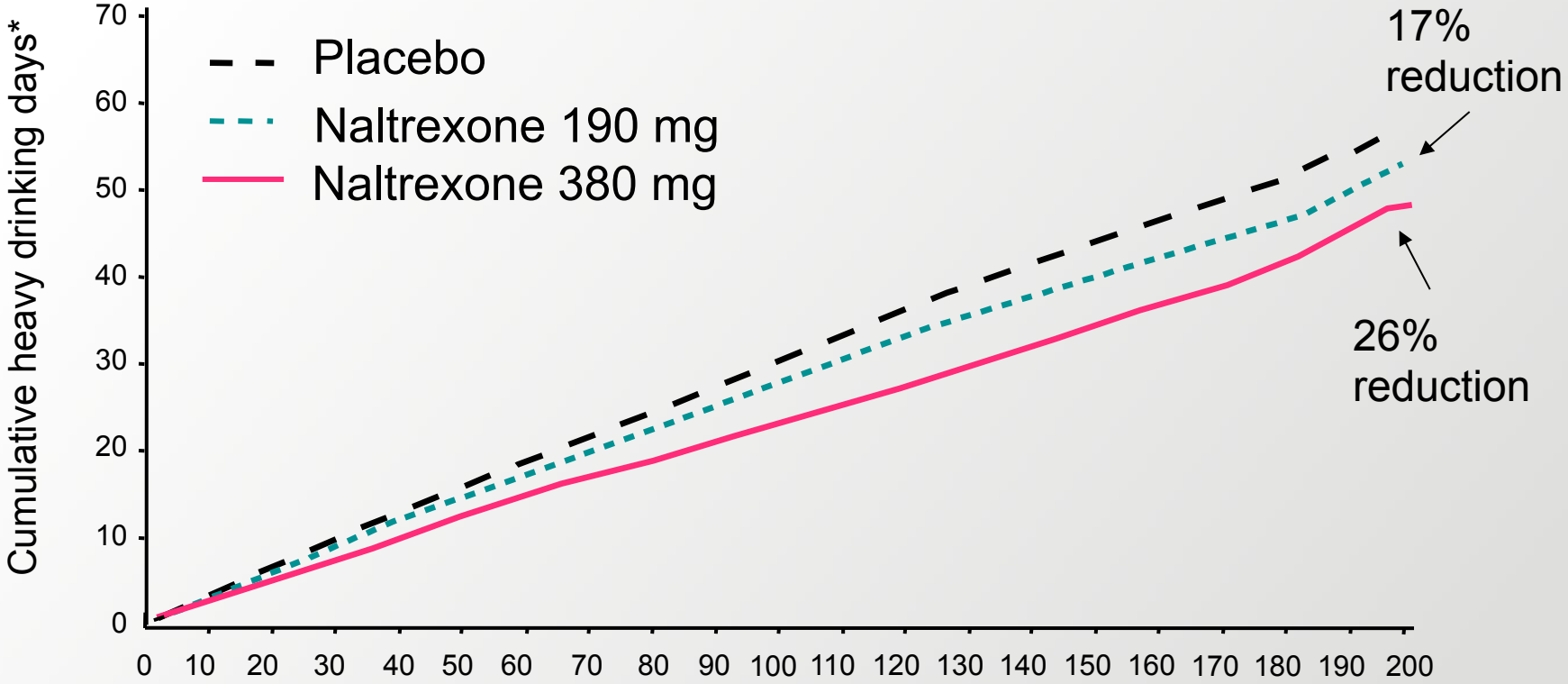
• Nausea	10%
• Headaches	7%
• Dizziness	4%
• Fatigue	4%
• Insomnia	3%
• Anxiety/nervousness	2%
• Sleepiness	2%

Croop RS et al., Arch Gen Psychiatry. 1997(Dec);54(12):1130-1135; Open label trial of 570 treated patients.

Naltrexone: Monitoring

- Do baseline and follow-up LFTs
- No generally accepted guidelines about what level is acceptable to start or unacceptable to continue
- Hepatotoxicity more likely with higher doses

Long-Acting Injectable Naltrexone Reduces Heavy Drinking Days



Naltrexone 380 mg vs. placebo, *P*=.03; naltrexone 190 mg vs. placebo, *P*=.07.

* Heavy drinking defined as ≥5 drinks per day for men and ≥4 drinks per day for women.

Garbutt et al., *JAMA* 2005;293:1617.

Extended-Release Injectable Naltrexone for Alcohol Dependence

- Dose: 380 mg IM injection monthly
- Reduces heavy drinking days
- Beneficial effect in men, not in women
- Appears to achieve beneficial effect in 2-3 days after initial injection*

*Ciraulo et al., 2008.

Extended-Release Injectable Naltrexone for Alcohol Dependence *cont'd*

- Same side effects as oral naltrexone
- Same contraindications, black box warning
- May cause injection site problems
- Since it is long-acting, need to consider need for opioids carefully

*Ciraulo et al., 2008.

Naltrexone: Advantages

- Won’t make you sick if you drink
- May reduce desire to drink
- May be particularly helpful for combined alcohol and opioid dependence

Naltrexone: Disadvantages

- Relatively small effect size
- Some negative trials
- Promotes reduction in heavy drinking, not necessarily abstinence
- Problem for those who need opioids on an emergency basis
- May work only in subgroup of alcohol dependent patients

Acamprosate (N-acetylhomotaurine)

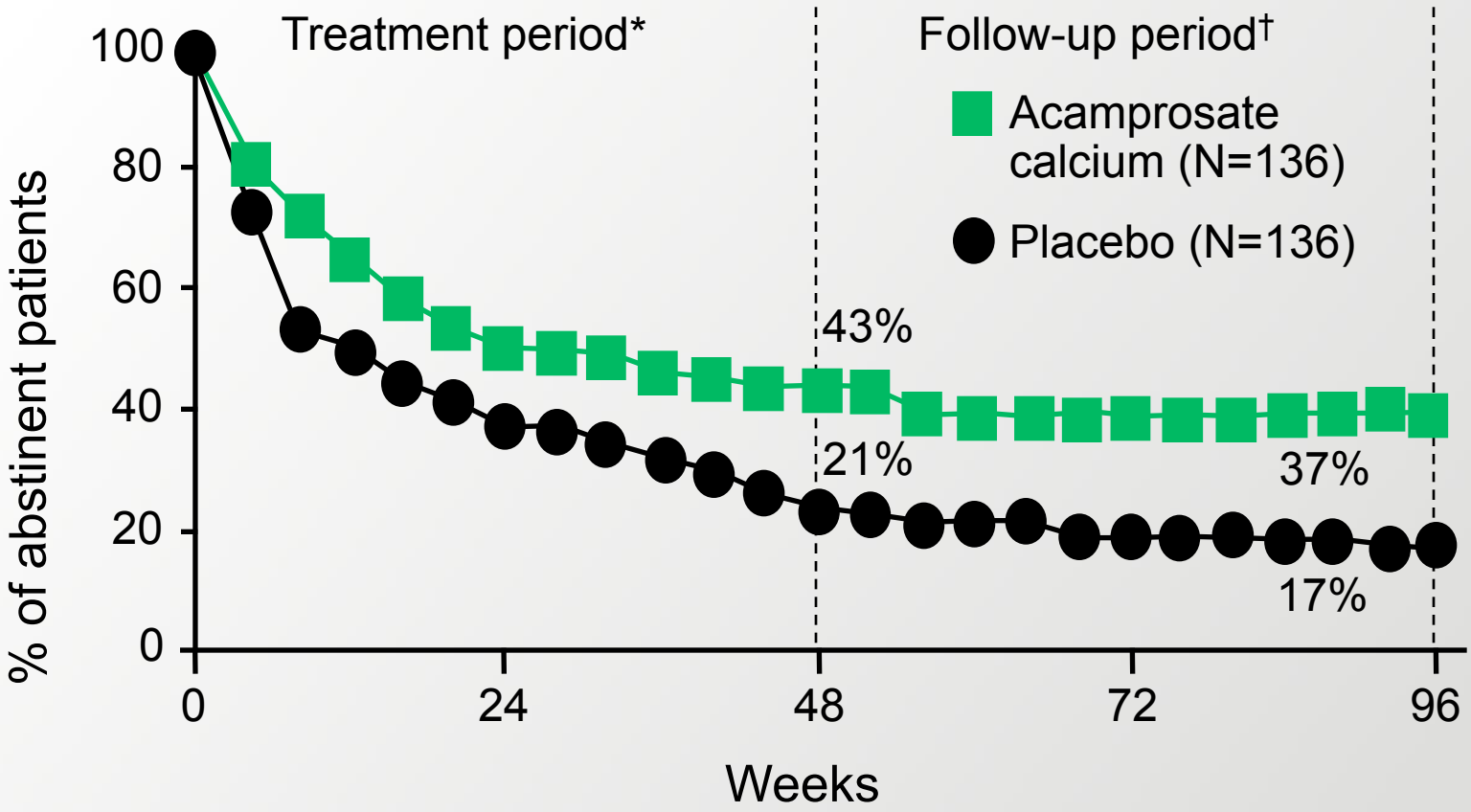
- Mechanism of action: interacts with glutamate and GABA neurotransmitters systems
- In animal models of alcohol dependence, acamprosate reduced deprivation-induced drinking
- Does not cause dependence or withdrawal
- May reduce protracted withdrawal symptoms

Acamprosate in Alcohol Dependence Treatment[1]

- Study conducted in Germany/Austria
- 272 patients receiving routine counseling and treated with 2 g/day acamprosate or placebo for 48 weeks

1. Sass,1996 Sass H et al., *Arch Gen Psychiatry*. 1996(Aug);53(8):673-680.

Acamprosate in Alcohol Dependence Treatment[1] *cont'd*



*p=0.001; †p=0.003; 272 patients were entered into the study over 2 years; Kaplan-Meier survival analysis (survival function estimate); continuous abstinence for the treatment and follow-up periods

1. Sass,1996 Sass H et al., *Arch Gen Psychiatry*. 1996(Aug);53(8):673-680.

Practical Considerations with Acamprosate Treatment

- Usual dosage: two 333-mg tablets 3x daily
- Excreted in kidney, not metabolized in liver, so can be given in face of severe liver disease, unlike naltrexone or disulfiram
- Steady state plasma concentrations in 5 d
- Contraindicated if patient has severe renal disease (creatinine clearance of 30 mL/min or less) or is hypersensitive to acamprosate
- Precaution if severely depressed

Acamprosate Side Effects

- Diarrhea (17% acamprosate vs. 10% placebo)
- Nausea
- Depression
- Anxiety
- Bloating
- Rash

Acamprosate: Advantages

- Won’t make you sick if you drink
- May reduce desire to drink
- Helpful for those with liver disease
- Increases likelihood of abstinence

Acamprosate: Disadvantages

- Relatively small effect size
- Recent negative trials
- Requires 3x a day dosing

NIAAA COMBINE Study

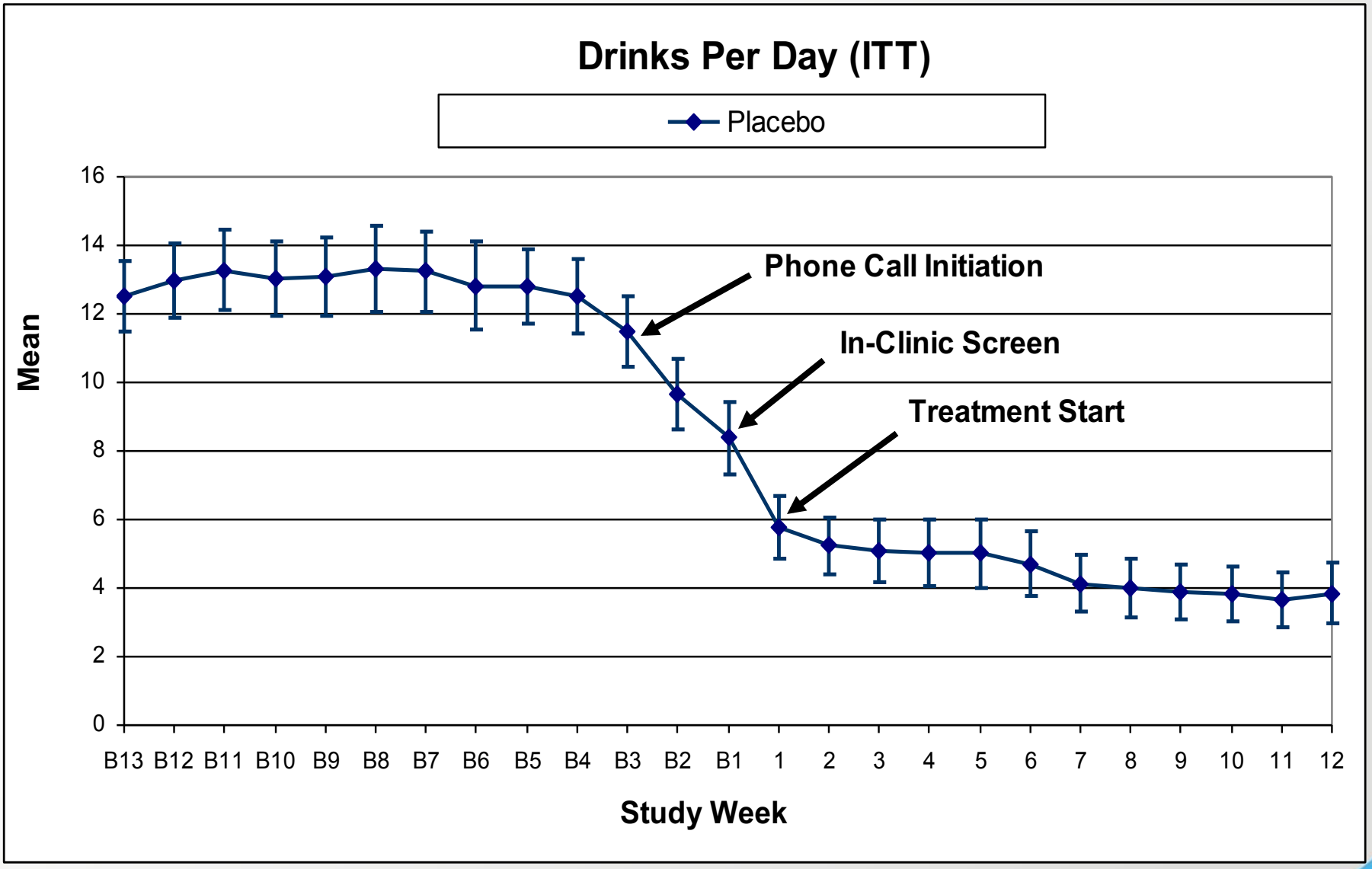
- Studied optimal combinations of medications, behavioral Tx for alcohol dependence
- Patients received naltrexone, acamprosate, both, or neither
- Half of patients received psychotherapy in addition to medical management
- One patient cohort received psychotherapy alone, no pills

COMBINE Study: Results

- For patients receiving MM, naltrexone or CBI therapy improved outcomes over placebo plus MM
- Acamprosate did not add benefit to naltrexone or CBI, and was no more effective than placebo plus MM
- Taking pills and seeing a health care professional was more effective than receiving CBI alone (possible placebo effect)

Placebo Effect

- Very strong in substance dependent populations
- Difficult to distinguish between placebo effect & study participation effect, particularly in disorders involving voluntary behavior such as substance use disorders


Drinks Per Day (ITT)
Placebo
Mean
16
14
12
10
8
6
4
2
0
Phone Call Initiation
In-Clinic Screen
Treatment Start
B13 B12 B11 B10 B9 B8 B7 B6 B5 B4 B3 B2 B1 1 2 3 4 5 6 7 8 9 10 11 12
Study Week

Topiramate (Not FDA-Indicated)

- 371 pts at multiple sites received topiramate 50-300 mg/d (tapered upward) or placebo x 14 weeks, then 2-week taper
- Patients were drinking heavily at study entry
- Topiramate pts had better drinking outcomes, beginning at 100 mg
- Fewer heavy drinking days
- Greater likelihood of abstinence

Johnson et al., 2007 – multi-site study.

Heterogeneity of the Population

- Anton (2008): only those pts in COMBINE with a specific genetic variant related to the opiate receptor responded to naltrexone
- Johnson (2011): only those with a specific variant at the serotonin transporter gene responded to ondansetron
- Kranzler (2014): only pts with snp related to glutamate activity responded to topiramate
- Combining heterogeneous pts can wash out a tx effect, but we may not know this

As-Needed Nalmefene

- 667 pts instructed to take nalmefene (mu opioid antagonist) 18 mg or placebo if they felt at risk to drink, 1-2 hours ahead of time; 2 study cohorts in Europe
- Heavy drinking days at end of 6-month tx: 14 vs. 9 in one study cohort, 12 vs. 10 in another
- 9 vs. 11 abstinent days per month
- Statistically significant differences
- How clinically significant?

Van den Brink et al., 2013.

Pharmacotherapy of Co-occurring Alcohol Use Disorder and Psychiatric Illness

Diagnosing Psychiatric Disorders in Patients with SUDs

- How long should you wait until a patient has been off all drugs and alcohol before you can diagnose any psychiatric disorder?
- How much does diagnosis or primary vs. secondary depression matter?

Pharmacotherapy of SUD & Depression

- Most recent controlled studies show improvement in depression
- Tricyclics have most robust effect
- SSRIs most helpful in late-onset alcoholics, may worsen early-onset alcoholics
- Less improvement in substance use (often correlated with mood improvement), but not worsening (ie, not enabling)
- Pneumonia model

Naltrexone & Disulfiram in patients with alcohol dependence and co-occurring Axis I psychopathology

Results

- 70% reported total abstinence; 83% med adherence
- Both active med groups had fewer drinking days than placebo
- Disulfiram pts had less drinking compulsion than ntx pts
- No advantage to receiving both medications
- Side effects similar to those reported in non-dually diagnosed populations
- Less paranoia in active medication group vs. placebo
- Naltrexone, disulfiram may be useful for motivated dually diagnosed patients

Valproate for Alcohol Dependence & BD

- 24-week trial of valproate vs. placebo in 59 pts on lithium

Valproate patients had:

- Fewer heavy drinking days
- Less drinking on heavy drinking days
- No differences in manic, depressive sx

Salloum et al., 2005

Choosing an Alcoholism Medication

- Goal of treatment, patient wishes
- Current status, i.e., abstinence duration
- Liver, kidney function
- Other medications, e.g., opioids