ANTICONVULSANTS IN ALCOHOL WITHDRAWAL TREATMENT: A BETTER WAY?

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SIGNS AND SYMPTOMS OF EARLY ALCOHOL WITHDRAWAL

Autonomic Hyperactivity (increased P, BP)

Tremor

Diaphoresis

Nausea / Vomiting

Anxiety-Agitation

Insomnia

Transient Perceptual Disturbances

Seizures

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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

Myrick H, Anton R. *CNS Spectrums*. 2000;5:22-32.

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SEVERE ALCOHOL WITHDRAWAL

- Alcohol withdrawal seizures
  - Usually occur 6 to 48 hours from last drink
- Delirium tremens
  - Gradual onset 2 to 3 days from last drink, peak at 4 to 5 days

Myrick H, Anton R. *CNS Spectrums*. 2000;5:22-32.

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MEDICATION TREATMENT OF UNCOMPLICATED WITHDRAWAL

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

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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.

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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**

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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 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

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 ?

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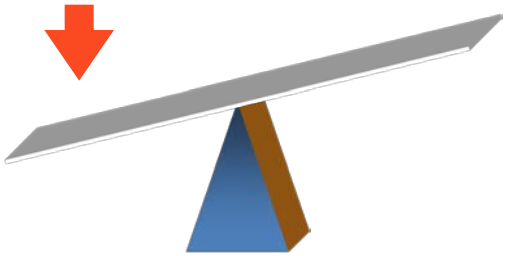
EFFECTS OF ALCOHOL ON NEUROCHEMICAL BALANCE

Normal

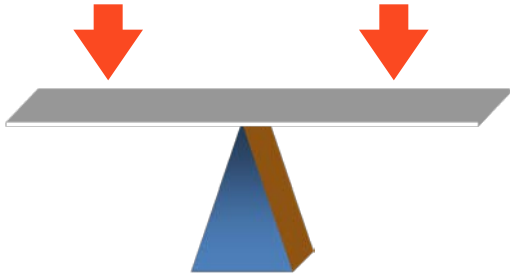
GABA Glutamate

Acute Alcohol Intake



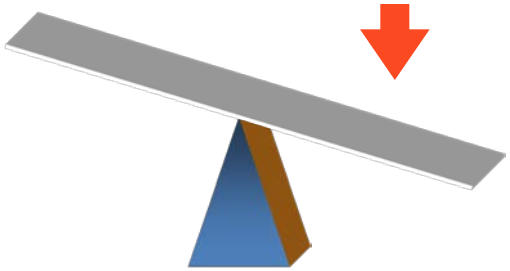
GABA Glutamate

Chronic Intake/Dependence



GABA **Glutamate**

Acute Withdrawal



GABA **Glutamate**

Ries- 2012

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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)

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[1], Smith TL, Irwin M, Kripke DF, Schuckit M.

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 to the amount of delta sleep**

Alcohol Clin Exp Res. Spring;5(2):318-25.

Altered Sleep Physiology in Chronic Alcoholics: reversal with abstinence

Williams HL Rundell OH Jr

Abstract

Somnograms obtained from recently 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.

Am J Addict 2002
Spring;11(2):141-50

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

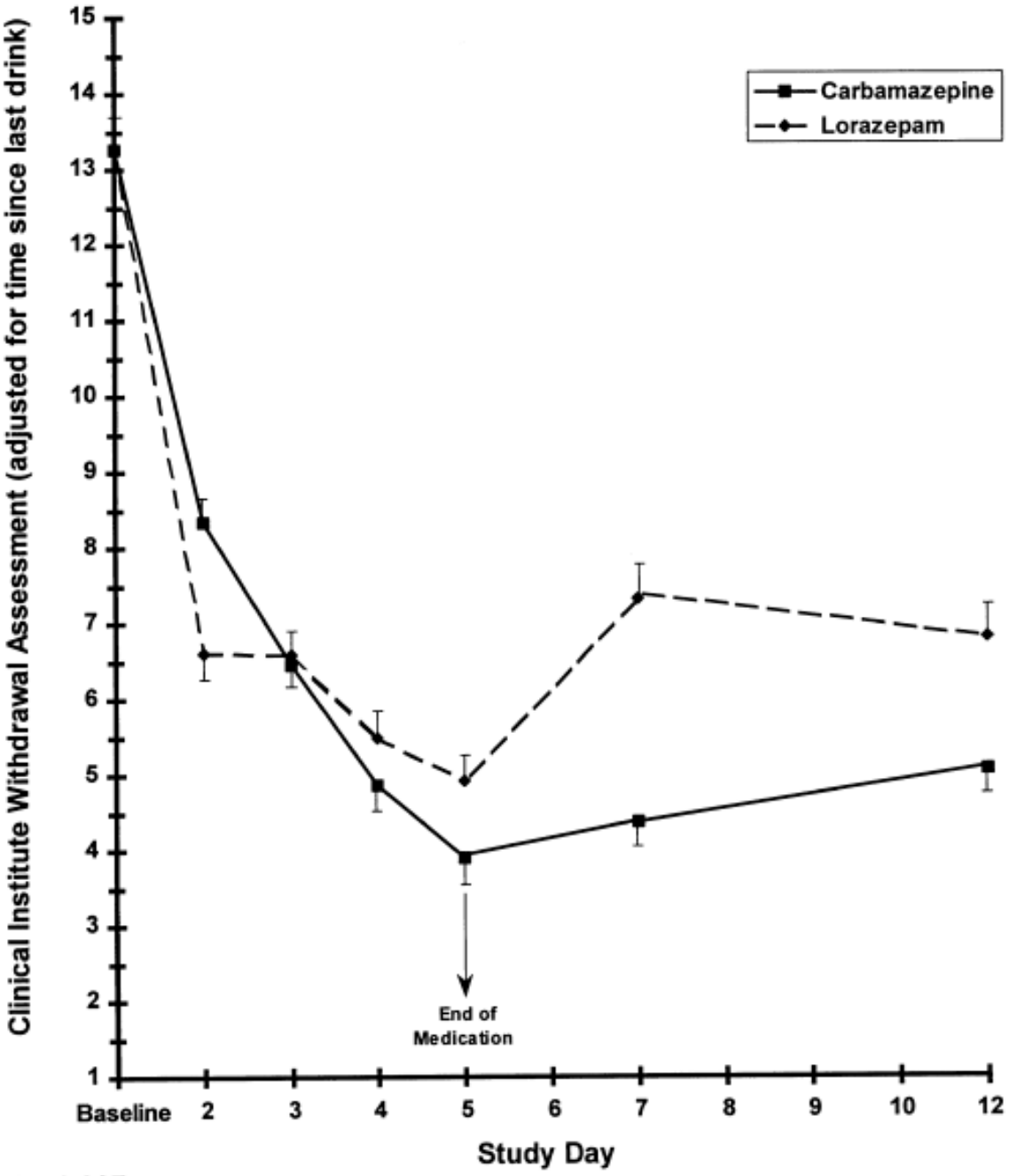
Malcolm R, Myrick H, Roberts J, Wang W, Anton RF.

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)

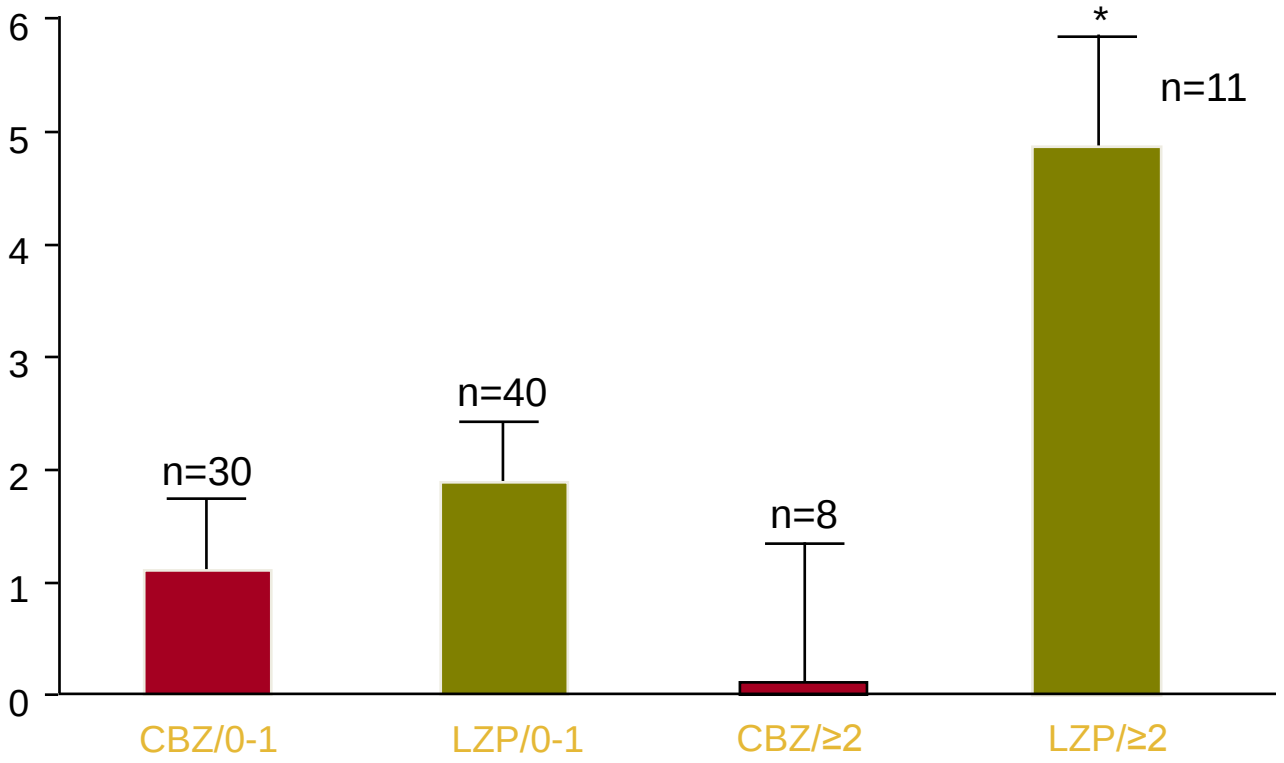
Improving sleep (p = 0.0186)



CARBAMAZEPINE VS. LORAZEPAM IN ALCOHOL WITHDRAWAL

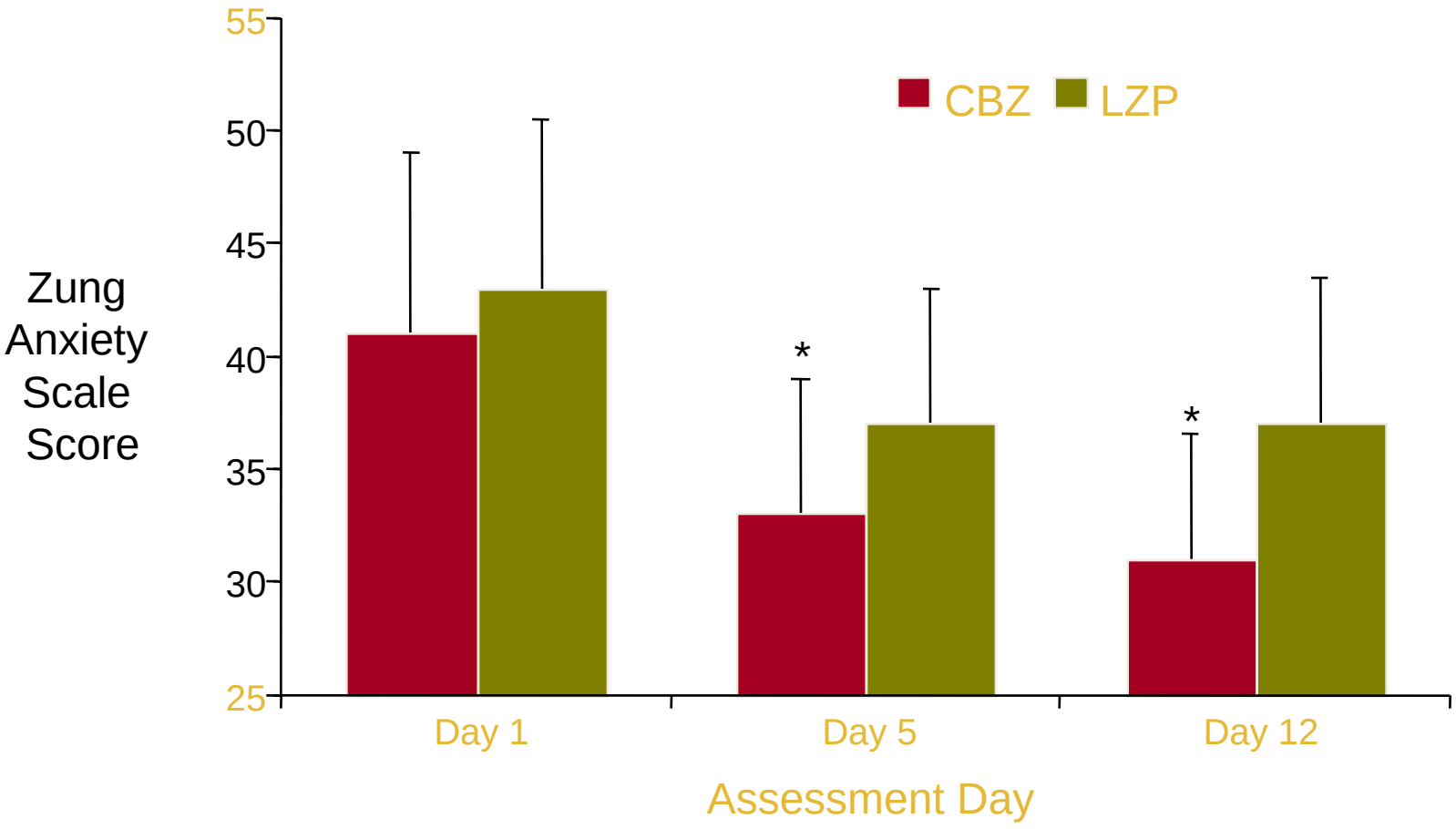
- Double-blind, outpatient trial (n=136)
- CIWA-AR ≥ 10 for inclusion
- 5 day tapering dose
  - CBZ = 600-800 mg/d tapered to 200mg by day 5
  - LZ = 6-8 mg/d tapered to 2 mg by day 5
- Compared single (0-1) vs. multiple (≥ 2) medicated detoxifications

DRINKS PER DRINKING DAY: DAY 6 TO DAY 12

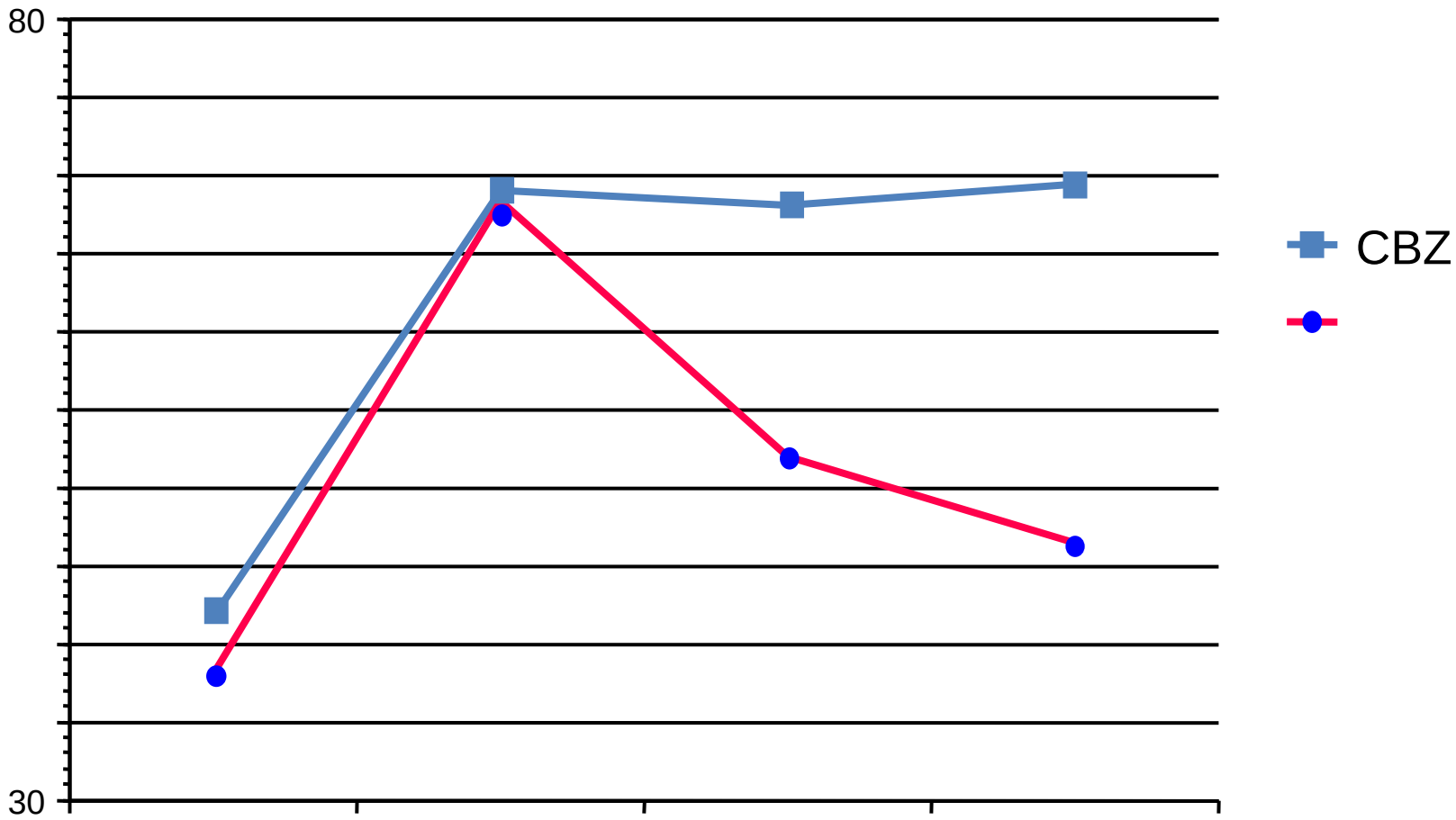


* main effect, *P*=.0032; Drug x Detox Hx, *P*=.0333.

ZUNG ANXIETY SCALE SCORES



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)	*N*	Design	Comparison	Results
Bocci and Beretta (1976)	25	Open-label	None	"56%" improved CGI
Brausseur (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 BPAD/AW	None	Rapid CIWA ↓ Reduced LZP prn Reduced mania
Rosenthal, Perkel, Singh, Anand, and Miner (1998)	37	Randomized open-label	Phenobarbital	Half as much prn 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.

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 Topiramate (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.

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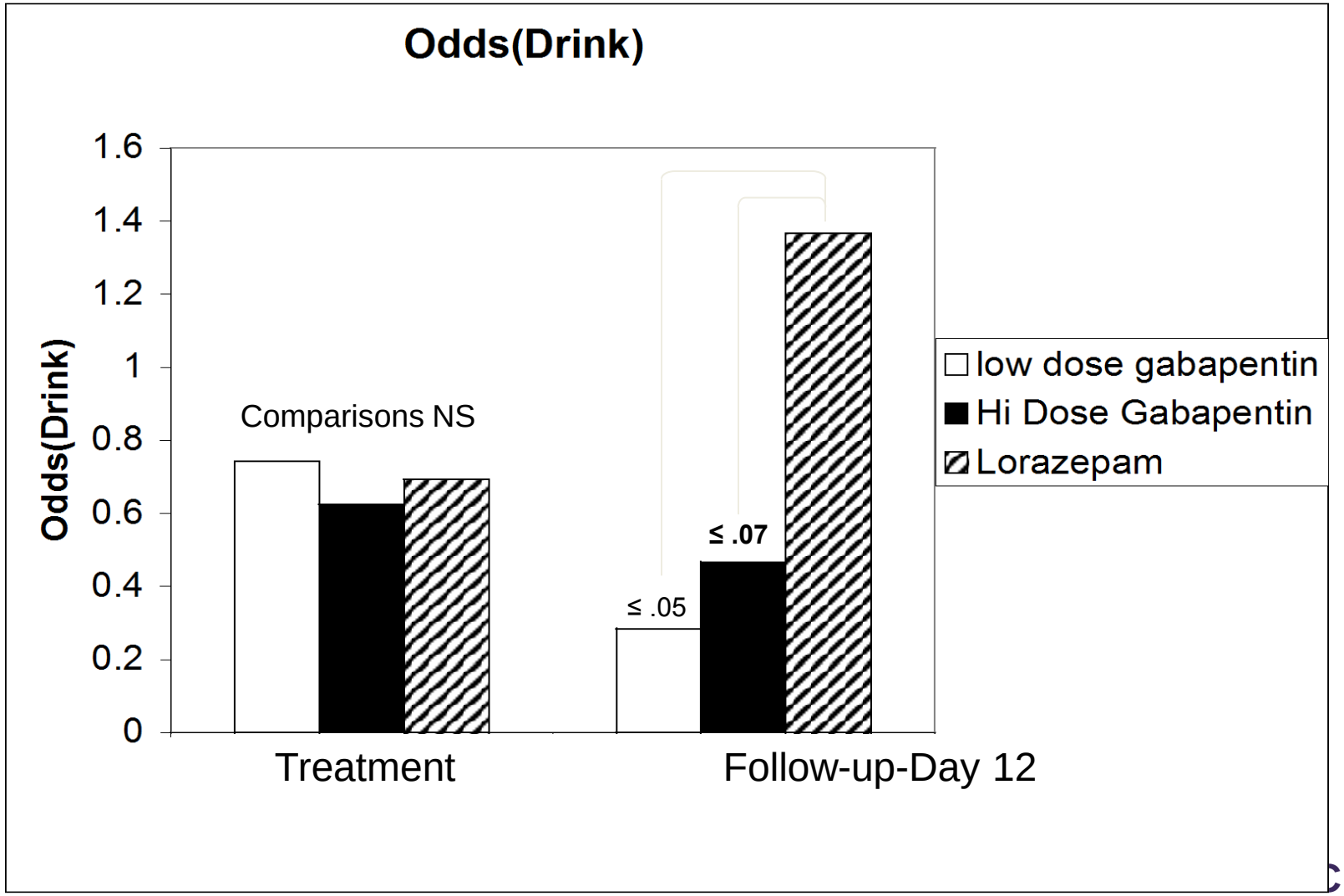
GABAPENTIN VS. LORAZEPAM IN ALCOHOL WITHDRAWAL

- Double-blind, outpatient trial (n=101)
- CIWA-AR ≥ 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



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

Gabapentin treatment for alcohol dependence: a randomized clinical trial

Mason BJ

DESIGN, PARTICIPANTS AND SETTING:
A 12-week, double-blind, placebo-controlled, randomized dose-ranging trial of 150 men and women with current alcohol dependence
Oral gabapentin (dosages of 0 [placebo], 900 mg, or 1800 mg/d) and concomitant manual-guided counseling.

RESULTS
Abstinence Rate
4.1% placebo group,
11.1% 900-mg group, and
17.0 % 1800-mg group (P = .04 for linear dose effect; number needed to treat [NNT] = 8 for 1800 mg).

No Heavy Drinking rate
22.5% placebo
29.6 % 900-mg group
44.7 %1800-mg group (P = .02 for linear dose effect; NNT = 5 for 1800 mg)

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

Gabapentin treatment for alcohol dependence: a randomized clinical trial

Mason BJ

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.

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Am J Psychiatry.

Gabapentin Combined with Naltrexone for the Treatment of Alcohol Dependence.

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

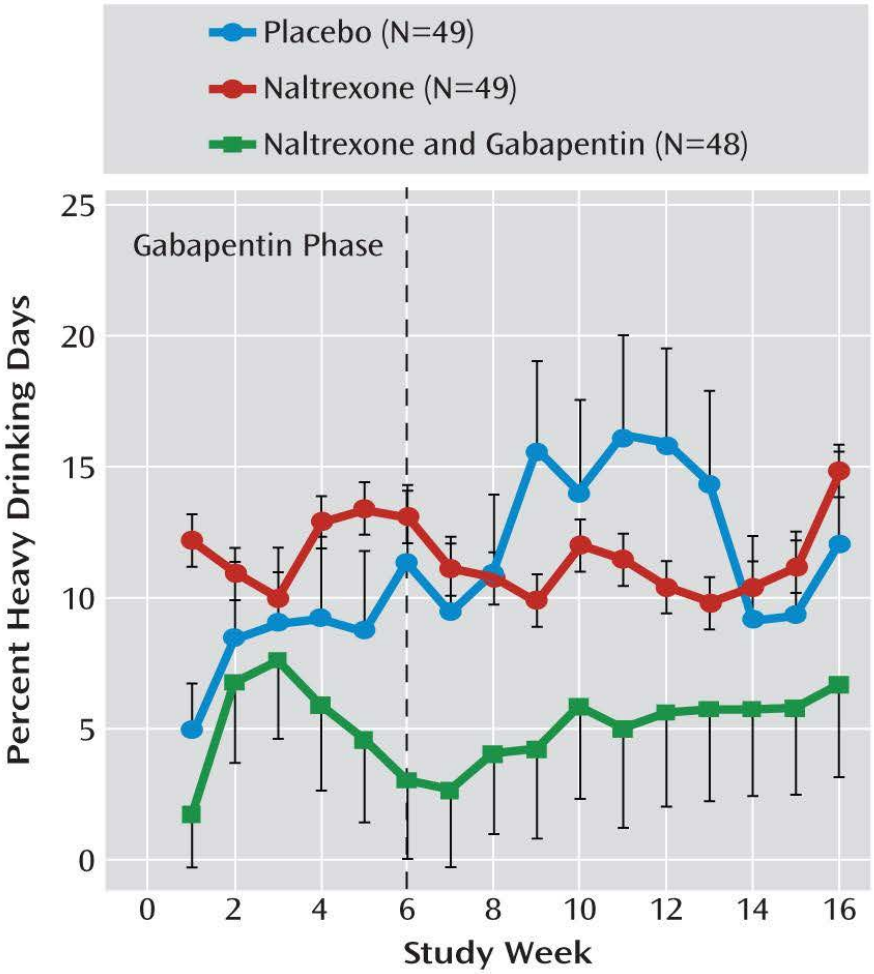
A total of 150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

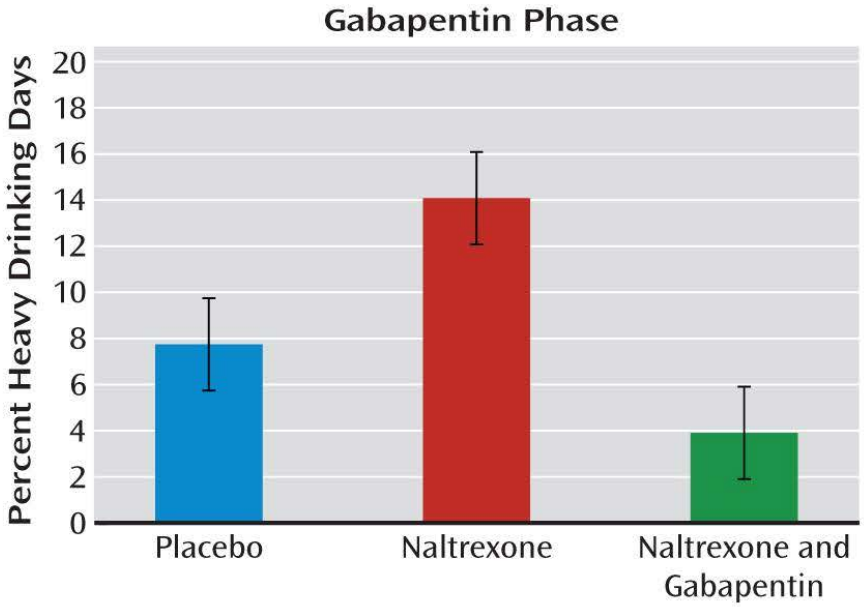
RESULTS:

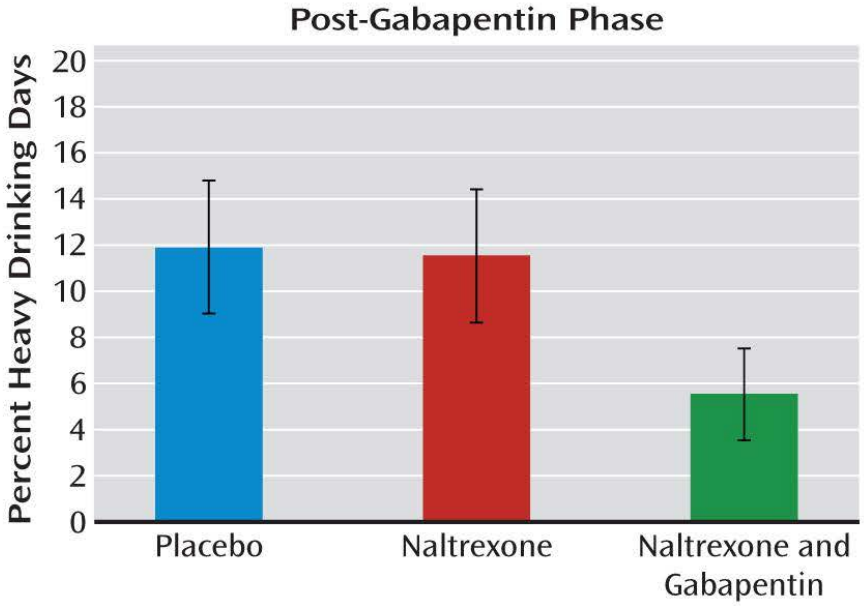
During the first 6 weeks, the naltrexone-gabapentin group had a longer interval to heavy drinking than the naltrexone-alone group, which had an interval similar to that of the placebo group;.

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.







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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 ??

JAMA Intern Med.

Gabapentin Treatment for Alcohol Dependence: A Randomized Clinical Trial.

Mason BJ Quello S Goodell V Shadan F Kyle M Begovic A

no heavy drinking rate

22.5% (95% CI, 13.6%-37.2%)

29.6% (95% CI, 19.1%-42.8%) 900-mg group,

44.7% (95% CI, 31.4%-58.8%) 1800-mg group (P = .02 NNT = 5).

Similar linear dose related effects for:

mood (F2 = 7.37; P = .001),

sleep (F2 = 136; P < .001),

craving

No group differences in serious side effects of completion rate (85 of 150 participants)

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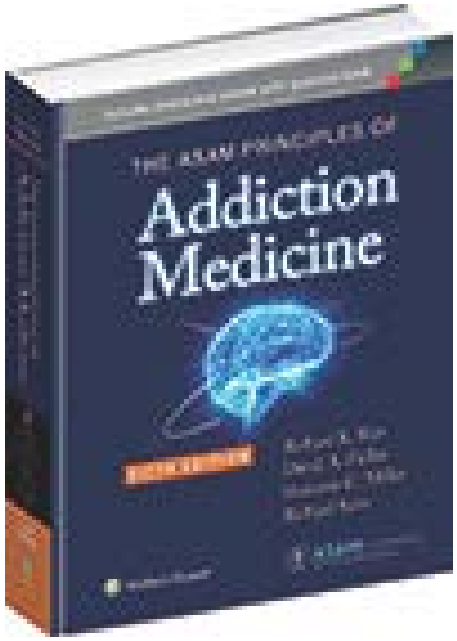
RELATIVE INDICATIONS FOR OUTPATIENT ALCOHOL DETOXIFICATION

- 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

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



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QUESTIONS ?

CASES AND CONUNDRUMS