



**UW PACC**

Psychiatry and Addictions Case Conference

UW Medicine | Psychiatry and Behavioral Sciences

**GABAPENTIN AFTER A LONG  
DISCUSSION OF  
ANTICONVULSANTS IN ALCOHOL  
WITHDRAWAL TREATMENT:  
A BETTER WAY?**

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# GENERAL DISCLOSURES

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# PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose:

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# SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?

# SIGNS AND SYMPTOMS OF EARLY ALCOHOL WITHDRAWAL

- Autonomic Hyperactivity (increased P, BP)
- Tremor
- Diaphoresis
- Nausea / Vomiting
- Anxiety-Agitation
- Insomnia
- Transient Perceptual Disturbances
- Seizures

# MILD-TO-MODERATE ALCOHOL WITHDRAWAL

- Time course
  - ◆ 6 to 8 hours after last drink
  - ◆ Peaks at 24 to 48 hours after last drink
- Symptoms may include some or all of the following:
  - ◆ Anxiety, insomnia, irritability, tremor, headache, gastrointestinal disturbance, diaphoresis, increased blood pressure and heart rate

# SEVERE ALCOHOL WITHDRAWAL

- Pt has chronic and severe use disorder
- Hx of Multiple Withdrawals
- Alcohol withdrawal seizures
  - ◆ Usually occur 6 to 48 hours from last drink
- Ultra Severe= Delirium tremens
  - ◆ Gradual onset 2 to 3 days from last drink, peak at 4 to 5 days
  - ◆ IV high dose Benzos/ Propofol and others !!!!

# MOST PSYCHIATRIC INPTS AND OUTPATIENTS AT RISK FOR ALCOHOL WITHDRAWAL .....

1. Are at low to moderate risk
2. Severe risk pts are treated in ER/Medicine,  
not psych inpt
3. Rarely see in Out-pt psych
4. In outpt addictions referred to Detox or Inpt  
med



# MEDICATION TREATMENT OF UNCOMPLICATED WITHDRAWAL

- Gold Standard: Benzodiazepines
  - **Long acting vs. Short Acting**
  - **Symptom-triggered vs. Scheduled**
- Older= Barbiturates, Paraldehyde, Alcohol
- Antacid, Thiamine, MVI, Magnesium
- Anticonvulsants ?
- Baclofen ?
- *We are NOT talking about DT/ICU management*

# BENZODIAZEPINES

	onset	dist	half-life	Excretion
Lorazepam	Int	Int	Int	Renal
Oxazepam	Slow	Int	Short	Renal
Diazepam	Fast	Fast	Long	Liver
Chlordiazepoxide	Int	Slow	Long	Liver

Onset for PO administration; all are fast IV.

Lorazepam most reliable if IM administration needed.

# SYMPTOM-TRIGGERED

*SAITZ ET AL JAMA AUG 17, 1994; 272(7): 519*

- 50mg Q6h x 4 then 25mg Q6h x 8  
plus 25-100mg prn
  - **68 hrs medication administration**
  - **425mg / patient**
- Scheduled Placebo plus prn
  - **9 hrs medication administration**
  - **100 mg / patient**
- Same Rates of Improvement and complications
- **Faster DC from Inpt Detox**

# UNCOMPLICATED WITHDRAWAL INPATIENT PROTOCOL *EXAMPLE*

- Chlordiazepoxide
- Give 50 mg PRN CIWA-Ar 10 or Greater
  - **continue hourly until CIWA-Ar score < 10**
  - **hold if signs of alcohol or benzodiazepine intoxication**
- Measure CIWA-Ar 1 Hour After Each Dose
  - **and at least Q shift until acute withdrawal resolved**
- *Modify if Needed* for Individual Patients
- Diazepam 10mg, Lorazepam 2mg

# TRADITIONAL ALCOHOL WITHDRAWAL TREATMENT

- Substitute cross-dependent drug (BZ)
- Gradually withdraw substitute drug
- Supplement vitamins and minerals
  - ◆ thiamine
  - ◆ folic acid
  - ◆ multi-vitamin
- Supportive treatment
  - ◆ decrease stimulation
- Increasingly an outpatient procedure  
increase

# RELATIVE INDICATIONS FOR OUTPATIENT OR MILD/MOD ALCOHOL DETOXIFICATION

- Negative history for DT' s and Seizures
- Medically stable/Negative lab work up
- Psychiatrically stable
- Stable living environment / Social Support
- Ability to follow up in clinic
- Mild-moderate withdrawal
- Good adherence—esp with BZP's
- Low risk for BZP diversion/abuse
- Anti-convulsants may be superior

**WHILE AN EPISODE OF DEPRESSION IS MEDICALLY TREATED FOR AT LEAST A 6 MO TO A YEAR-- GENERALLY WITH LITTLE OR NO ACTUAL PHYSIOLOGICAL EVIDENCE OF A DISORDER PRESENT....**

*--- Alcohol WD, it is usually treated for hours or days,*

*----However, there is STRONG evidence that it lasts weeks or months*

- IN fact one could argue that it is one of the only disorders in which we have clear laboratory evidence that the disorder exists*

[Biol Psychiatry](#). 1990 Mar 1;27(5):477-88.

## **EEG sleep studies in "pure" primary alcoholism during subacute withdrawal: relationships to normal controls, age, and other clinical variables.**

[Gillin JC](#)<sup>1</sup>, [Smith TL](#), [Irwin M](#), [Kripke DF](#), [Schuckit M](#).

### **Abstract**

(EEG) sleep recordings in 34 controls and 31 inpatients with relatively pure primary alcoholism who had been abstinent for about 17 days.

### **Compared with normal controls, primary alcoholics**

- 1. took longer to fall asleep,**
- 2. slept less, and had poor sleep efficiency.**
- 3. Sleep loss reflected reduced non-rapid eye movement (NREM) sleep, especially stage 2 sleep, stage 4 sleep, and total delta (stage 3 and 4) sleep.**
- 4. Alcoholic patients had higher REM density of the first REM period.**
- 5. The number of drinks per drinking day in the 3 months before admission was directly related to the duration of the first REM period.**
- 6. In addition, the maximum number of withdrawal symptoms the patient had ever experienced was inversely related**



# Altered Sleep Physiology in Chronic Alcoholics: reversal with abstinence.

[Williams HL](#) [Rundell OH Jr](#)

## Abstract

Somnograms obtained from recently ( 1-2 weeks) abstinent chronic alcoholics reveal gross disruption succinctly described as "fractured" sleep.

**Sleep onset is delayed and the rhythmic properties of the sleep pattern are markedly disturbed with numerous brief arousals and changes of sleep stage.**

**Excessive stage 1 and stage rapid eye movement sleep are present while the high voltage slow wave sleep is markedly reduced or absent.**

**With continued sobriety (9 mo or more) the sleep stage percentages tend to return to normal levels,**

**but the disruption of the sleep pattern persists after as much as 21 mo of abstinence.**

[Biol Psychiatry.](#)

## **Hypothalamic-pituitary-adrenal system adaptation to detoxification in alcohol-dependent patients is affected by family history of alcoholism.**

[Zimmermann U](#) [Hundt W](#) [Spring K](#) [Grabner A](#) [Holsboer F](#)

[Author information](#)

**RESULTS:**

**CONCLUSIONS:**

One week after WD symptoms resolved ---

Recovery from alcohol withdrawal-induced impairment of HPA system regulation occurs earlier in FH-P than FH-N patients, indicating that the efficacy of central neuroadaptation to this ethanol-related stimulus may be related to genetic factors.

# ANTICONVULSANTS FOR ALCOHOL WITHDRAWAL

- Anti-kindling
- GABA Enhancement
- Glutamate Inhibition
- Used More Extensively in Europe
- Recent RCT's in USA may outperform BZP's
- May hold special advantages for Out-pt Detox.

# ANTICONVULSANTS AS ALCOHOL DETOXIFICATION AGENTS

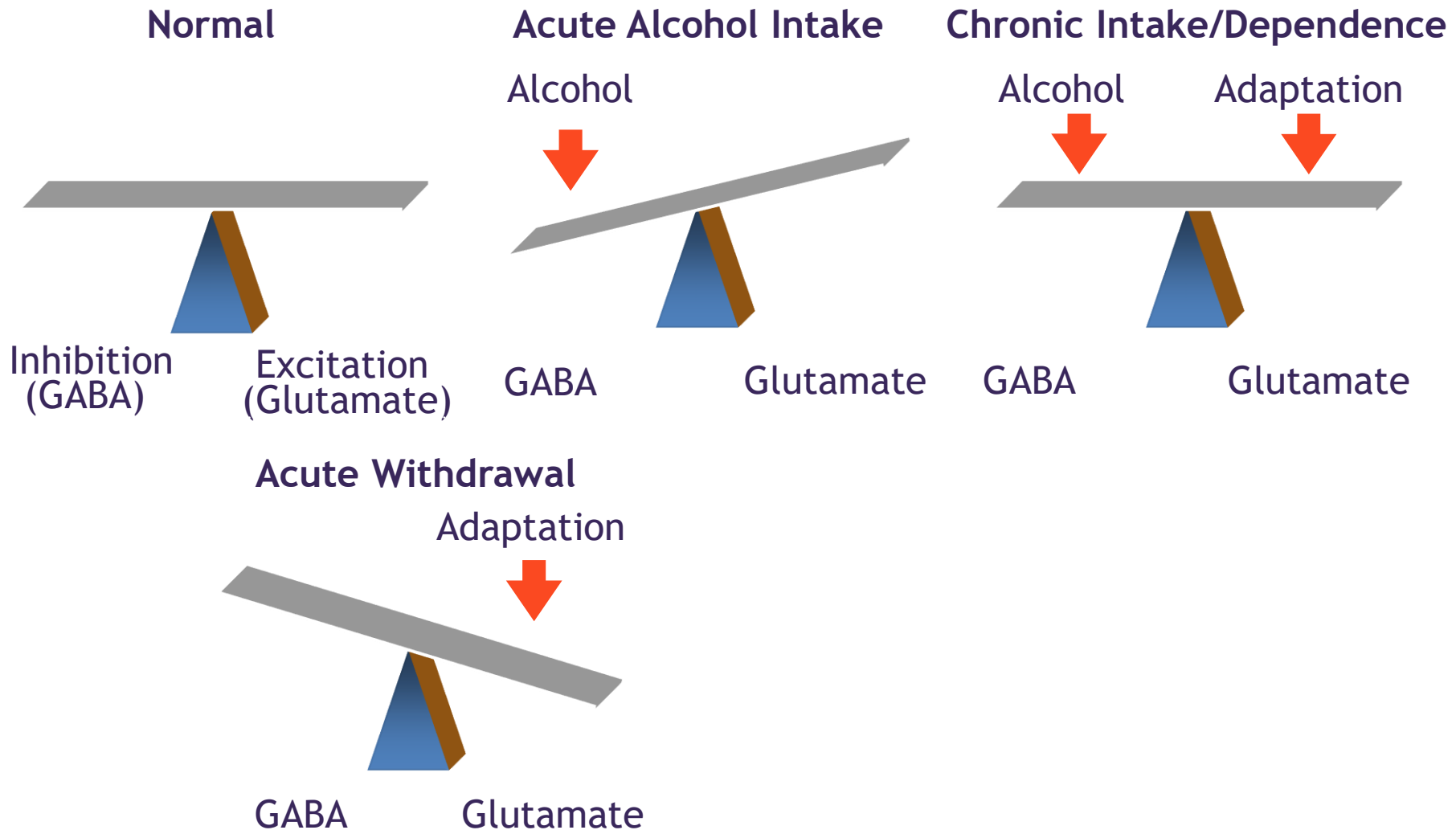
## Advantages

- No abuse liability
- Seizure medication
- Neuroprotective
- Cognition
- Extended time Rx

## Disadvantages

- Limited clinical experience
- Heme side effects
- Liver toxicity (not gabap)
- Confusion (topiramate)
- DT role/Acute Sz role ?

# EFFECTS OF ALCOHOL ON NEUROCHEMICAL BALANCE



# ANTICONVULSANTS: “POST ACUTE WITHDRAWAL”

- Alcohol withdrawal physiological symptoms may be abnormal for weeks or months in many individuals
  1. Dexamethasone suppression tests
  2. Abnormal sleep and Sleep EEG's
- Anticonvulsants may be used for weeks or months for ongoing alcohol withdrawal Rx without causing tolerance and dependence
- How to identify which pts need this? (likely repeat WD's and extended detox sx in past (not researched))

**WHILE AN EPISODE OF DEPRESSION IS MEDICALLY TREATED FOR AT LEAST A YEAR-- GENERALLY WITH LITTLE OR NO ACTUAL PHYSIOLOGICAL EVIDENCE OF A DISORDER PRESENT....**

*--- Alcohol WD, it is usually treated for hours or days,*

*----However, there is STRONG evidence that it lasts weeks or months*

- IN fact one could argue that it is one of the only disorders in which we have clear laboratory evidence that the disorder exists*

# The Differential Effects of Medication on Mood, Sleep Disturbance, and Work Ability in Outpatient Alcohol Detoxification.

Malcolm R, Myrick H, Roberts J, Wang W, Anton RF.

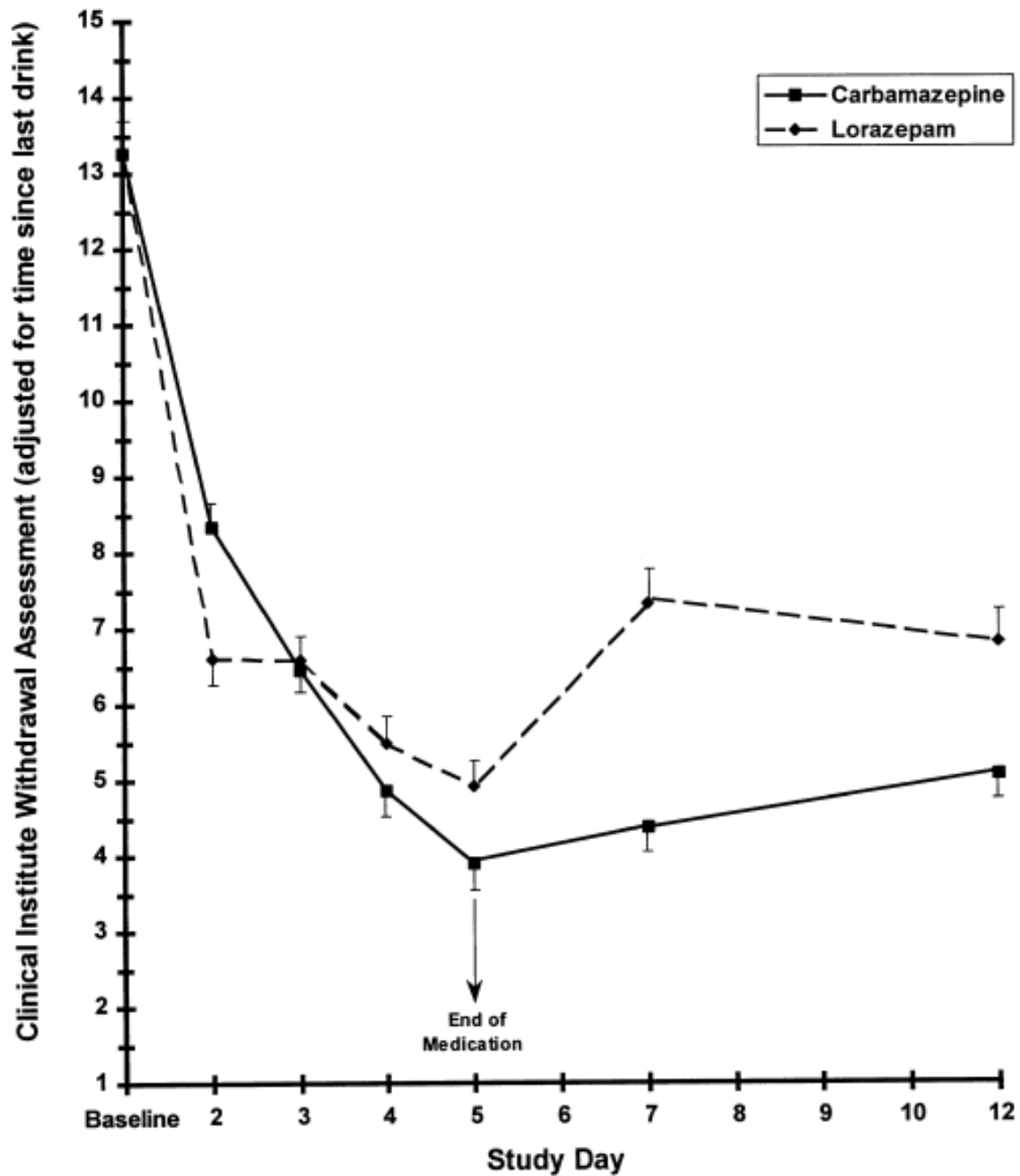
A double-blind, randomized controlled trial of patients (n = 136) meeting DSM-IV criteria for alcohol withdrawal and stratified based on detoxification history were treated with carbamazepine or lorazepam for 5 days on a fixed dose tapering schedule. Mood symptoms improved for all subjects regardless of medication or detoxification history.

**Carbamazepine > Lorazepam for:**

**Reducing anxiety (p = 0.0007)**

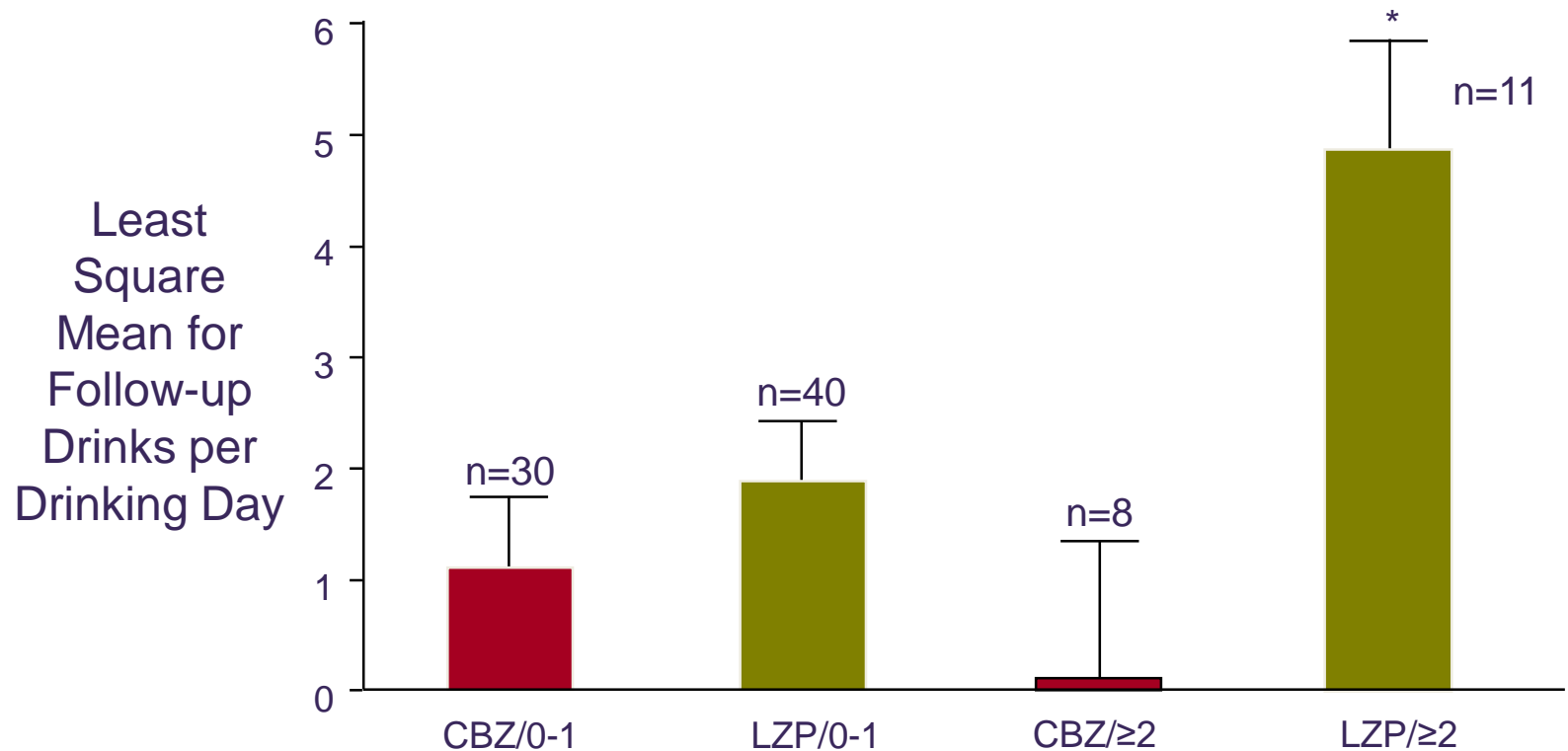
**Improving sleep (p = 0.0186)**





\*p=0.007

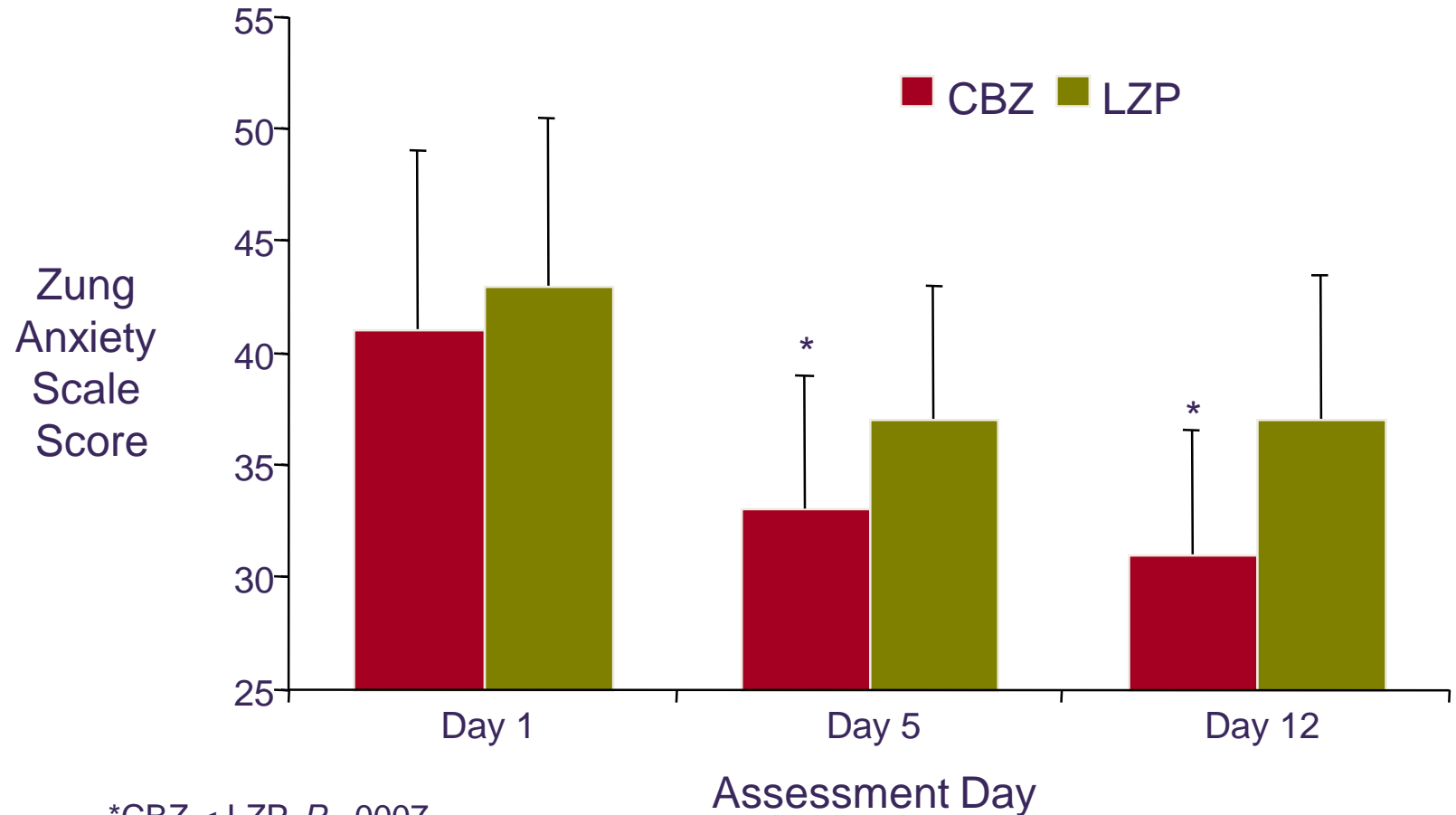
# DRINKS PER DRINKING DAY: DAY 6 TO DAY 12 --IE AFTER MEDS STOPPED



\* $P=.044$ . Drug main effect,  $P=.0032$ ; Drug x Detox Hx,  $P=.0333$ .

Malcolm R et al. *J Gen Intern Med.* 2002;17:349-355.

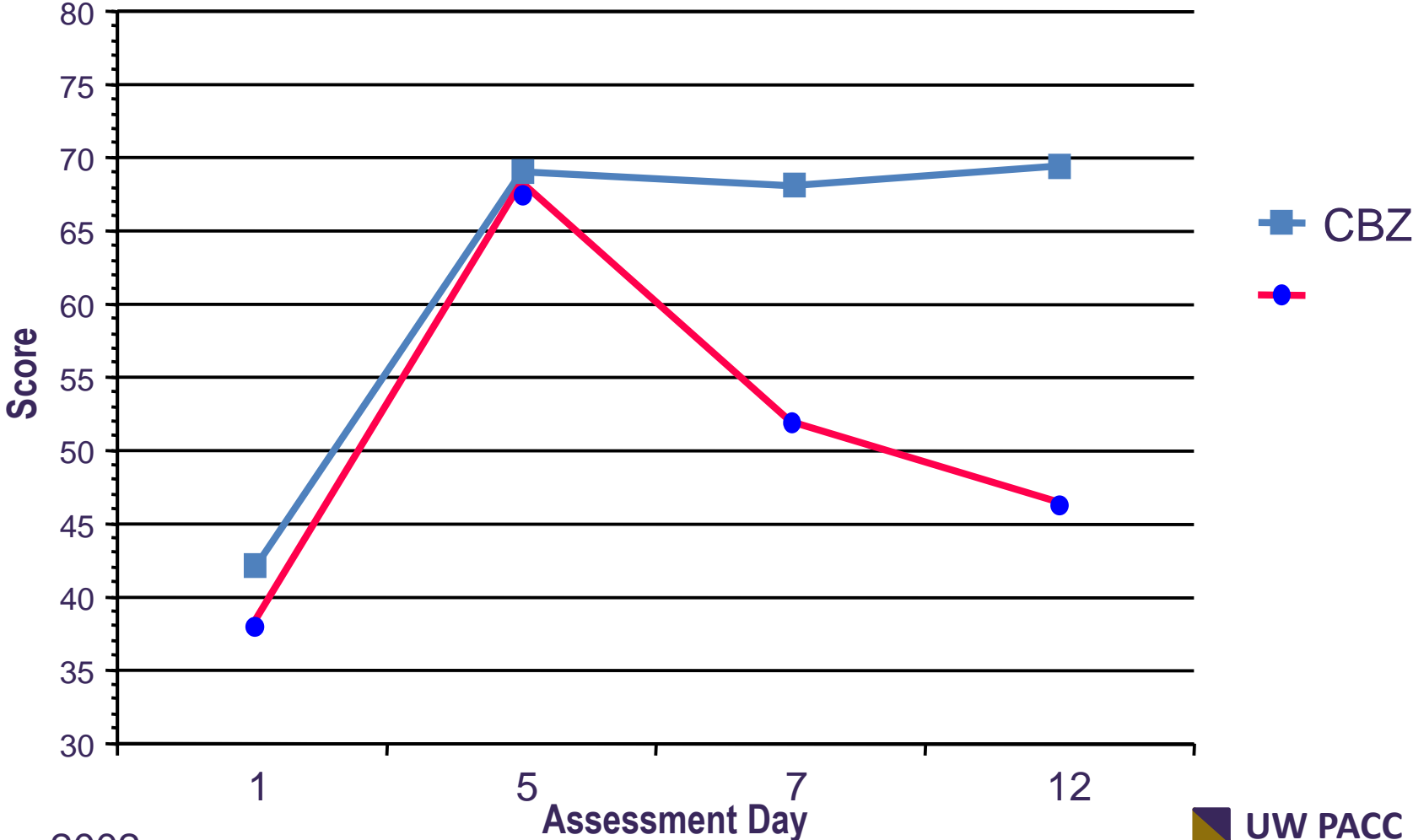
# ZUNG ANXIETY SCALE SCORES



\*CBZ < LXP,  $P=.0007$ .

Malcolm R et al. *Am J Addict.* 2002;11:141-150.

# IMPROVEMENT IN SLEEP



# CARBAMAZEPINE

- Carbamazepine
  - 600-800mg/d tapered over 5 days
  - vs. lorazepam 6-8mg/d tapered over 5 d
- Equal Reduction in CIWA-Ar Scores
- Better Sleep, Greater Reduction in Anxiety
  - *(Malcolm et. al, Am J Add, 11:141-50, 2002)*
- Less Rebound, Reduced Alcohol Use
  - *(Malcolm et. al, J Gen Int Med, 17:349-55, 2002)*

# Valproic Acid for Alcohol Withdrawal

Table 1  
Valproic acid

Investigators (Year)	<i>N</i>	Design	Comparison	Results
Bocci and Beretta (1976)	25	Open-label	None	"56%" improved CGI
Brausseau (1978)	375	Open-label	None	"78%" excellent results
Lambie, Johnson, Vijayasenan, and Whiteside (1980)	49	Open-label	VPA vs. no treatment	VPA=0 seizures No treatment=5 seizures
Hillbom et al. (1989)	138	Double-blind	PBO, VPA, CBZ	Adverse effects of VPA and CBZ
Hammer and Brady (1996)	2	Case reports	None	Rapid CIWA ↓ Reduced LZP pm Reduced mania
Rosenthal, Perkel, Singh, Anand, and Miner (1998)	37	Randomized open-label	Phenobarbital	Half as much pm phenobarbital in VPA group
Myrick, Brady, and Malcolm (2000)	11	Open-label	LZP	VPA=LZP
Reoux et al. (2001)	36	Double-blind	Oxazepam	Use of VPA led to reduced use of oxazepam

BMC Psychiatry. 2011 Mar 14;11:41.

# **Treatment of alcohol dependence with Low-Dose Topiramate: an open-label controlled study.**

Paparrigopoulos T, Tzavellas E, Karaiskos D, Kourlaba G, Liappas I.

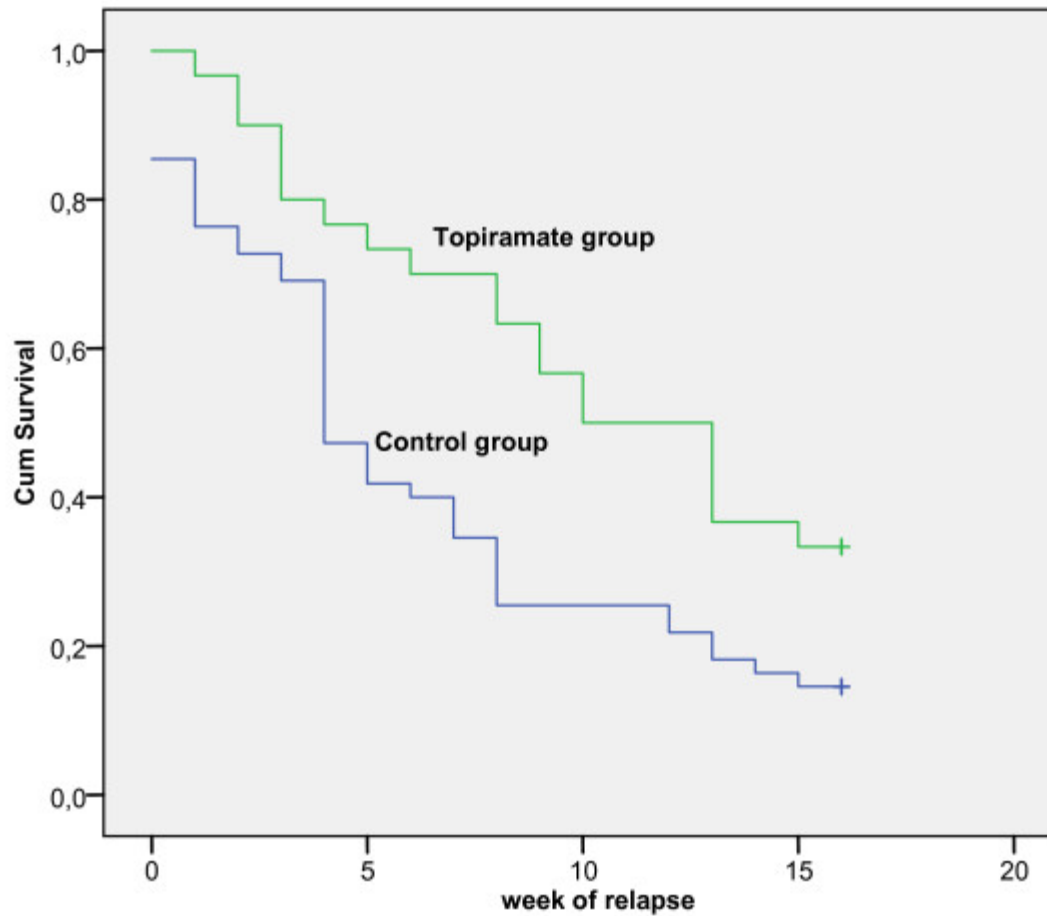
Following a 7-10 day inpatient alcohol detoxification protocol, 90 patients were assigned to receive either topiramate (up to 75 mg per day) in addition to psychotherapeutic treatment (n = 30) or psychotherapy alone (n = 60).

**Relapse rate lower Top (66.7%) vs (85.5%), (p = 0.043).**

**Time to relapse longer (log rank test, p = 0.008).**

**median duration of abstinence Top 10 wks vs 4 weeks**

No serious side effects of topiramate were recorded throughout the study.





**OK--- NOW ITS TIME FOR**

***GABAPENTIN !!!***

JAMA Intern Med. 2014 Jan;174(1):70-7.

## **Gabapentin treatment for alcohol dependence: a randomized clinical trial.**

Mason BJ<sup>1</sup>, et al

Placebo vs Gabapentin 900 mg or 1800 mg/day

Similar linear dose effects were obtained with measures of

mood (P = .001)

sleep (P < .001)

craving (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.

# HOW EFFECTIVE?

MASON 2014

- Gabapentin significantly improved the
- rates of abstinence (Placebo vs Active)
  - 4.1% vs 11.1% 900 mg group, and
  - 4.1% vs 17.0% 1800 mg group ( $p = 0.04$ 
    - NNT = 8 for 1800 mg).
- No heavy drinking rate
  - 22.5% vs 29.6% 900 mg group, and
  - 22.5% vs 44.7% 1800 mg group ( $p = 0.02$ ) NNT = 5

• 2019 Jan;43(1):158-169.

doi: 10.1111/acer.13917. Epub 2018 Dec 9.

## **Gabapentin Enacarbil Extended-Release for Alcohol Use Disorder: A Randomized, Double-Blind, Placebo-Controlled, Multisite Trial Assessing Efficacy and Safety**

N=336, dose 600 bid

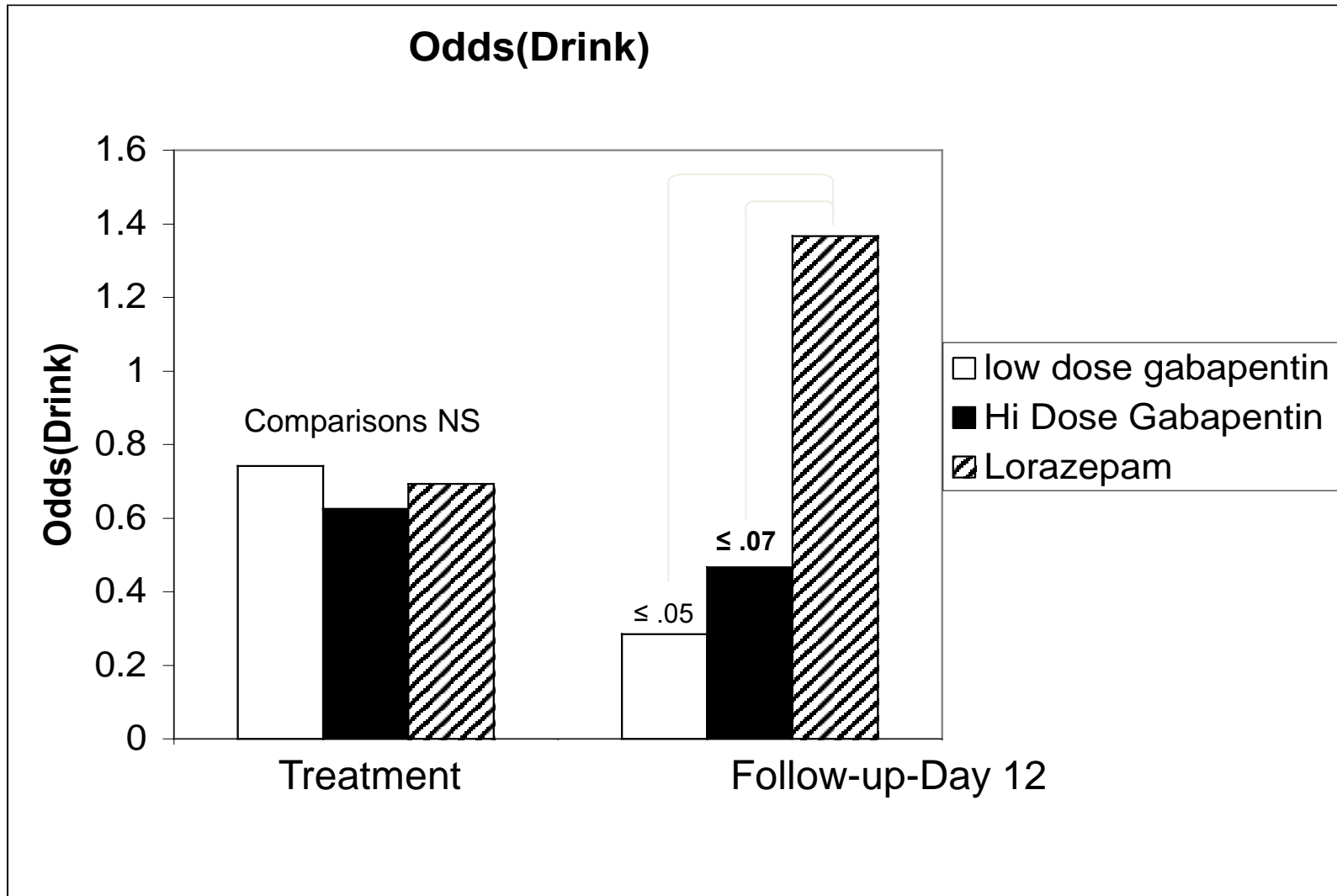
The GE-XR and placebo groups did not differ significantly on the primary outcome measure, percentage of subjects with no heavy drinking days (28.3 vs. 21.5, respectively,  $p = 0.157$ ).

Similarly, no clinical benefit was found for percent days abstinent, percent heavy drinking days, drinks per week, drinks per drinking day), alcohol craving, alcohol-related consequences, sleep problems, smoking, and depression/anxiety symptoms. Common side-effects were fatigue, dizziness, and somnolence

# GABAPENTIN VS. LORAZEPAM IN ALCOHOL WITHDRAWAL

- Double-blind, outpatient trial (n=101)
- CIWA-AR  $\geq 10$  for inclusion
- Tapering dose
  - GBP = 900-1200 mg/d tapered over 4 days
  - LZ = 6 mg/d tapered over 4 days
- Acoustic Startle assessed on Days 0, 4, and 7
- Follow-up at Day 7 and 12

# DRINKING ODDS



Am J Psychiatry. 2011 Jul;168(7):709-17. Epub 2011 Mar 31.

## **Gabapentin Combined with Naltrexone for the Treatment of Alcohol Dependence.**

Anton RF, Myrick H, Wright TM, Latham PK, Baros AM, Waid LR, Randall PK.

### **METHOD:**

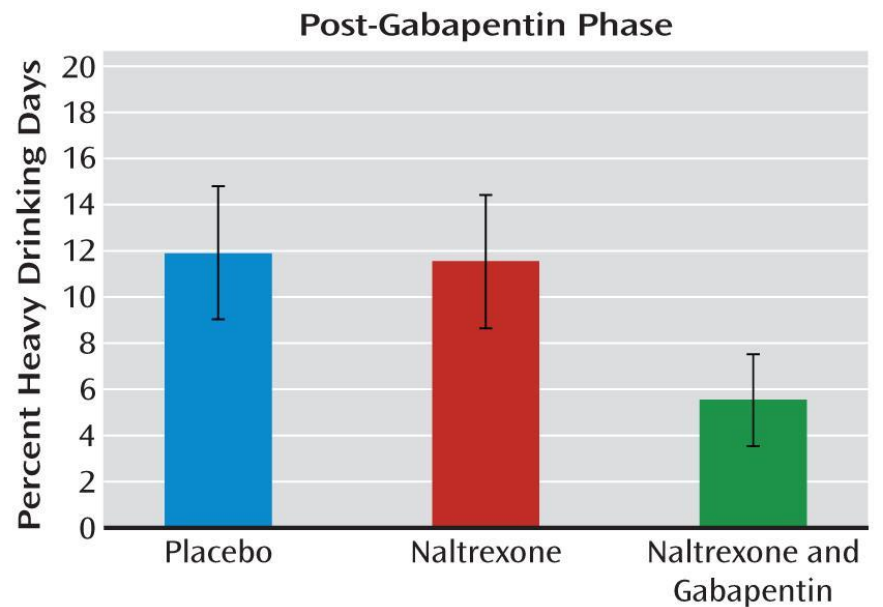
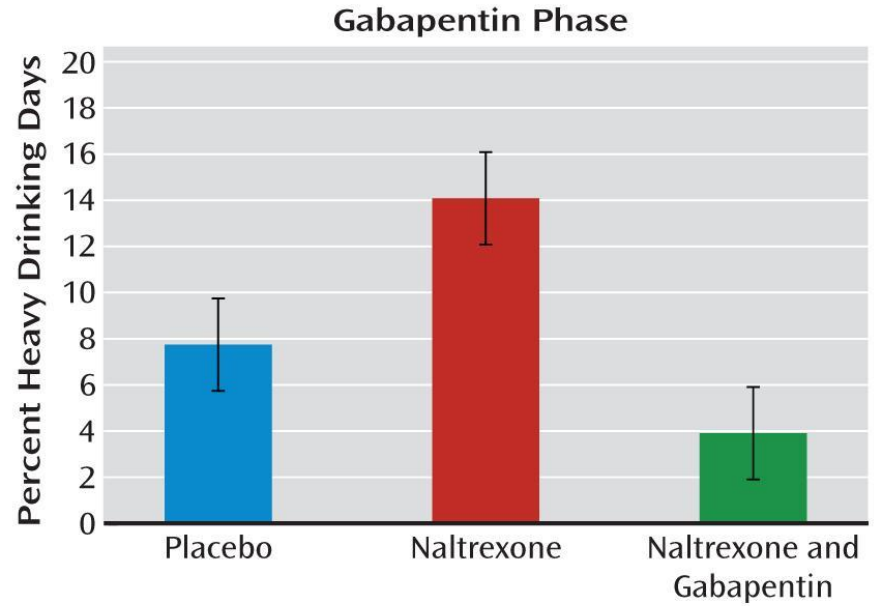
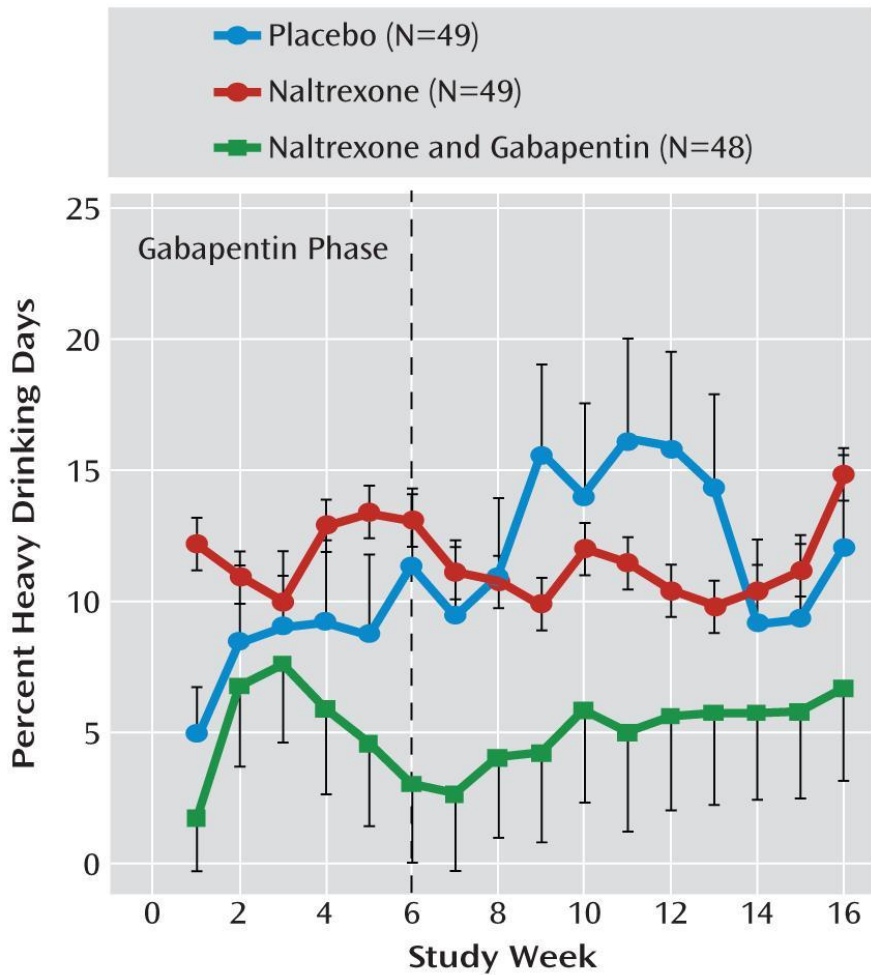
A total of 150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

### **RESULTS:**

**During the first 6 weeks, the naltrexone-gabapentin group had a longer interval to heavy drinking than the naltrexone-alone group, which had an interval similar to that of the placebo group;**

**Poor sleep was associated with more drinking in the naltrexone-alone group but not in the naltrexone-gabapentin group, while**

**a history of alcohol withdrawal was associated with better response in the naltrexone-gabapentin group.**





## **Self-reported Sleep, Sleepiness, and Repeated Alcohol Withdrawals: a Randomized, Double blind, Controlled Comparison of Lorazepam vs Gabapentin.** Malcolm R, Myrick LH, Veatch LM,.

**METHODS:** Outpatients in treatment for alcohol withdrawal received a 4-day fixed-dose taper of gabapentin or lorazepam in a double-blind, randomized, controlled trial with an 8-day follow-up. Daily across a 5 day outpatient treatment and Days 7 and 12 post-treatment, patients self-reported daytime sleepiness

**Gabapentin compared with lorazepam, was**

- 1. superior on multiple sleep measures, in patients who had previous withdrawals.**
- 2. Lorazepam subjects experienced insomnia rebound symptoms.**
- 3. Early drinking was related to persisting insomnia with both drugs.**

# ANTICONVULSANTS FOR SLEEP IN RECOVERING ALCOHOLICS AND ADDICTS

- Sedative
- Non-Addictive
- Relatively friendly to REM architecture
- Direct Rx of Post Acute WD for Alc and BZP's
- Certain Pain syndromes ( neurogenic pain- Gabapentin/ Cluster headaches Topiramate
- ? Enhance Sobriety/Decrease drinking

# GABAPENTIN SIDE EFFECTS

- Sedation- Good ? Bad ?
- Augmentation of Intox/sedation
- Sexual Side effects
- Addiction?
- Others ?

# DETOX IS NOT ADDICTION TREATMENT

- Acute Stabilization
  - Safe Physiological/Psychological Withdrawal
  - Environment Conducive to Abstinence
- Assessment
  - Co-occurring Disorders, Treatment Needs
- Preparation for Addiction Treatment
  - Begin Forming Therapeutic Relationships
  - Psychosocial Stabilization
  - Begin to Address Co-occurring Disorders
  - Relapse Prevention Strategies
- Initiate Pharmacotherapy ??

**QUESTIONS ?**

**CASES AND CONUNDRUMS**