Medications for Treating Alcohol Use Disorder

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Disclosures

- Scientific advisory board: Altimmune, Clearmind Medicine
- Consultant: Altimmune, Sobrera Pharmaceuticals
- Member: American Society of Clinical Psychopharmacology's Alcohol Clinical Trials Initiative (ACTIVE), which in the last three years was supported by Alkermes, Dicerna, Ethypharm, Imbrium, Indivior, Kinnov, Lilly, Otsuka, and Pear
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- Inventor: U.S. provisional patent 63/710,270 "Multi-ancestry Genome-wide Association Meta-analysis of Buprenorphine Treatment Response," filed 29 October 2024.

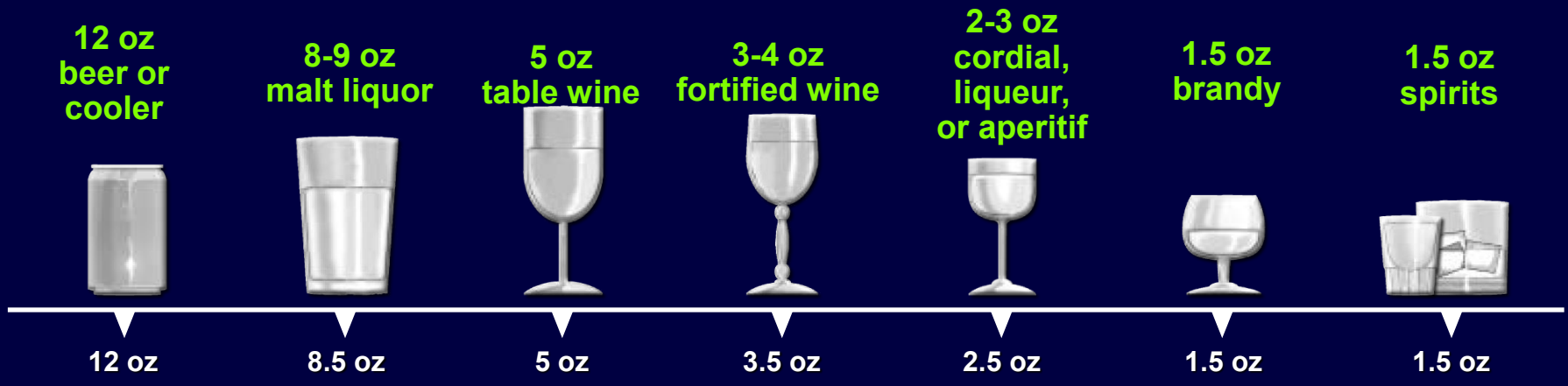
Topics

- Background
- FDA-approved medications
- Off-label prescribing
- Future directions

Defining the “Standard Drink”

Standard drink = 0.6 oz of ethanol = The amount an average person metabolizes per hour

- 12 oz of regular beer or cooler (5% alcohol)
- 5 oz of table wine (12% alcohol)
- 1.5 oz of hard liquor (40% alcohol, 80 proof)



DSM-5 Alcohol Use Disorder

- Problematic pattern of alcohol use leading to clinically significant impairment or distress.
  - 2 (of 11) diagnostic criteria within a 12-month period
  - Mild = 2-3 criteria; moderate = 4-6 criteria; severe, 7-11 criteria

Unmet Treatment Needs

- National survey data indicate that <20% of adults with a lifetime AUD diagnosis ever receive treatment
- In decreasing frequency of use:
  - Self-help groups (most common)
  - Psychotherapy
  - Pharmacological treatments

Cohen et al. *Drug Alcohol Depend*, 2007

Which Medications Are Approved by the US FDA for Treating AUD?

Medications Approved in the US to Treat Alcohol Dependence

- Disulfiram (Antabuse): 1949
- Naltrexone (ReVia): 1994
- Acamprosate (Campral): 2004
- Long-Acting Naltrexone (Vivitrol): 2006

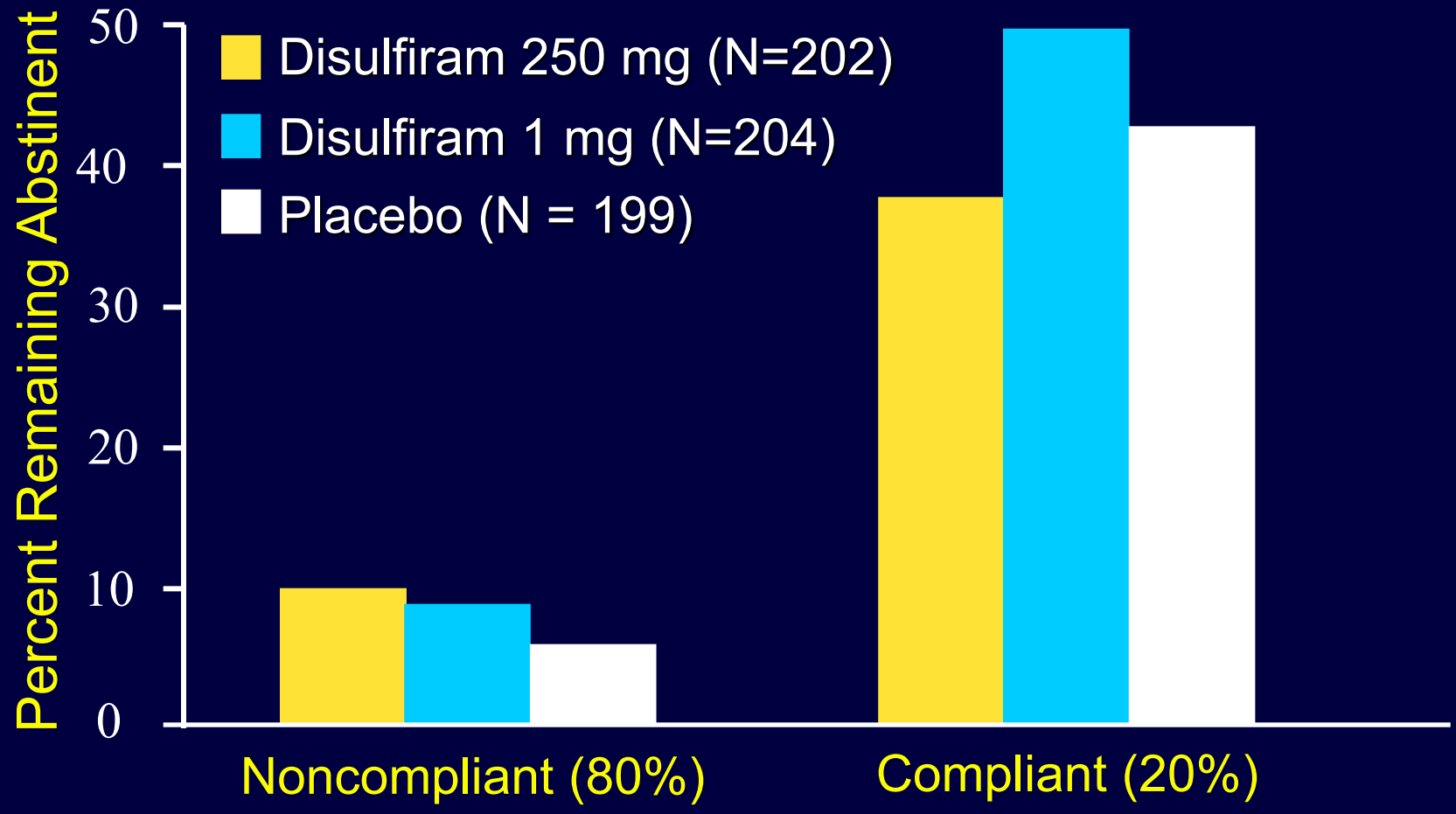
- What is Disulfiram's Mechanism of Action?
- How Efficacious is Disulfiram for Treating AUD?

Disulfiram Inhibits ALDH2

Disulfiram-Ethanol Reaction

facial flushing
lightheadedness
palpitations
nausea

Disulfiram and Abstinence Rates (VA Cooperative Study)



Fuller et al. *JAMA,* 1986

Summary

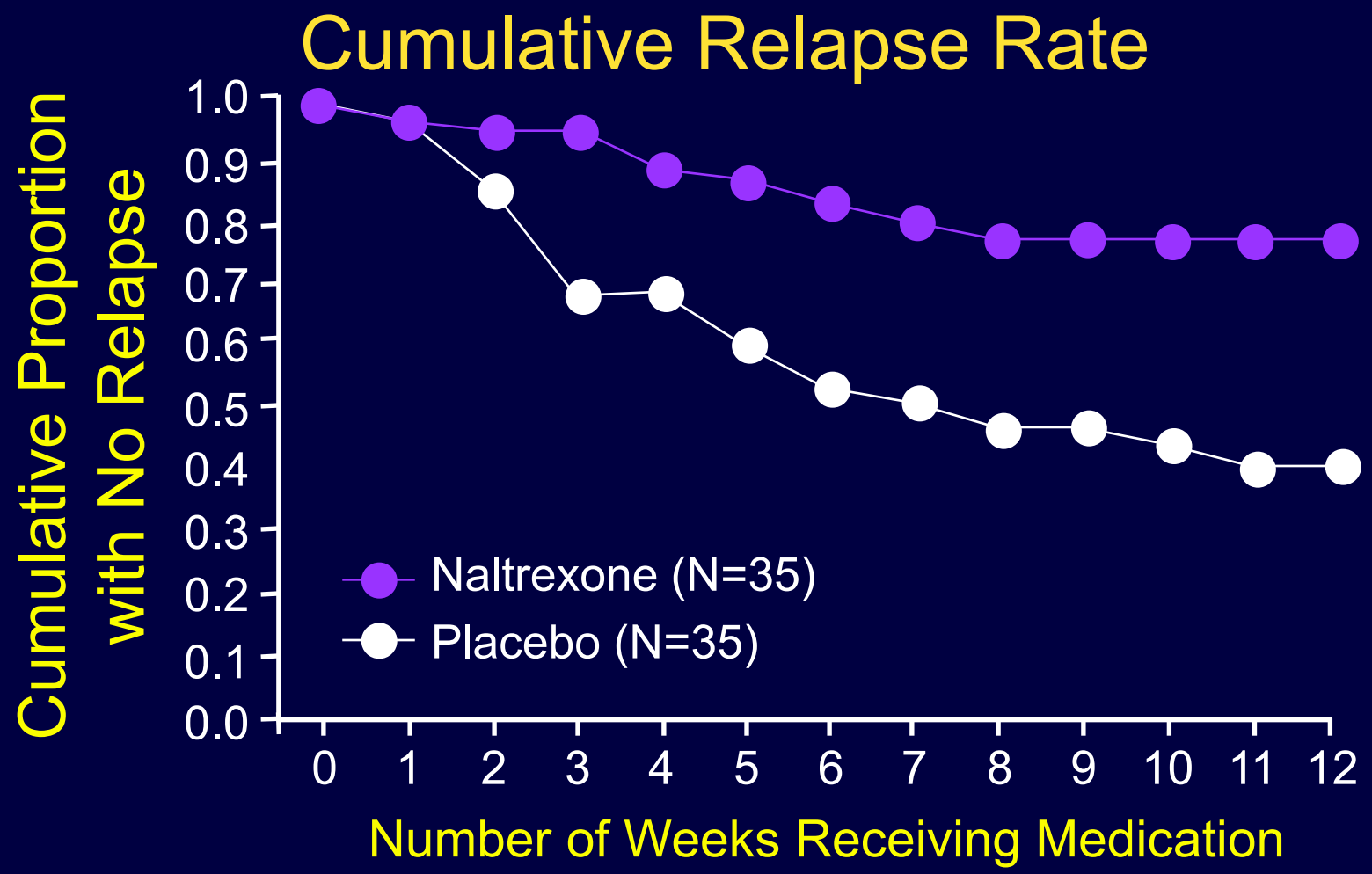
- Disulfiram does not promote abstinence without supervision to ensure adherence.
- To initiate disulfiram treatment, the patient's breath alcohol level should be zero.
- Given the potential for the disulfiram-ethanol reaction, it is not a first-line drug for treating AUD.

- What is Naltrexone's Mechanism of Action?
- How Efficacious is Naltrexone for Treating AUD?

Pharmacology of Naltrexone

- Orally bioavailable antagonist of mu, delta, and kappa opioid receptors
- Reduces dopamine release associated with expectation of alcohol and alcohol ingestion
- FDA-approved oral dosage: 50 mg/day, but safe for use at 100 mg/day

Naltrexone Treatment of Alcohol Dependence



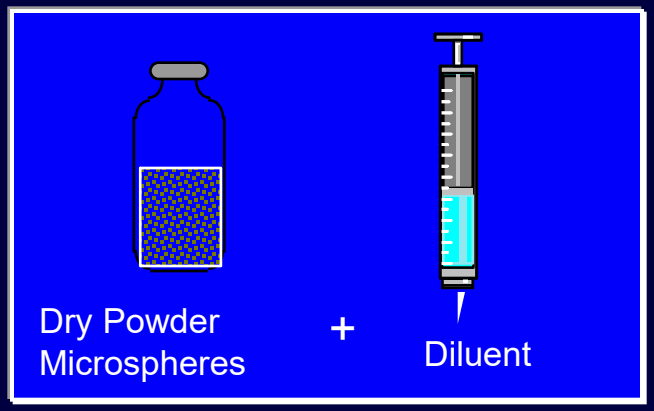
Volpicelli et al. *Arch Gen Psychiatry*, 1992

Meta-analysis of Naltrexone's Effects in Treating AUD

- The number needed to treat (NNT) is that required to prevent 1 person from experiencing a specific outcome.
- In 16 studies and 2,347 patients, oral naltrexone (50 mg/d) was associated with a lower rate of return to any drinking than placebo (NNT=18).
- In 23 studies in 3,170 patients, the NNT=11 for preventing a return to heavy drinking.

McPheeters et al. 2023

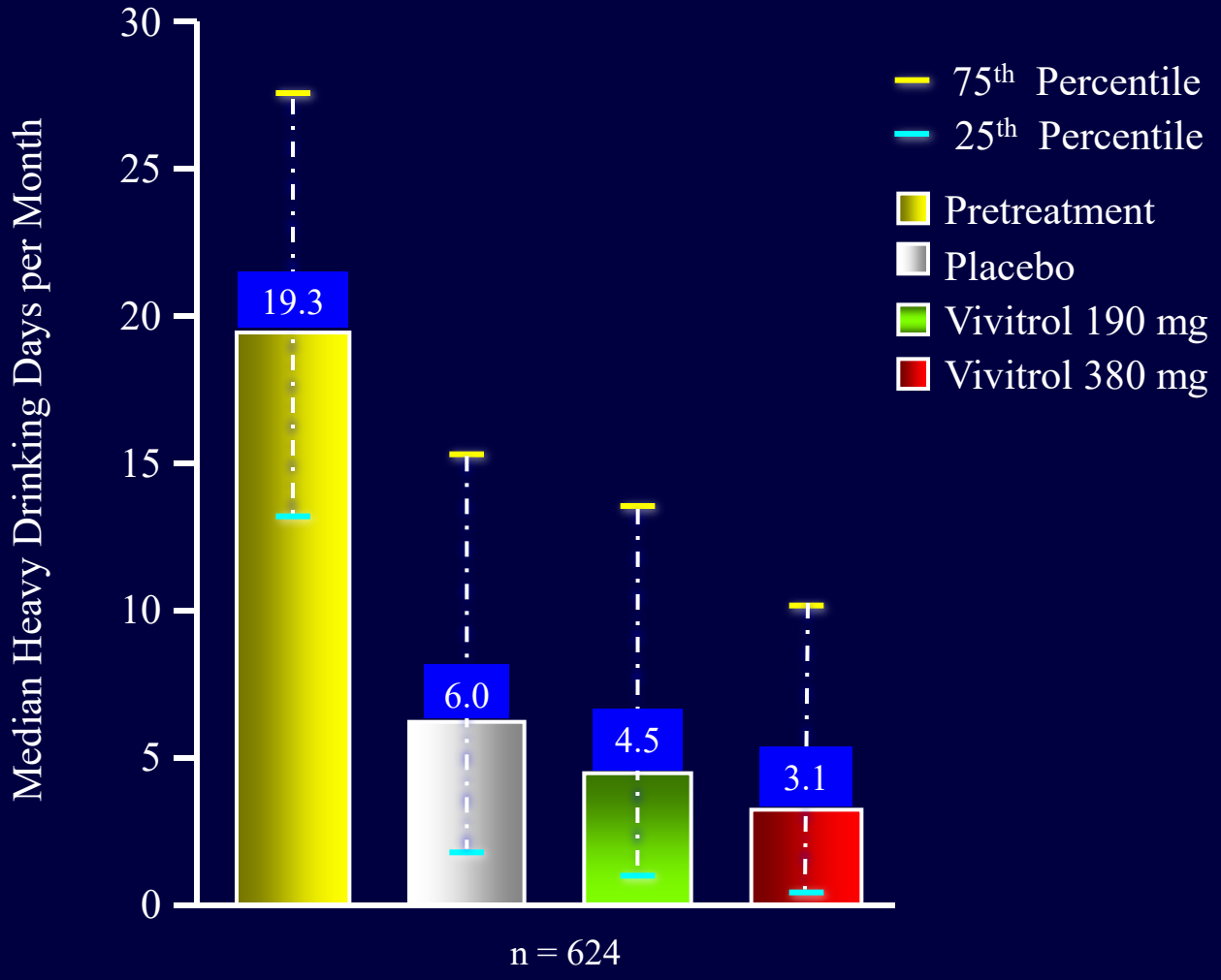
Long-Acting Naltrexone: Vivitrol®



- Common biodegradable medical polymer (e.g., for sutures)
- Metabolized to CO_2 and H_20

Once Monthly Dosing

Results: Heavy Drinking Days



Garbutt et al. *JAMA*, 2005

Summary

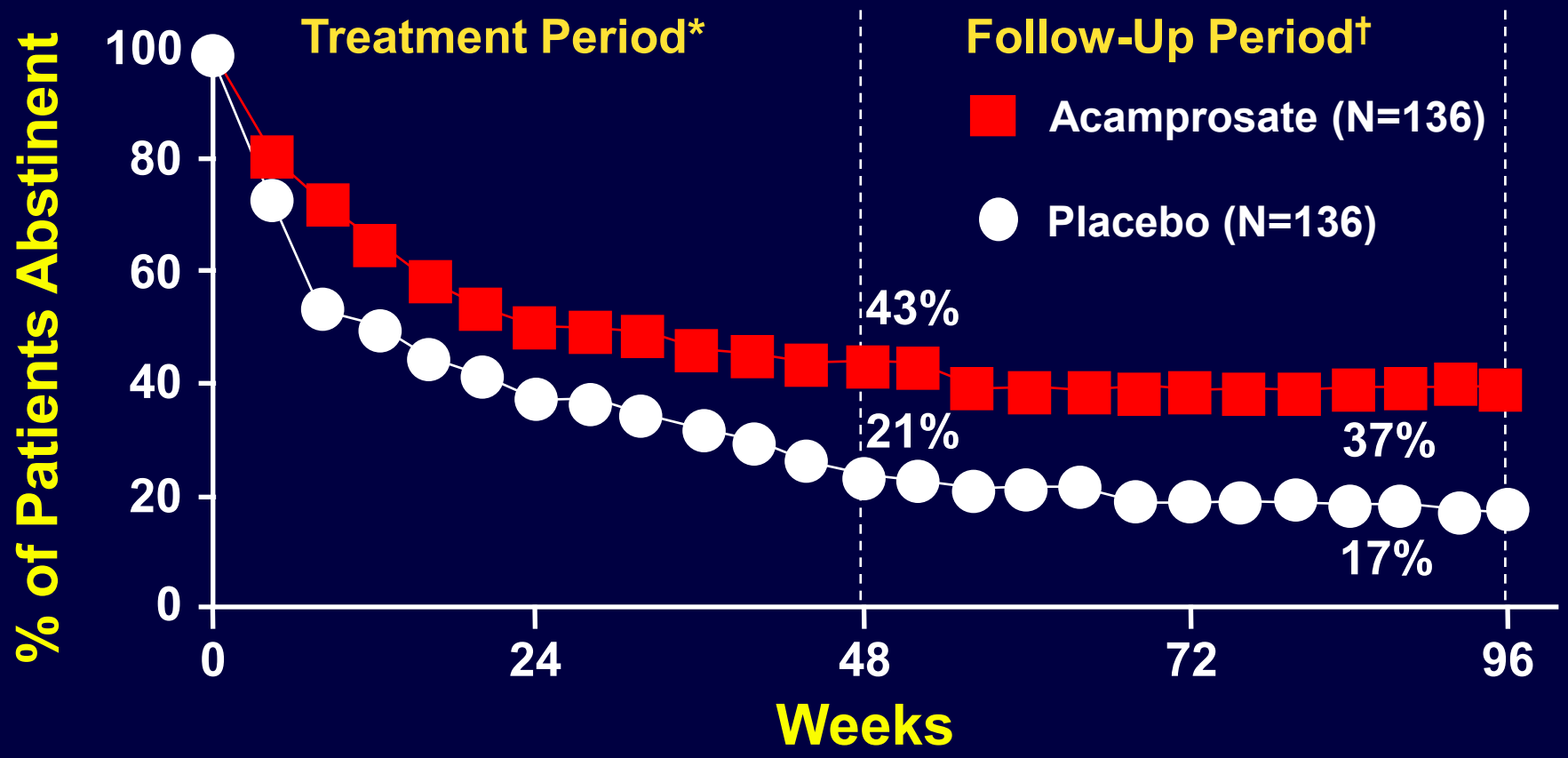
- Naltrexone reduces the risk of heavy drinking
- Long-acting naltrexone is an alternative for patients who are non-adherent with oral medication or who prefer an injectable medication to daily oral medication.

- What is Acamprosate's Mechanism of Action?
- How Efficacious is Acamprosate for Treating AUD?

Pharmacology of Acamprosate

- Acamprosate affects glutamate-NMDA activity and is a GABA agonist.
- In animals trained to drink alcohol, acamprosate reduces deprivation-induced drinking.
- FDA-approved dosage is 1998 mg/day (divided in 3 doses of 666 mg)

German Acamprosate Study



*p=0.001; †p=0.003

Sass et al., *Arch Gen Psychiatry*, 1996

Meta-analysis of Acamprosate's Effects in Treating AUD

- In 20 studies and 6.380 patients, acamprosate was associated with a lower rate of return to any drinking than placebo (NNT=11).
- In 7 studies in 2,496 patients, there was not a significant difference from placebo in preventing a return to heavy drinking.

McPheeters et al. 2023

Which Medications Are Used Off-label for Treating AUD?

Medications with Evidence of Efficacy in Reducing Heavy Drinking (Off-label Use)

- Gabapentin (Neurontin)
- Topiramate (Topamax)

These anticonvulsant medications are not approved in the United States for treating AUD

Pharmacology of Gabapentin

- Structurally related to GABA, but no effect on GABA binding, uptake, or degradation.
- Actions include:
  - Selective inhibition of voltage-gated calcium channels
  - Enhancement of voltage-gated potassium channels
  - Modulation of GABA activity

Precise mechanism of its therapeutic action is unknown.

Meta-analysis of the Efficacy of Gabapentin for Treating Alcohol Use Disorder

- Studies of the efficacy of gabapentin for treating AUD have yielded mixed findings.
- Meta-analysis of 7 RCTs of gabapentin's effects on 6 alcohol-related outcome measures
- Significantly better than placebo only on the percentage of heavy drinking days (p=0.03), with no difference on the remaining five outcome measures.

Kranzler et al., *Addiction*, 2019

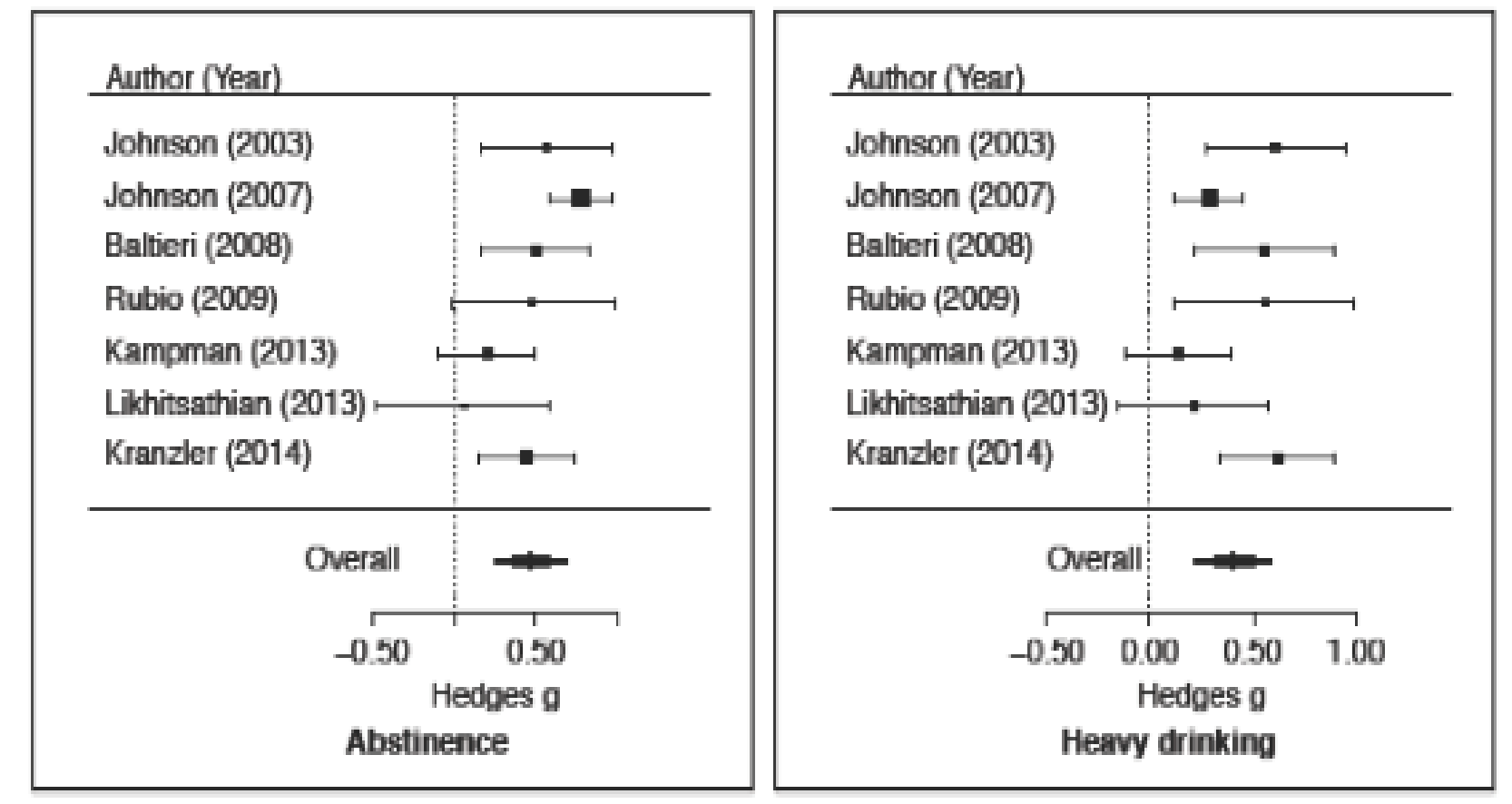
Conclusions

- Gabapentin was efficacious on only 1 of 6 alcohol treatment outcome measures
- Has been associated with clinically significant adverse events, particularly at higher dosages, and frequent misuse, particularly in opioid-dependent individuals
- Despite these limitations, because gabapentin may be useful in treating alcohol withdrawal, further research on its use in treating AUD is warranted.

Pharmacology of Topiramate

- Antagonist at AMPA and kainate receptors
- Allosteric agonist at the GABA-A receptor
- Blocks voltage-dependent Na and l-type voltage-gated Ca channels
- Inhibits carbonic anhydrase
- Enhances K+ conductance

Meta-analysis of Topiramate's Effects on Drinking



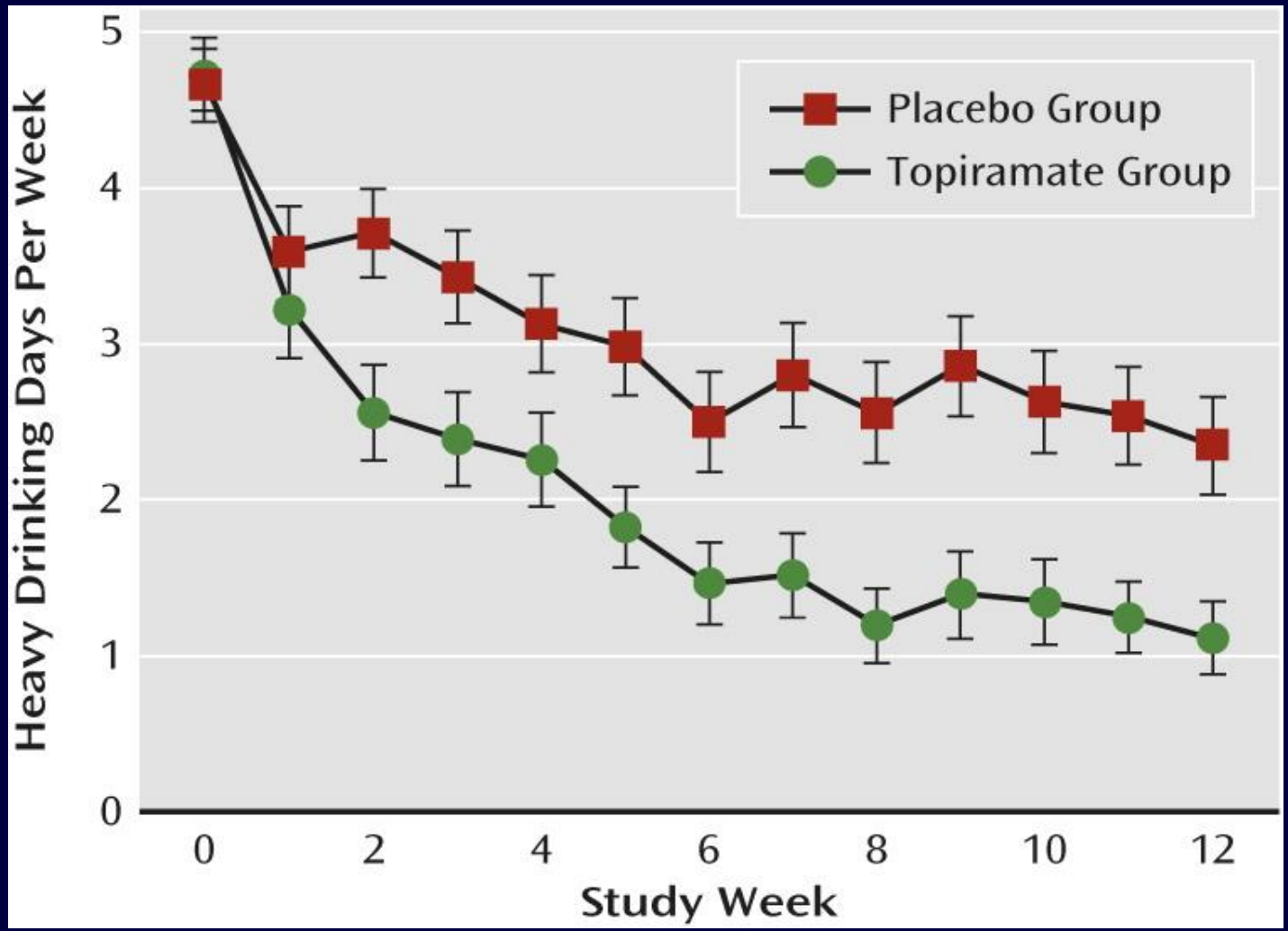
Blodgett et al. *Alcohol Clin Exp Res*, 2014

Placebo-Controlled Trial of Topiramate to Reduce Heavy Drinking

- 12-week study of 138 heavy drinkers whose goal was to reduce drinking to safe levels
- Topiramate 100 mg twice daily (N=67) or matching placebo (N=71) with dosage increased gradually over 6 weeks
- Brief behavioral counseling at each visit

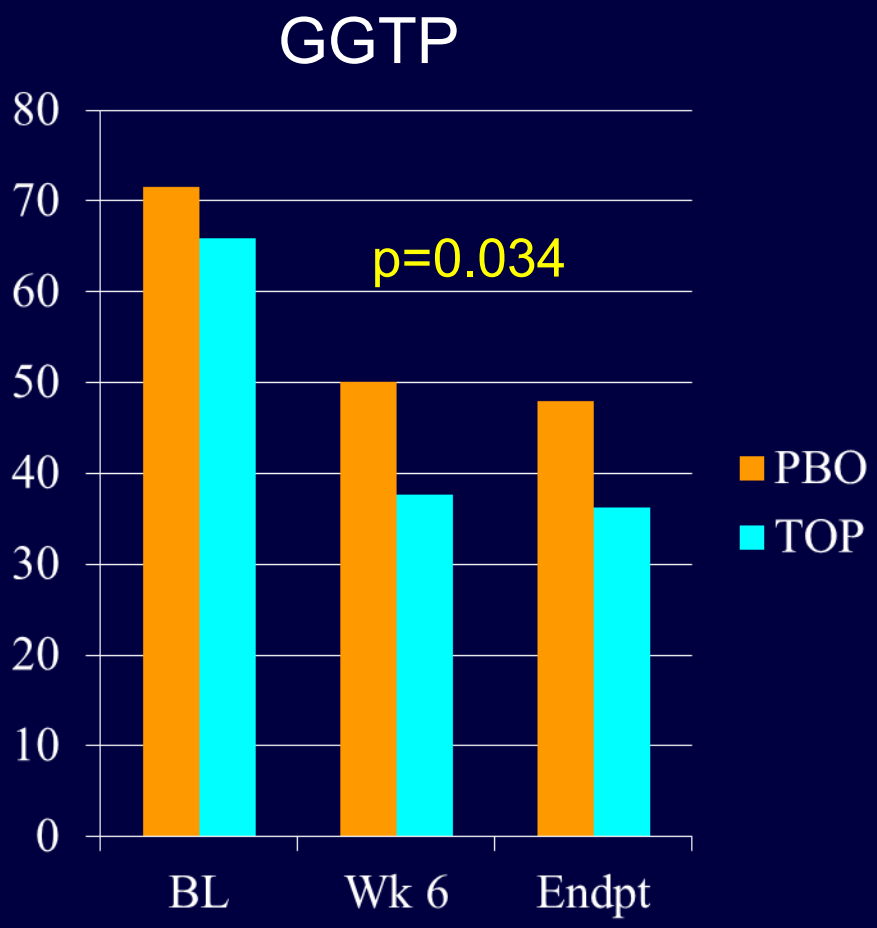
Kranzler et al., *Am J Psychiatry*, 2014

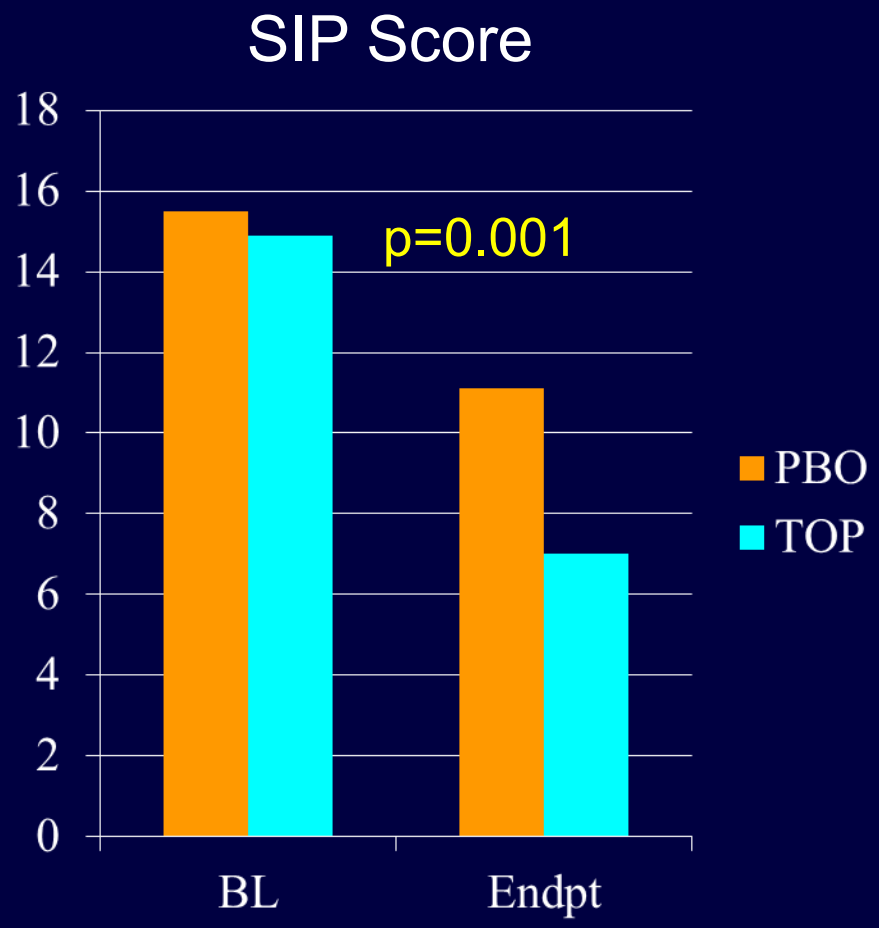
Within-Treatment Heavy Drinking Days/Week



Kranzler et al., *Am J Psychiatry*, 2014

Measures to Validate Self-Reported Drinking





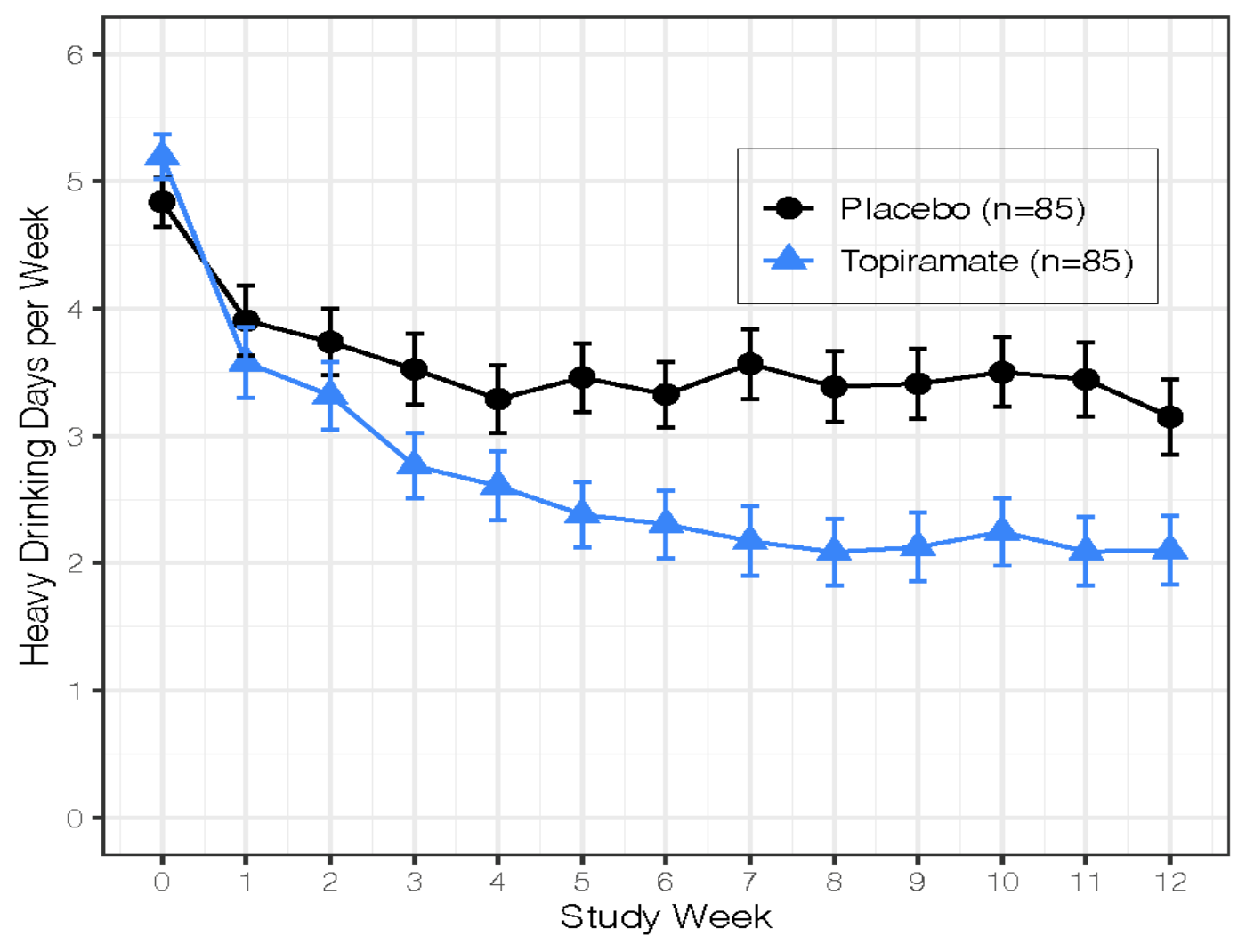
Kranzler et al., *Am J Psychiatry*, 2014

Prospective Randomized Pharmacogenetic Study of Topiramate for Treating Alcohol Use Disorder

- 12-week study of 170 patients with AUD whose goal was either to reduce drinking or become abstinent
- Topiramate 100 mg twice daily (N=85) or matching placebo (N= 85) with dosage increased gradually over 6 weeks
- Brief behavioral counseling at each visit

Kranzler et al., *Neuropsychopharmacology*, 2021

Heavy Drinking Days During Treatment



Kranzler et al., *Neuropsychopharmacology*, 2021

Conclusions

- There is consistent evidence that topiramate has beneficial effects on heavy drinking and other outcomes, e.g., alcohol-related problems.
- Clinically significant adverse events occur, which require a gradual increase in dosage and, at times, a reduction in dosage
- May be most appropriate for an addiction specialist to prescribe topiramate for treating AUD

Novel Candidate Medications for Treating AUD

Novel Medications of Current Interest for Treating AUD

- Psychedelics
  - Early literature on LSD (meta-analysis by Krebs and Johansen 2012)
  - Initial evidence of efficacy of psilocybin (Bogenschutz et al. 2022)
- GLP-1 agonists
  - Initial evidence of efficacy of exenatide in reducing drinking only in obese patients with AUD (Klausen et al. 2022)

Not approved in the US for treating AUD

Overall Summary

- Heavy drinking and AUD are common in the U.S. general population.
- Using psychosocial treatments and self-help group participation as a foundation for behavior change, efficacious medications can help to reduce drinking or promote abstinence in patients with AUD.