Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial

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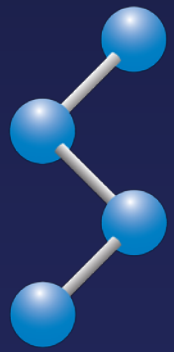

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Faculty Disclosure

Company	Nature of Affiliation	Unlabeled Product Usage
• Pfizer	• Provided study drug (Neurontin) and placebo	• Gabapentin

Financial Disclosure

Investigators have no relevant financial interests to disclose.

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Educational Objectives:

1. Identify symptoms of an alcohol use disorder
2. Understand the role of medications in treating alcohol dependence
3. Identify symptoms of relapse risk after alcohol withdrawal
4. Evaluate the research data assessing the risks and benefits of gabapentin in patients with alcohol dependence

What is a Standard Drink?

Definitions

- **Moderate “Low Risk” Drinking**
  - **Women: ≤ 3 drinks on any single day AND ≤ 7 drinks per week**
  - **Men: ≤ 4 drinks on any single day AND ≤ 14 drinks per week**

- **Heavy “At Risk” Drinking**
  - **Women: ≥ 4 drinks on any single day OR > 7 drinks per week**
  - **Men: ≥ 5 drinks on any single day OR > 14 drinks per week**

- **Binge Drinking: BAC reaches 0.08g/dL within 2 hours**
  - **Women: ≈ 4 drinks**
  - **Men: ≈ 5 drinks**

DSM IV: Alcohol Dependence (≥3 of the following):
DSM V: Alcohol Use Disorder (≥2; moderate severity ≥4 of the following):

A problematic pattern of alcohol use within a 12-month period:

1. Often drinking more than was intended
2. Unsuccessful attempts to cut-down or control alcohol use
3. A great deal of time spent in alcohol-related activities
4. Activities given up or reduced because of drinking
5. Continue drinking despite alcohol-related physical or psychological problems
6. Tolerance
7. Withdrawal
8. Craving
9. Drinking impairs functioning at work, school or home
10. Continued drinking despite alcohol-related social or interpersonal problems
11. Drinking in physically hazardous situations

Differences in Past Year Prevalence, Diagnosis and Treatment of Alcohol Use Disorders in Diverse Populations Residing in San Diego County

Compiled by the Center for Applied Research Solutions (CARS, 2010) for the California Dept. of Alcohol and Drug Programs (ADP)

MALES vs FEMALES	Males	Females
Binge Drinking	37%	25%
Alcohol or Drug (AOD) Treatment	65%	35%
Alcohol Related Car Accidents	73%	23%
Hospitalization Due to Alcohol-Related Causes	38%	32%

Race/Ethnicity

Race/Ethnicity	Binge Drinking	AOD Treatment	Alcohol Related MVA	Hospitalization Due to AOD
American Indian	37%	2%		.1%
Asian	13%	3%		.6%
Black	30%	12%	6%	2.6%
Hispanic	32%	32%	33%	8.1%
White	34%	47%	51%	50%
Other	38%	5%	10%	39%

Hospitalizations and Deaths Due to Alcohol in San Diego County in 2007

	Hospitalizations	Deaths
Alcohol Polyneuropathy	8	1
Alcohol Cardiomyopathy	10	5
Alcohol Poisoning	38	17
Alcoholic Gastritis	79	1
Alcohol Abuse	112	40
Alcohol Dependent Abuse	266	
Alcoholic Liver Disease	659	253
Alcohol Psychosis	698	7
Alcohol Dependence Syndrome	1,578	29
Total	3,448	353
Alcohol-Involved Motor Vehicle Injuries	*2,068*	*116*

Alcohol Use Disorders Can Undermine Diagnosis and Treatment of Comorbid Medical Conditions

- Postpone seeking treatment
- Engage in risky behaviors
- Failure to follow medication regimens
- Contribute to conditions such as liver disease
- Weaken immune system
- Increase risk of side effects from some medications
- Can reduce efficacy of some medications

Background

Alcohol Use Disorder is a large unmet medical need

- **Accounts for 3.8% of all deaths and 4.6% of disability-adjusted life-years globally**

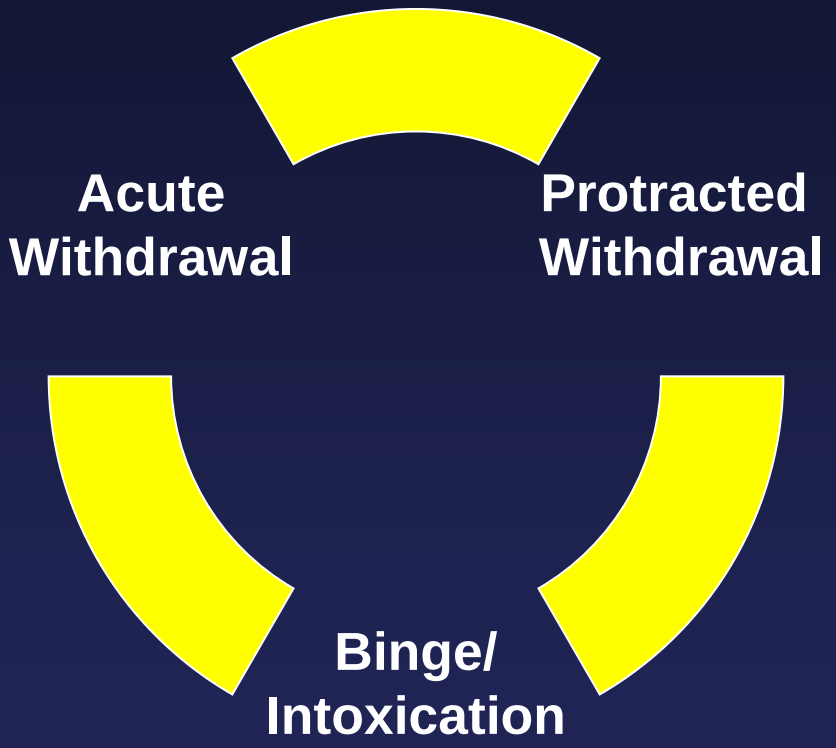
- **Costs exceed 1% of the gross national product of high and middle income countries**

Existing treatments are grossly underutilized

- **Approved pharmacological treatments are prescribed for < 9% of Americans with alcohol dependence**

- **Worldwide sales of approved treatments**
  - **Disulfiram (Antabuse): ?**
  - **Naltrexone (ReVia, Vivitrol): $41M**
  - **Acamprosate (Campral): $81M**

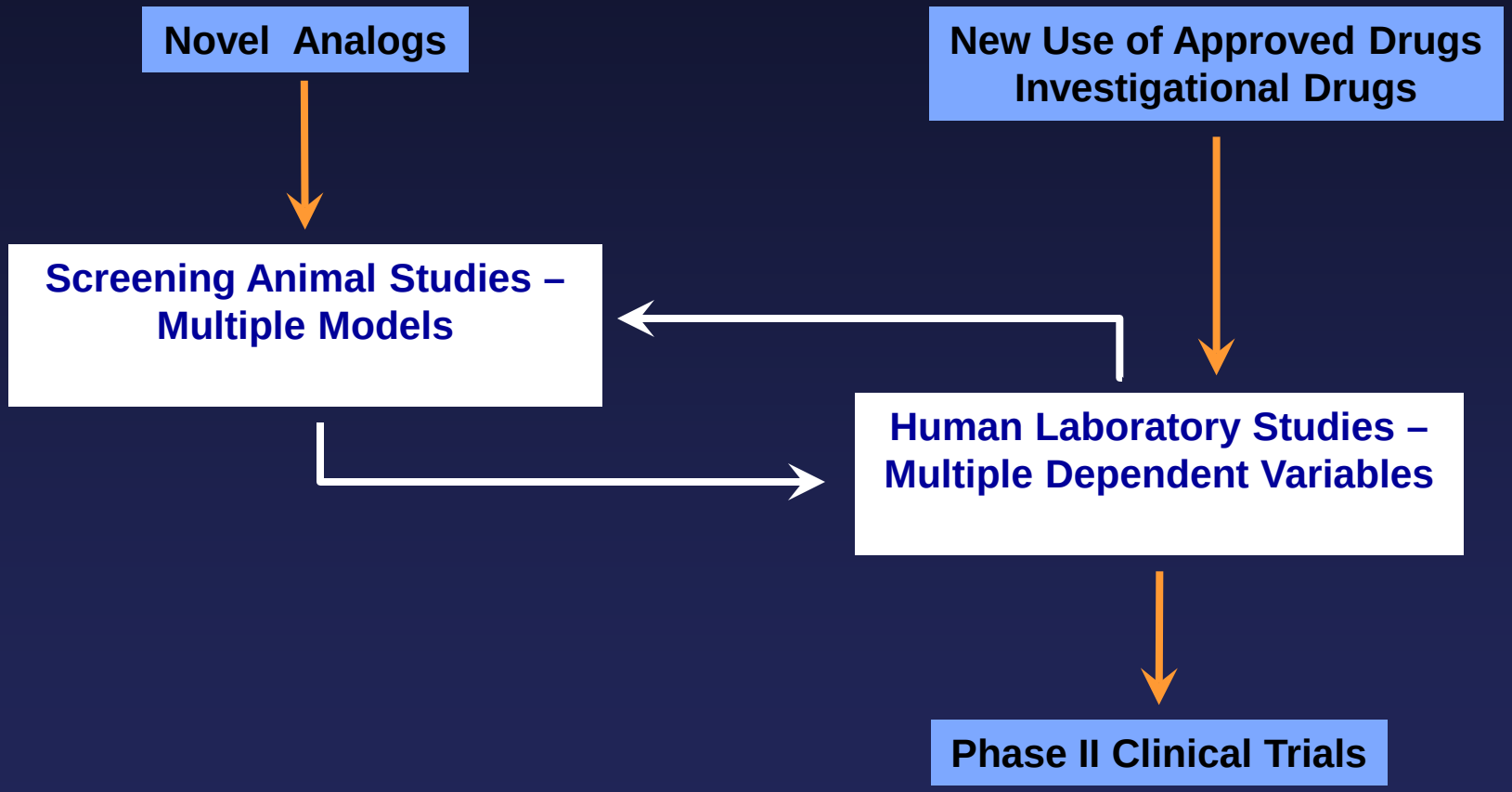
Medication Targets in the Cycle of Alcoholism



Rational Drug Development for Alcohol Use Disorder

- Identify and preclinically validate targets relevant to treating persisting negative emotional states associated with the withdrawal/negative affect and preoccupation/anticipation ("craving") stages of the addiction cycle
- Reliable, valid and correct human laboratory models for proof of concept (POC)
- New pharmacotherapies with larger effect sizes and good safety and tolerability profiles

Medications Development for Treatment of Alcoholism and Addiction



Koob GF, Lloyd GK, Mason BJ. *Nat Rev Drug Discovery* 2009; 8:500

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Rationale for Gabapentin as a Potential Treatment for Alcohol Dependence

FDA-approved for epilepsy and pain (Neurontin)

- Enhances GABAergic function via an action on voltage-gated calcium channels (Sills, 2006)
- Normalizes alcohol-related dysregulation in GABA-CRF interactions in the extended amygdala (Roberto et al., 2008)

Used off-label to treat symptoms associated with protracted withdrawal and risk of relapse

- Disturbances in mood and insomnia (Brower et al., 2008)

Safe and well-tolerated in acute withdrawal and in combination with alcohol (e.g., Myrick et al., 1998, 2007)

-Not appreciably metabolized in the liver

Laboratory Studies: Gabapentin Effects on Drinking and Craving

Human Studies

- **Safe, but no efficacy for a single dose in an alcohol administration paradigm in normal subjects**

  - Bisaga & Evans, 2006

- **Safe, but no efficacy for 1-week dosing in an alcohol administration /consumption paradigm in alcoholics**

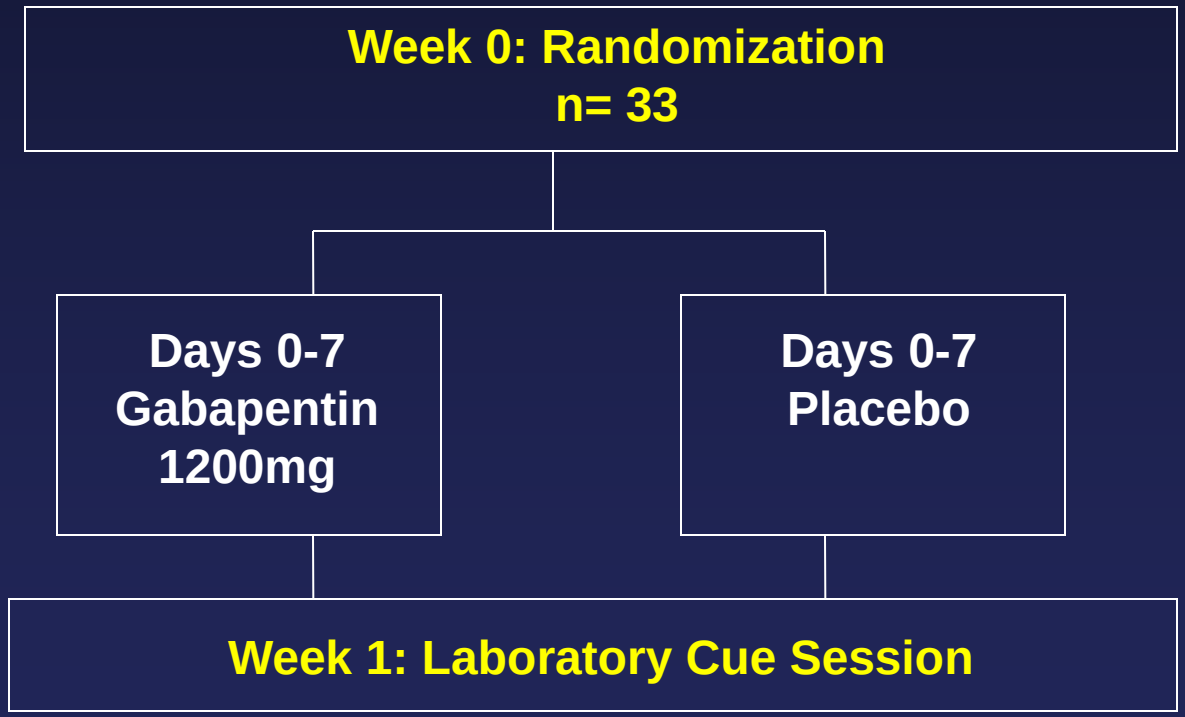
  - Myrick et al., 2007

Pre-Clinical

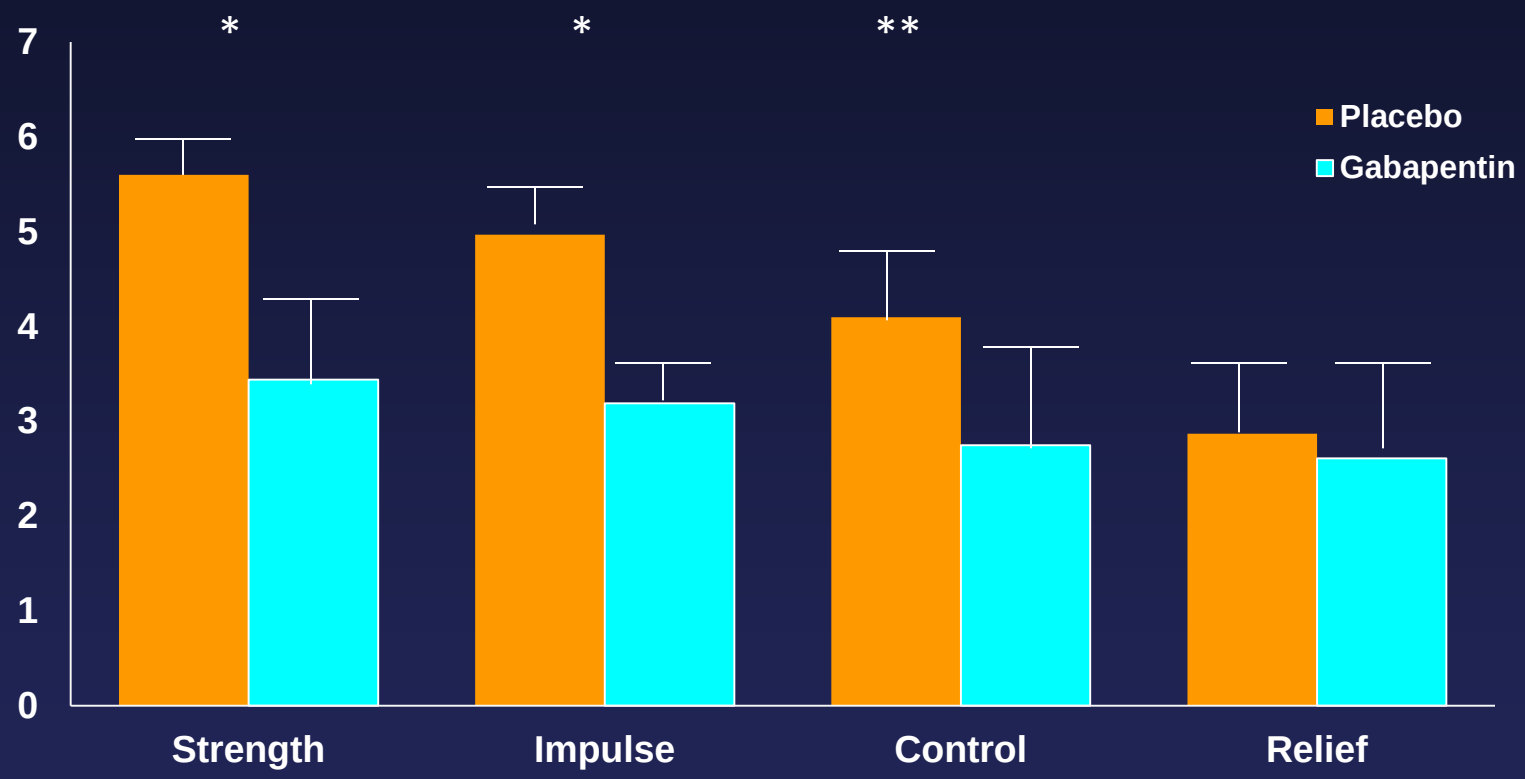
- **Dose-dependent reduction in ethanol self-administration in dependent rats**
- **No effect in non dependent rats**

  - Roberto et al., 2008

POC Human Laboratory Cue Reactivity Study: Gabapentin in Alcohol Dependence

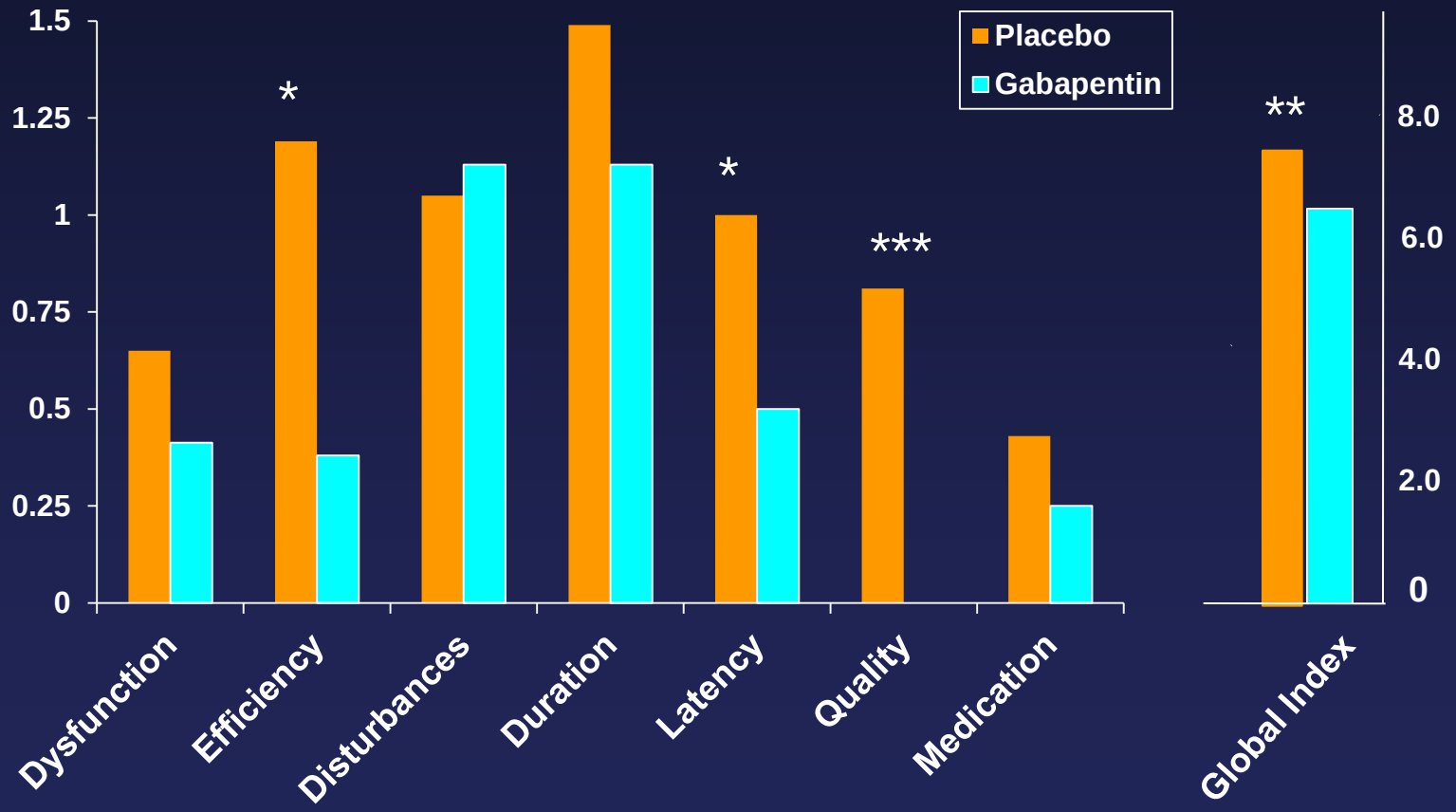


VAS Craving Scores: Alcohol Minus Water



*p< 0.05
**p< 0.1

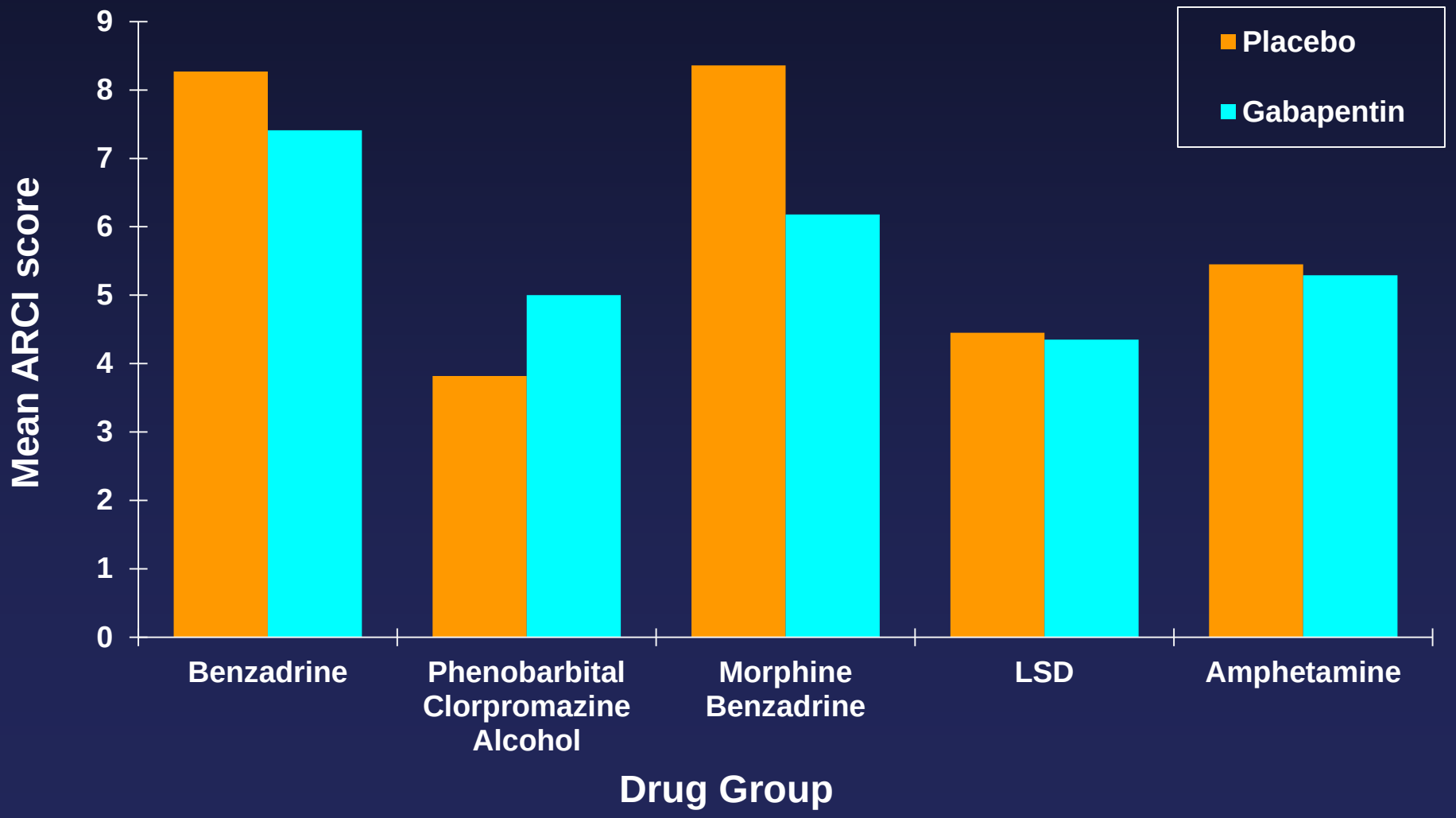
Effect of Gabapentin vs Placebo on Pittsburgh Sleep Quality Index[1]



[1] Higher values indicate greater disturbance; subscale range 0-2

***$p < 0.001$; **$p < 0.05$; *$p < 0.06$

Gabapentin Does Not Show Abuse Potential on the Addiction Research Center Inventory (ARCI)



POC Cue Reactivity Human Laboratory Study

Gabapentin vs placebo was associated with

- **decreased craving ($p < .05$)**
- **improved sleep ($p < .05$)**
- **good safety and tolerability**
- **no evidence of abuse potential**

A randomized controlled trial (RCT) to evaluate the efficacy of gabapentin for relapse prevention in alcohol dependence is warranted.

Mason et al., 2008

Original Investigation

Gabapentin Treatment for Alcohol Dependence
A Randomized Clinical Trial

Barbara J. Mason, PhD; Susan Quello, BA, BS; Vivian Goodell, MPH; Farhad Shadan, MD; Mark Kyle, MD; Adnan Begovic, MD

IMPORTANCE Approved medications for alcohol dependence are prescribed for less than 9% of US alcoholics.

OBJECTIVE To determine if gabapentin, a widely prescribed generic calcium channel/γ-aminobutyric acid–modulating medication, increases rates of sustained abstinence and no heavy drinking and decreases alcohol-related insomnia, dysphoria, and craving, in a dose-dependent manner.

DESIGN, PARTICIPANTS AND SETTING A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women older than 18 years with current alcohol dependence, conducted from 2004 through 2010 at a single-site, outpatient clinical research facility adjoining a general medical hospital.

INTERVENTIONS Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

MAIN OUTCOMES AND MEASURES Rates of complete abstinence and no heavy drinking (coprimary) and changes in mood, sleep, and craving (secondary) over the 12-week study.

RESULTS Gabapentin significantly improved the rates of abstinence and no heavy drinking. The abstinence rate was 4.1% (95% CI, 1.1%-13.7%) in the placebo group, 11.1% (95% CI, 5.2%-22.2%) in the 900-mg group, and 17.0% (95% CI, 8.9%-30.1%) in the 1800-mg group ($P = .04$ for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg). The no heavy drinking rate was 22.5% (95% CI, 13.6%-37.2%) in the placebo group, 29.6% (95% CI, 19.1%-42.8%) in the 900-mg group, and 44.7% (95% CI, 31.4%-58.8%) in the 1800-mg group ($P = .02$ for linear dose effect; NNT = 5 for 1800 mg). Similar linear dose effects were obtained with measures of mood ($F_2 = 7.37$; $P = .001$), sleep ($F_2 = 136$; $P < .001$), and craving ($F_2 = 3.56$; $P = .03$). There were no serious drug-related adverse events, and terminations owing to adverse events (9 of 150 participants), time in the study (mean [SD], 9.1 [3.8] weeks), and rate of study completion (85 of 150 participants) did not differ among groups.

CONCLUSIONS AND RELEVANCE Gabapentin (particularly the 1800-mg dosage) was effective in treating alcohol dependence and relapse-related symptoms of insomnia, dysphoria, and craving, with a favorable safety profile. Increased implementation of pharmacological treatment of alcohol dependence in primary care may be a major benefit of gabapentin as a treatment option for alcohol dependence.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00391716.

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Invited Commentary

Supplemental content at jamainternalmedicine.com

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Hypothesis

Gabapentin will have efficacy for the treatment of alcohol dependence by

- **acting directly on drinking behavior**
  - **rates of abstinence and no heavy drinking**
  - **drinking quantity and frequency**
- **acting on symptoms of protracted withdrawal that may modulate drinking behavior, e.g., craving and disturbances in mood and sleep**

Methods

Procedures

- Double-blind
- Random assignment
- Dose-ranging: 0, 900, 1800 mg/d gabapentin
- 12-week study duration and post treatment follow up at Weeks 13 and 24
- Weekly abstinence-oriented counseling (www.alcoholfree.info)

Gabapentin Dose Titration Schedule: Number of 300 mg Capsules Dispensed

	Morning	Afternoon	Evening
Day 1	○○	○○	●○
Day 2	●○	○○	●○
Day 3	●○	●○	●○
Day 4	●○	●○	●●
Day 5	●●	●○	●●
Day 6 - 78	●●	●●	●●
Day 79 - 84	Reverse Titration		

Methods

Dependent Measures

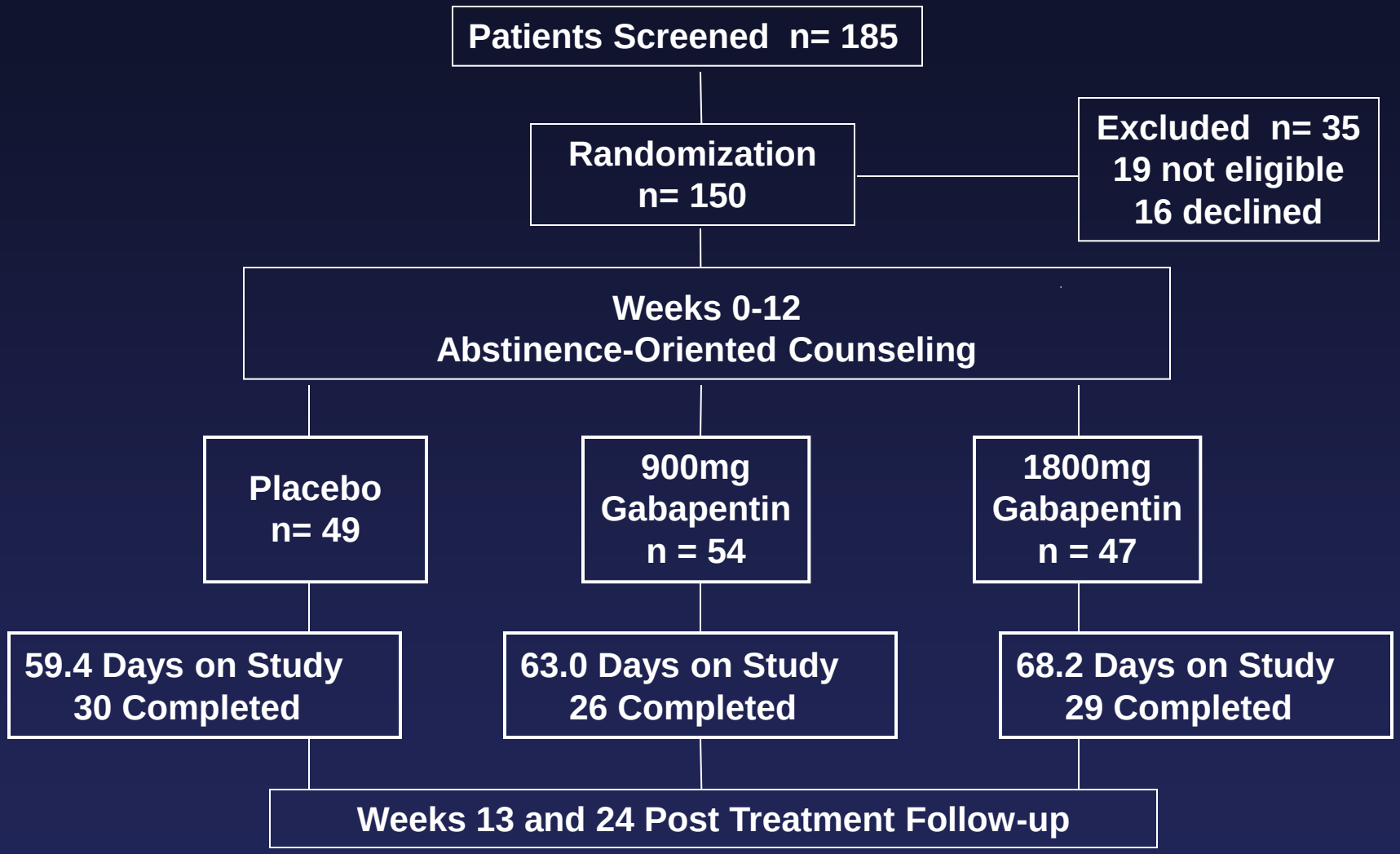
- Timeline Follow Back Interview (Sobell & Sobell, 1992)
- Alcohol Craving Questionnaire (Singleton et al., 1994)
- Pittsburgh Sleep Quality Index (Buysse et al., 1989)
- Beck Depression Inventory-II (Beck et al., 1996)

Methods

Admission Criteria

- Males or females over 18 years of age
- DSM IV criteria for current alcohol dependence
- Abstinent 3 to 30 days
- No major medical or psychiatric conditions, including depressive, anxiety or dependence disorders other than alcohol or nicotine dependence
- No treatment with other psychoactive medications

Disposition of Patients

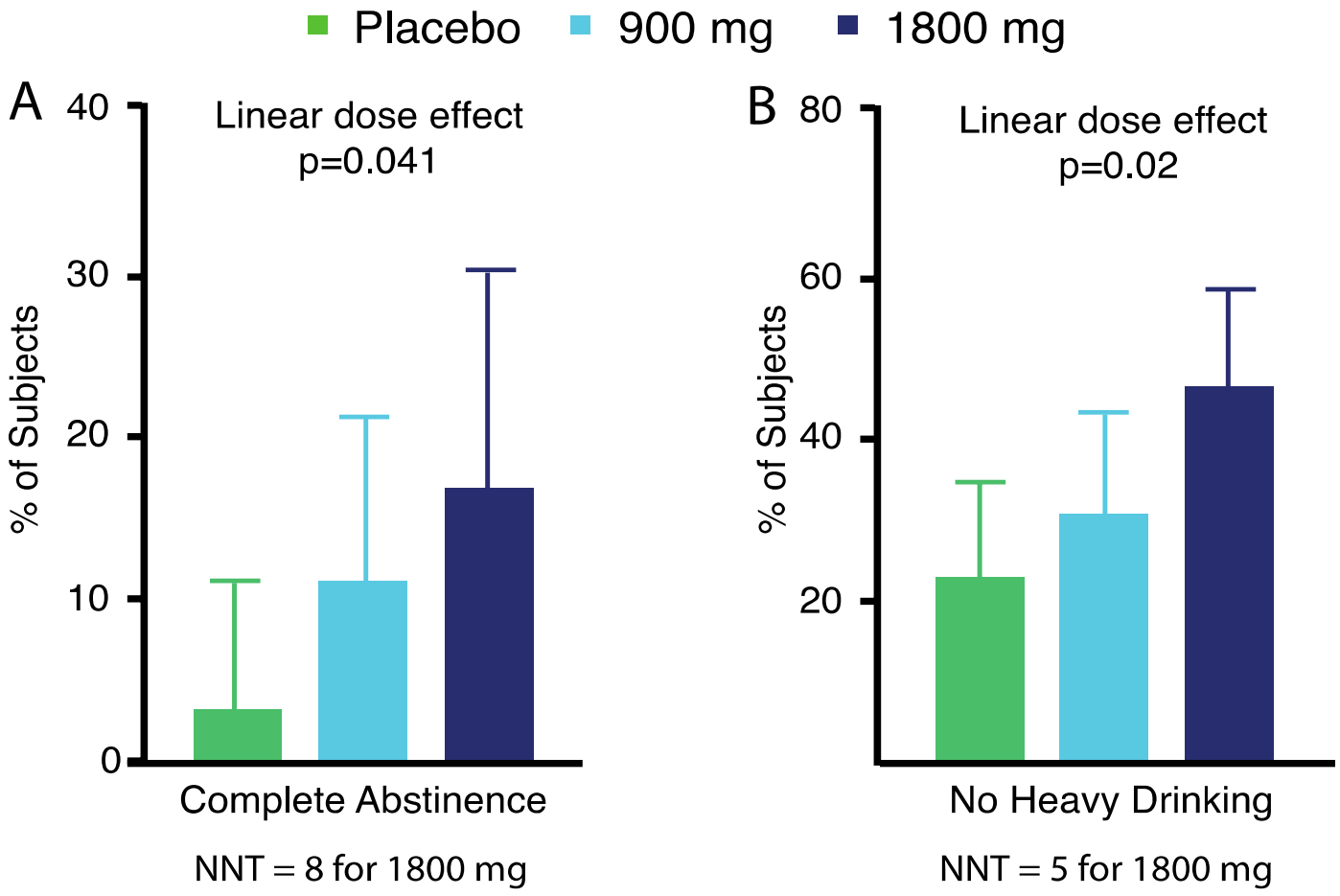


Baseline Characteristics (n = 150)[1]

	TOTAL
Demographics	
Age, years	44.5
Male	55%
White, non-Hispanic	81%
Drinking Characteristics	
Years heavy drinking[2]	14.4
Drinks per week[3]	42.8
Drinking days per week[3]	5.3
Consecutive days abstinent before study	3.0

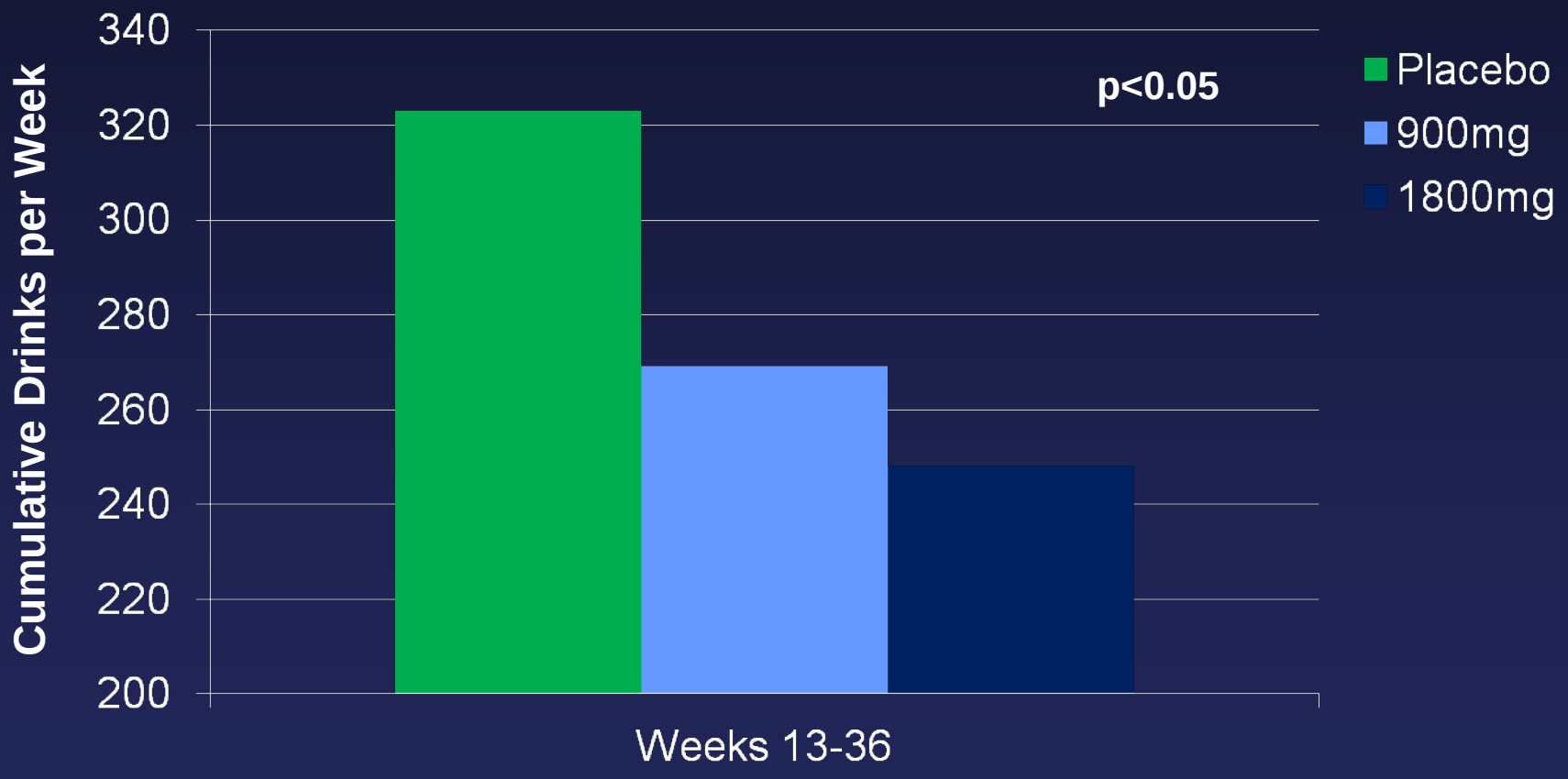
1- No between group differences
2- 5+ drinks per day (males), 4+ drinks per day (females)
3- During the 90 days before screening

Rates of Complete Abstinence and No Heavy Drinking on Study

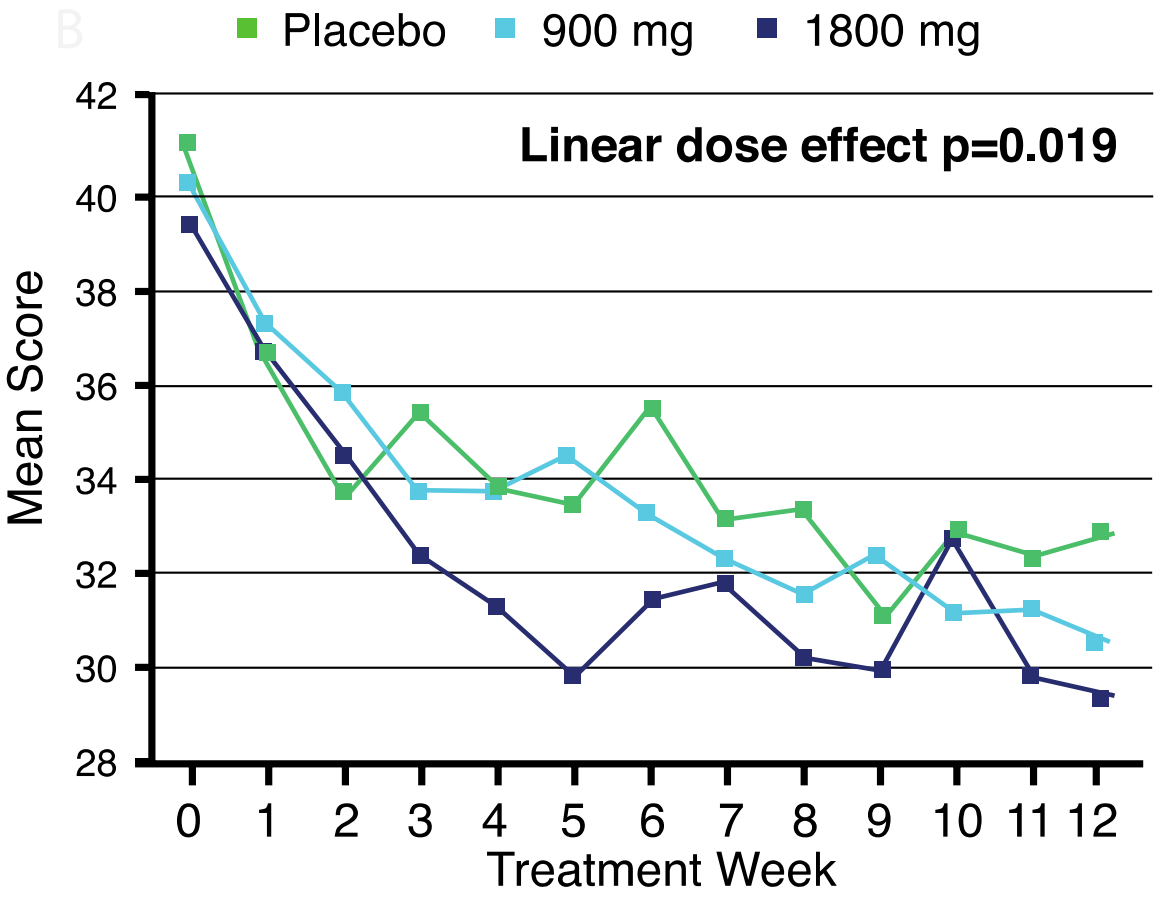


Gabapentin effects on number of drinks per week and number of heavy drinking days per week during the 12-week study in the intention-to-treat population (N=150).

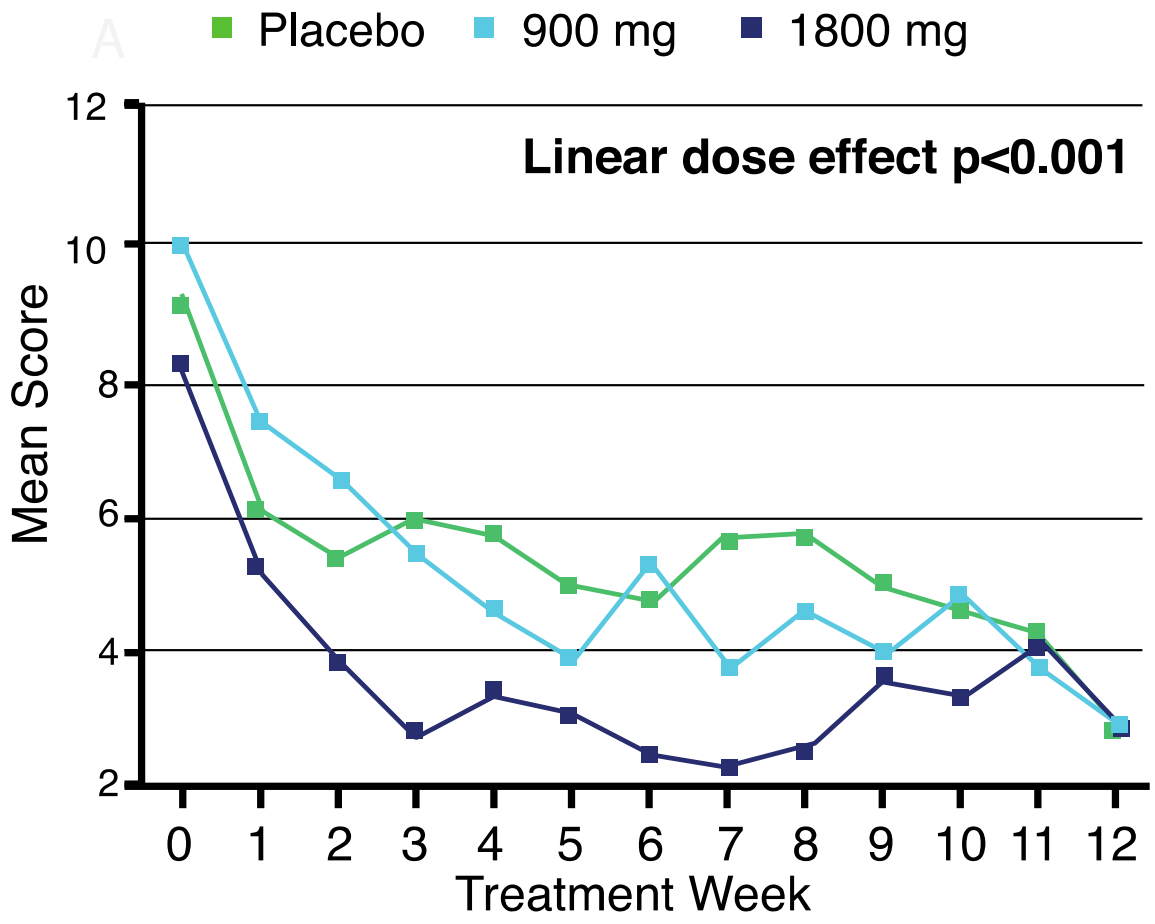
Cumulative Number of Drinks per Week Post Treatment Follow up



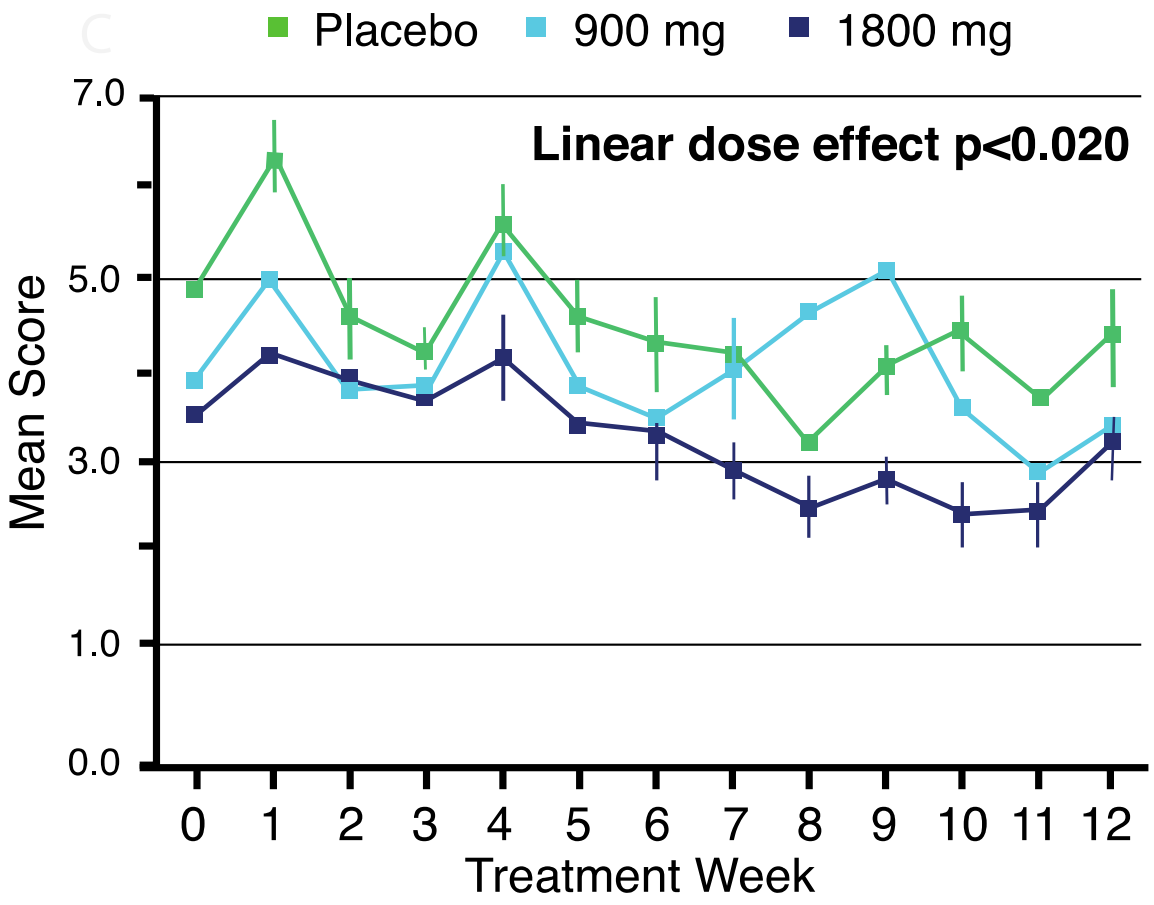
Alcohol Craving Questionnaire



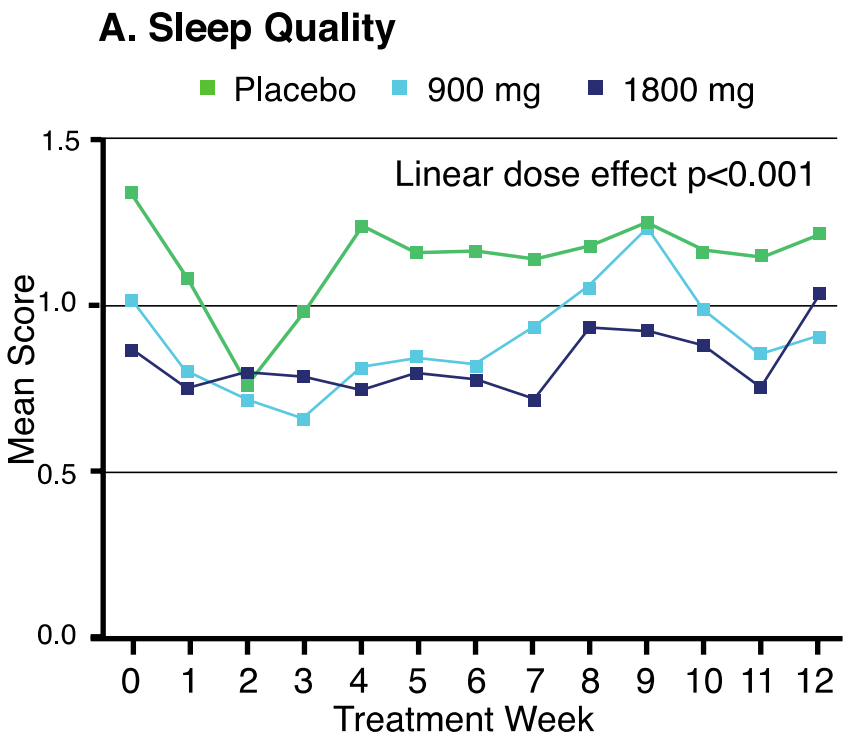
Beck Depression Inventory

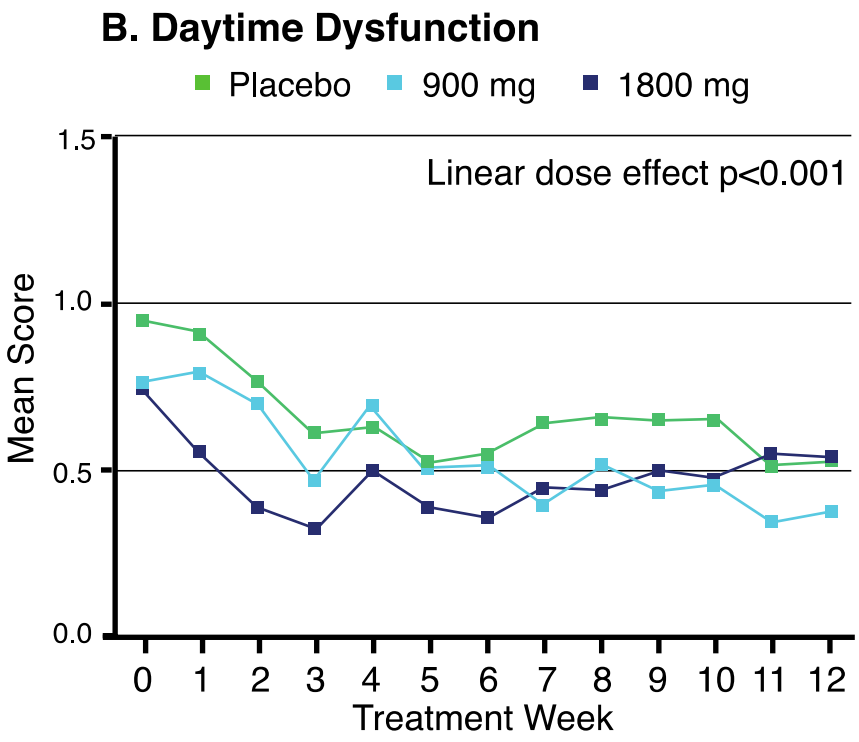


Pittsburgh Sleep Quality Index: Total Scores



Pittsburgh Sleep Quality Index





Medication Tolerability and Compliance

Adverse Events Occurring in > 10% in Any Treatment Group

Adverse Experience	Placebo N=49	900mg N=54	1800mg N=47
Fatigue	24%	24%	19%
Headache	16%	13%	13%
Insomnia	22%	19%	13%
Anxiety	12%	3.7%	11%
Compliance	**96.8%**	**95.6%**	**96.2%**

Summary

- **Gabapentin dose dependently, significantly improved**
  - **rates of complete abstinence and no heavy drinking**
  - **drinking quantity and frequency**
  - **GGT**
  - **alcohol craving**
  - **sleep disturbance**
  - **negative affective symptoms**

- **Gabapentin was well-tolerated with no serious or unexpected drug-related adverse events or evidence of abuse potential**

Clinical Implications

- Gabapentin is a cost- effective treatment for alcohol dependence
- Dose response effects on drinking were found throughout 12 weeks of double-blind treatment and 24 weeks of post treatment follow up, suggesting a return to homeostasis in brain stress systems with no evidence of tolerance or rebound symptoms with drug off titration
- Although non compliance may be an issue with disulfiram and naltrexone, patients complied with a treatment associated with reduced drinking and improved mood, sleep and craving
- Positive outcomes for gabapentin lend support to the role of neuromodulating drugs that target the dysregulation in brain stress systems associated with protracted abstinence for the treatment of alcohol dependence

Translating Our Research Into Practice

Challenges

No industry support for FDA approval of a new use for a generic drug that has shown promise for treating CNS disorders, e.g., alcohol dependence, that have few effective treatment options.

Advantages

Alcohol dependence is found – and gabapentin is widely used – across medical specialties. Reported benefits of gabapentin for alcohol dependence may result in a broader interest in alcoholism treatment across diverse medical settings.

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