



**UW PACC**

Psychiatry and Addictions Case Conference

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# **BENZODIAZEPINES: THE HIDDEN EPIDEMIC, PART 2**

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# GENERAL DISCLOSURES

The University of Washington School of Medicine also gratefully acknowledges receipt of educational grant support for this activity from the Washington State Legislature through the Safety-Net Hospital Assessment, working to expand access to psychiatric services throughout Washington State.

# RIES CONFLICT OF INTEREST STATEMENT

Richard Ries, MD has no financial relationships with an ACCME defined commercial interest.

# EDUCATIONAL OBJECTIVES

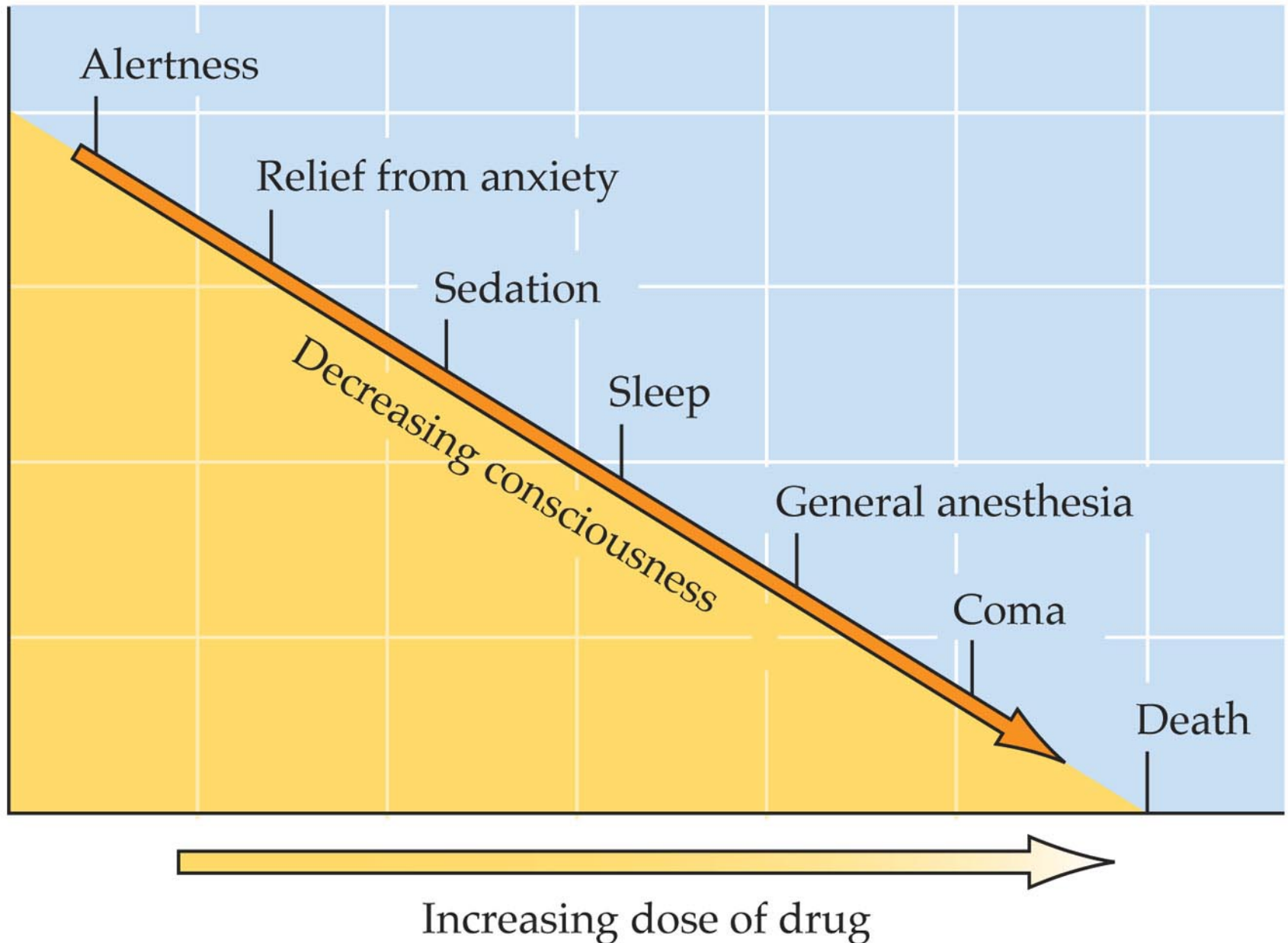
At the conclusion of this session, participants should be able to:

- ✓ Define both therapeutic and potentially harmful uses of Benzodiazepines in medical treatment
- ✓ Evaluate the risks of Benzodiazepine treatment
- ✓ Utilize alternative agents when indicated
- ✓ Differentiate toxicological urine screens utilized for Benzodiazepines

# BENZODIAZEPINE PSYCHOACTIVE EFFECTS

- Prescribed range= anti-anxiety, sedation
- Higher range= euphoria
- Intoxication ( double therapeutic range and up) similar to alcohol intoxication, loss of inhibition etc
- Higher level intoxication- ataxia, amnesia, stupor
- Delerium- impaired consciousness, nystagmus

# DOSE-DEPENDENT EFFECTS OF CNS DEPRESSANTS ON LEVELS OF CONSCIOUSNESS



# BENZODIAZEPINE: RISKS OF FALL IN ELDERLY

- Increased with short half-life BZDs (but short half-life confounds potency with half-life)
- Increased with high dose
- Falls also increased with SSRIs for unclear reasons (odds ratio 1.8)<sup>1</sup>
- SSRI fall rate close to that of BZDs in one study<sup>2</sup>

**BZDs=benzodiazepines; SSRIs=selective serotonin reuptake inhibitors.**

<sup>1</sup>Thapa PB et al. *N Engl J Med.* 1998;339:875-882.

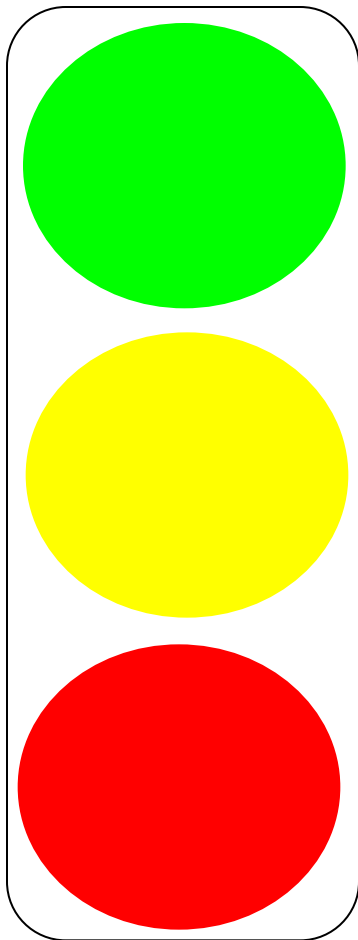
<sup>2</sup>Mendelson WB. *Sleep.* 1996;19:698-701.

# BENZODIAZEPINES: COGNITIVE EFFECTS

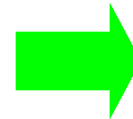
- Anterograde amnesia (new learning)
- Not retrograde amnesia (old information)
- Not procedural learning
- Unrelated to sedation
- Worse with high potency
- Transient global amnesia with triazolam
- Nighttime amnestic bingeing with Z-drugs



# DETERMINING IF BENZODIAZEPINE USE IS SAFE OR RISKY (DUPONT)

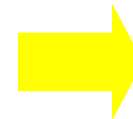


Green light zone:  
1/2 or less of  
maximum dose  
listed in PDR



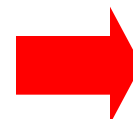
Nonaddictive patients  
with anxiety take  
benzodiazepines at  
low and stable doses

Yellow light zone:  
1/2 up to maximum  
dose listed in PDR



Not many  
anxious patients  
in this zone

Red light zone:  
above maximum  
dose listed in PDR



Addictive patients  
reach this zone of  
dosing very quickly

# TOTAL 24-HOUR DOSE LEVELS FOR THE MOST COMMONLY USED BENZODIAZEPINES

	Green Light Zone	Yellow Light Zone	Red Light Zone
Lorazepam	Up to 5 mg/d	> 5 mg up to 10 mg/d	> 10 mg/d
Clonazepam	Up to 2 mg/d	> 2 mg and up to 4 mg/d	> 4 mg/d
Diazepam	Up to 20 mg/d	> 20 mg up to 40 mg/d	> 40 mg/d
Alprazolam	Up to 2 mg/d	> 2 mg up to 4 mg/d	> 4 mg/d
Alprazolam XR	Up to 3 mg/d	> 3 mg up to 6 mg/d	> 6 mg/d

# PRESCRIPTION USE BEHAVIOR QUESTIONNAIRE

....DISCRIMINATED BETWEEN TWO GROUPS

- Use *more* than prescribed
- Use *more often* than prescribed
- Called for *early refills*
- Rx obtained from *>> 1 physician/doctor* shopping
- Use *when feeling upset*
- Used to *get high* or for euphoria

# URINE TOXICOLOGY IN MONITORING (CONT.)

## Test for what you're seeking:

- Immunoassays typically miss synthetics, semi-synthetics – SO ASK FOR THEM!
- GC/MS detects these
- May need to specify compounds sought (e.g. methadone)

## Use “therapeutic drug monitoring” codes:

- e.g., treat the test clinically like a Digoxin or aminophylline level.

# SO WHAT DO WE DO FOR SLEEP IN ACTIVE OR RECOVERING PERSONS WITH ALCOHOL DEPENDENCE ?

- *And why is this important?*

# **Insomnia, Self-medication, and Relapse to Alcoholism.** Continued

Brower KJ, Aldrich MS, Robinson EA, Zucker RA, Greden JF.

**Compared to patients without insomnia, patients with insomnia were more likely to report frequent alcohol use for sleep (55% versus 28%)**

**Among 74 alcoholics who were followed a mean of 5 months after treatment,**

**-60% with baseline insomnia  
versus**

**-30% without baseline insomnia**

**relapsed to any use of alcohol, a significant difference.**

[Sleep](#). 2011 Oct 1;34(10):1327-34.

## **Next-Day Effects of Ramelteon (8 mg), Zopiclone (7.5 mg), and Placebo on Highway Driving Performance, Memory Functioning, Psychomotor Performance, and Mood in Healthy Adult Subjects.**

[Mets MA](#),

### **CONCLUSIONS:**

**Ramelteon (8 mg) and zopiclone (7.5 mg) significantly impaired driving performance, cognitive, memory, and psychomotor performance the morning following bedtime administration.**

In contrast to zopiclone, ramelteon produced no balance impairments.

# Comparison of the Fatal Toxicity index of Zopiclone with Benzodiazepines.

[Reith DM](#), [Fountain J](#), [McDowell R](#), [Tilyard M](#).

RESULTS: Of the 200 poisoning deaths in NZ for 2001

The fatal toxicity for zopiclone was not significantly different from that for benzodiazepines as a group when adjusted for usage,

Whereas alprazolam and chlormethiazole had greater toxicity.

Hypnotosedatives are contributory factors rather than primary substances in poisoning deaths.



[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:**

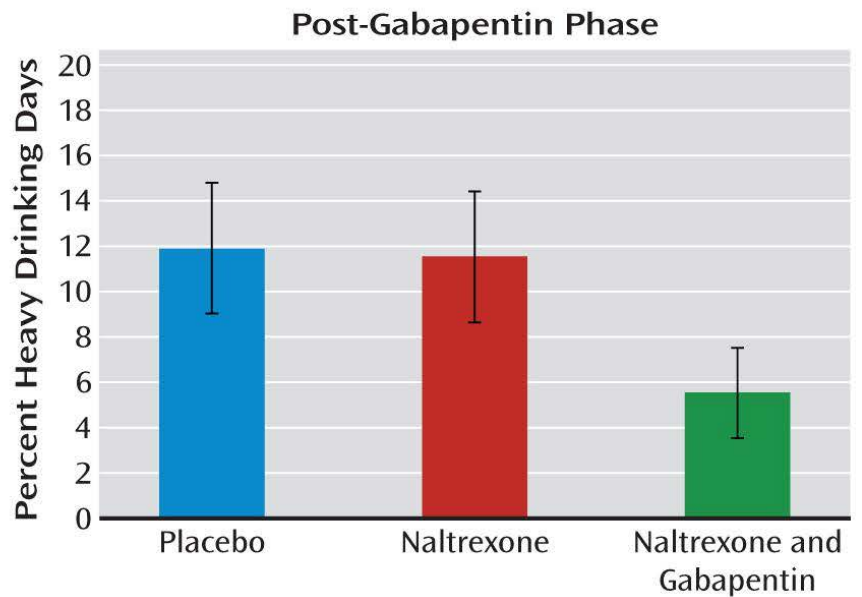
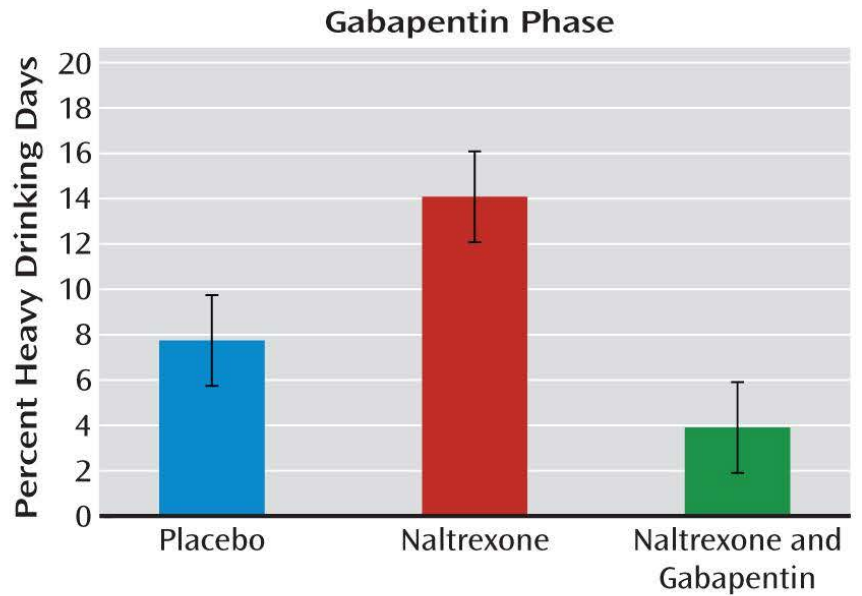
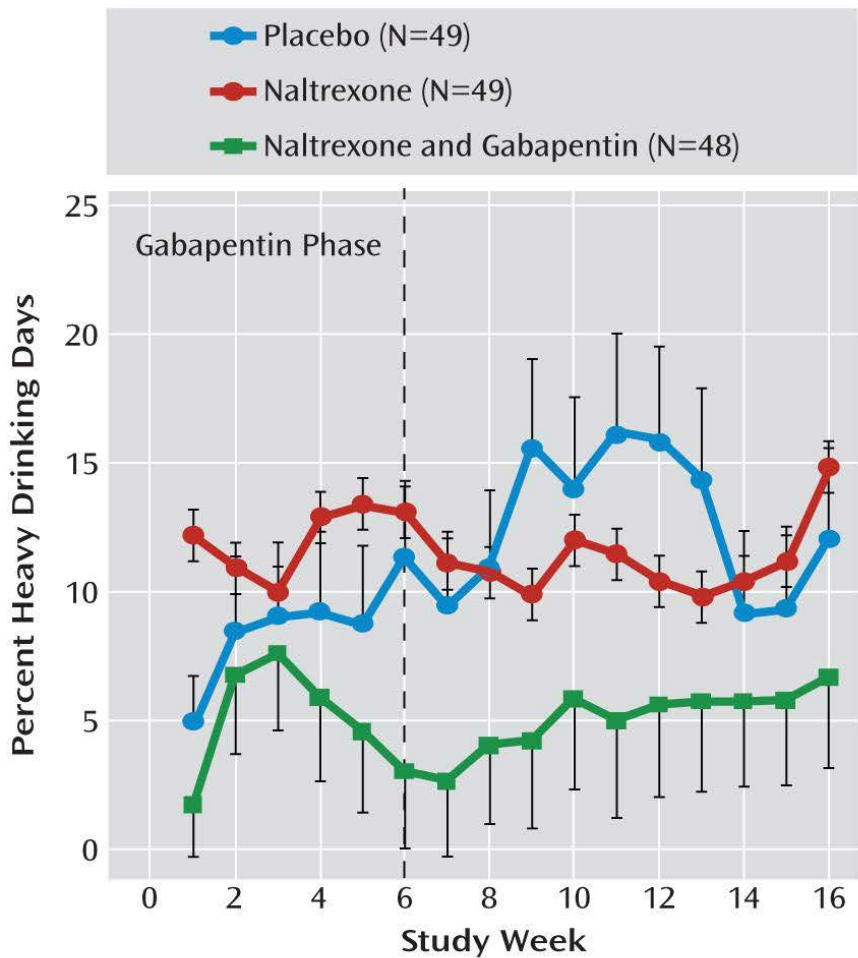
150 alcohol-dependent individuals were randomly assigned to a 16-week course of naltrexone alone (50 mg/day [N=50]), naltrexone (50 mg/day) with gabapentin (up to 1,200 mg/day [N=50]) added for the first 6 weeks, or double placebo (N=50). All participants received medical management.

### **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.**



# 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 outperformed Lorazepam-

Reducing anxiety (p = 0.0007)

Improving sleep (p = 0.0186)

# BZP WITHDRAWAL

- Like alcohol withdrawal, but variable in terms of length- longer for longer acting agents
- More likely to have Seizures
- Rebound and recurrence of Anxiety or sleep disorders
- Taper over Months, vs Crash 3 DAY WD using Anticonvulsants ( Depakote, Carbamazepine GabaPenting

# BENZODIAZEPINE DISCONTINUATION: TREATMENT FACTORS

- Duration of use (6 months vs 1 month)
- Dose
- Rate of taper
- Half-life

## 1. **Taper over Months:**

1. Convert to longer acting agent like Clonazepam or Diazepam
2. Taper gradually while starting alternative therapies if needed ( months)
3. Rebound Psych meds for Anxiety/Sleep

## 2. **Use of Anticonvulsants:**

### **Use of anticonvulsants in benzodiazepine withdrawal.**

- Pages KP, Ries RK: Use of anticonvulsants in benzodiazepine withdrawal. American Journal on Addictions 7(3):198-204, 1998.

- Ries RK et al; Journal of Psychoactive Drugs 23(1):73-76, 1991.

1. Start high dose Depa or Carba, or Gaba
2. Taper Benzo by 1/3 each day til DC
3. Continue Anticonvulsant for at least one month, longer better.
4. Check level of Depa and Carba after a week or two
5. Start SSRI's or other for Dep/Anxiety

# Use of Anticonvulsants in Benzodiazepine Withdrawal.

- Pages KP, Ries RK: Use of anticonvulsants in benzodiazepine withdrawal. American Journal on Addictions 7(3):198-204, 1998.
- Ries RK et al; Journal of Psychoactive Drugs 23(1):73-76, 1991.

1. Start high dose Depakote 500 tid  
or Carbamazepine 200 tid,  
or Gabapentin 800 tid
2. Taper Benzo by 1/3 each day til DC
3. Continue Anticonvulsant for at least one month, longer better.
4. Check level of Depa and Carba after a week or two
5. Start SSRI's or other for Dep/Anxiety
6. If dependent on only short acting agents- alprazolam etc, might use a one day conversion to clonazepam or diazepam then taper 1/3<sup>rd</sup> dose each day

These are case series NOT RCT's

# Withdrawal from Long-term Benzodiazepine use: randomised trial in Family Practice

. Vicens C, Fiol F, Llobera J et al.,

Mallorca, Spain. domicatrin@telefonica.net Comment in Br J Gen Pract. 2007 Mar;57(536):246.

--METHOD: Adult patients (n = 139) taking benzodiazepines daily for more than a year and visited by their family physician were randomised into

an intervention

biweekly support and taper vs “standard clinical management”

--RESULTS: Discontinued BZP's After 12 months,

**45.2%** patients in the intervention group and

**9.1%** in the control group

had discontinued benzodiazepine use;

**relative risk = 4.97 - ie very effective**



# Effects of Pregabalin on Subjective sleep disturbance symptoms during withdrawal from long-term Benzodiazepine use.

Rubio G, Bobes J, Cervera G, Terán A, Pérez M, López-Gómez V, Rejas J. Department of Psychiatry, University Hospital 12 de Octubre, Centro de Investigación Biomédica en Red dSalud Mental (CIBERSAM), Madrid, Spain. gabrielrubio@med.ucm.es

RESULTS: 282 patients were included in the analysis.

--Mean ( $\pm$ SD) pregabalin dose was  $315 \pm 166$  mg/day

Decreased Insomnia scores

**Pregabalin**  $55.8 \pm 18.9$  t

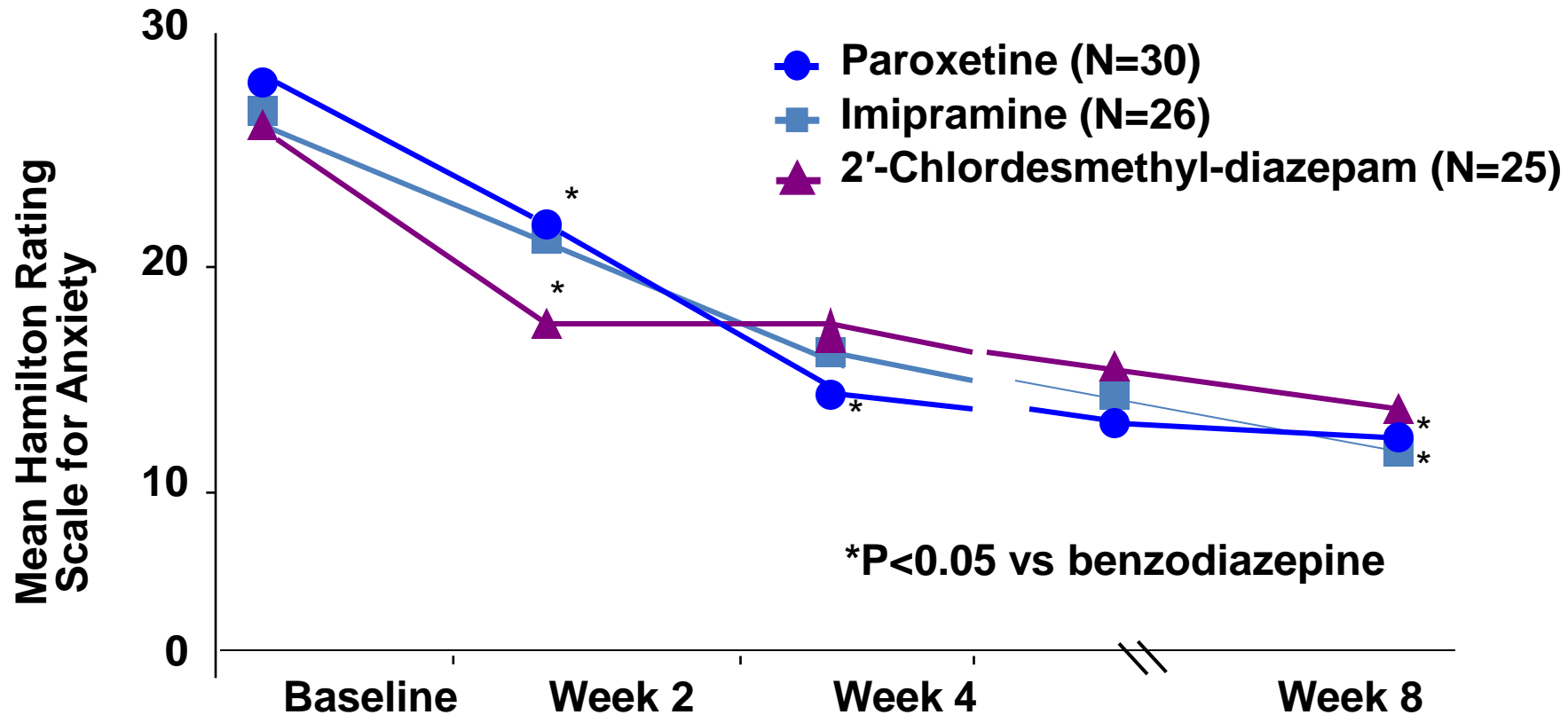
**Placebo**  $25.1 \pm 18.0$  at week 12

-- improvements in anxiety symptoms and disease severity.

# What do you do about the

# Co-occurring psychiatric disorder

# PAROXETINE, IMIPRAMINE, BENZODIAZEPINE IN GAD

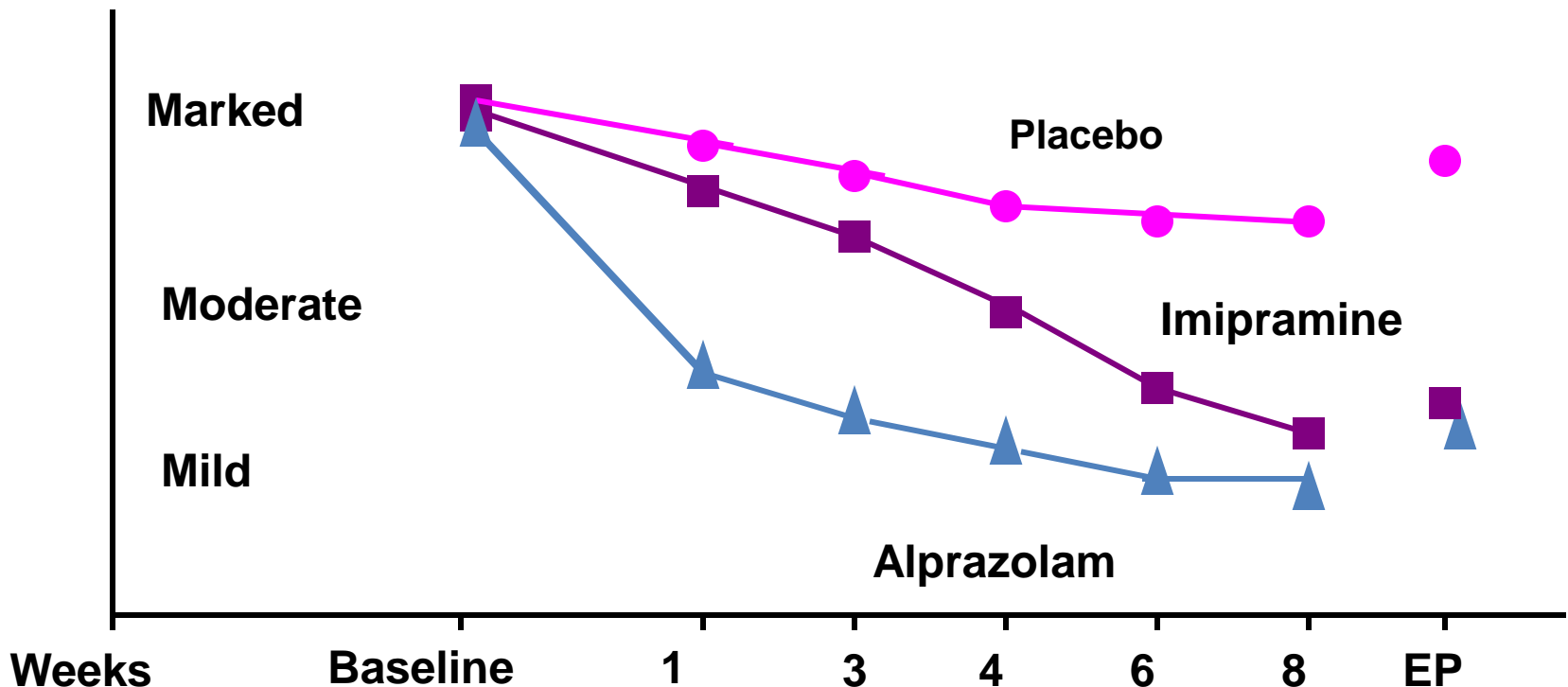


GAD=generalized anxiety disorder.

Rocca P et al. *Acta Psychiatr Scand.* 1997;95:444-450.

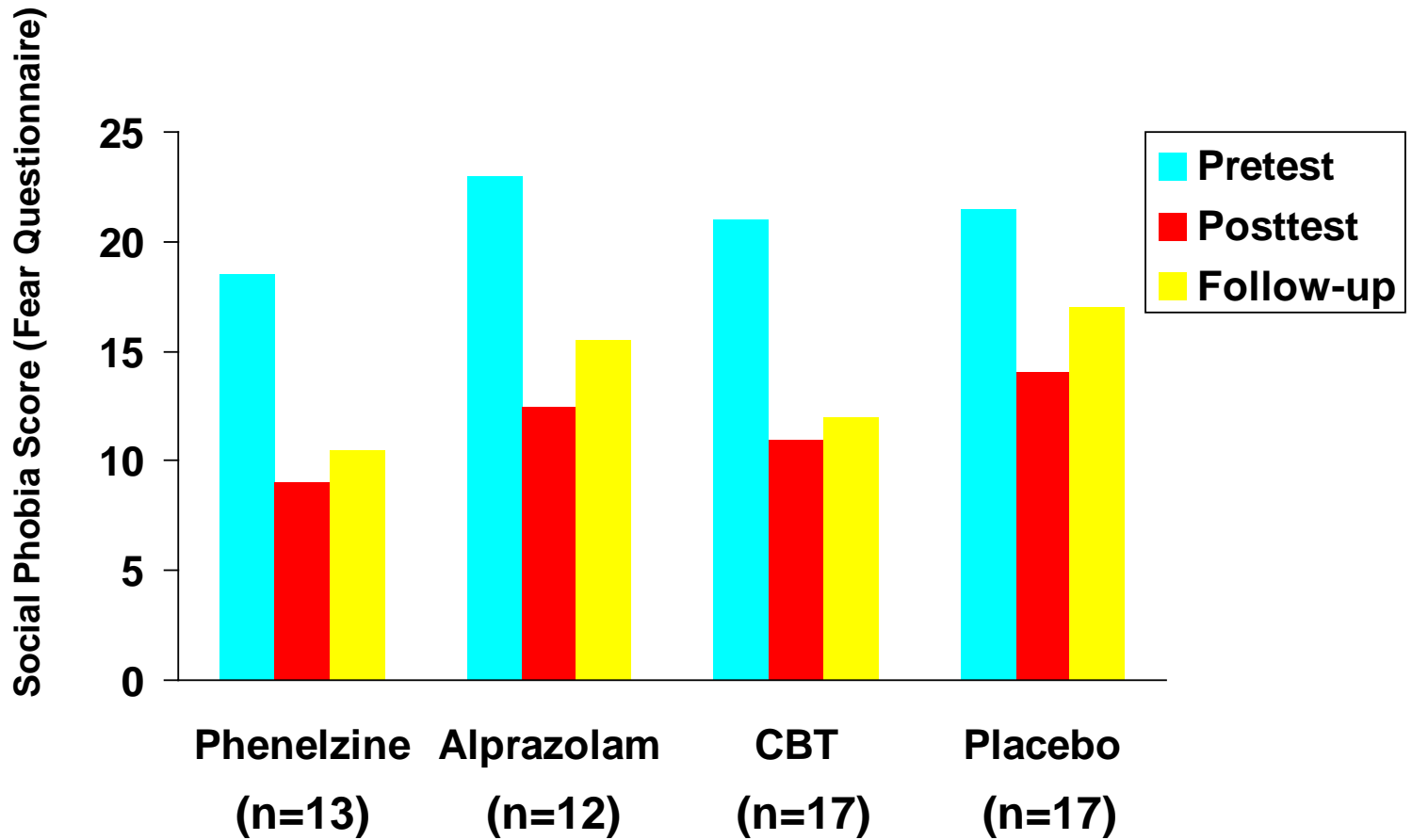
# PHASE II CROSS-NATIONAL COMPARISON OF ALPRAZOLAM, IMIPRAMINE, AND PLACEBO (N=1080)\*

## Clinical Outcome Measures



\*Global improvement, panic attacks, anticipatory episodes, overall phobia, work, social and leisure life disability, depression (Hamilton Depression Scale, not Symptom Checklist 90) all significantly different between both drugs and placebo (de la Fuente, APA, 1988).

# SOCIAL PHOBIA: PHENELZINE, ALPRAZOLAM, CBT, AND PLACEBO



CBT=cognitive-behavioral therapy.

Gelernter CS et al. *Arch Gen Psychiatry*. 1991;48:938-945.

# BENZO'S THE HIDDEN DRUG

- While there are hundreds of recent articles on Prescription Opiate problems-
- Most literature on Benzo Abuse/Dependence is > 10 years old
- Toxicology studies of Opiate deaths usually find Benzo's too –respiratory depression is additive.
- Sales of Benzo's have increased dramatically along with Opioids
- Simple Tox screens often miss Clon- and Alprazolam
- Benzo withdrawal is among the most dangerous, and can occur behind or on top of other drugs and can be missed

# CASE STUDY

- Ben was admitted acute and emergent to a psychiatry inpatient unit for combined suicidal plans ( jumping off bridge- caught by police in act) and alcohol dependence
- His Blood Alcohol ( BAL) on admission was 245, and ER point of care tox screen (cup) was negative for the NIDA 5 drugs. He had a history of suicide attempts and at least one detox from alcohol, at least one seizure, and possible dx of Bipolar. He says he was only drinking for a week.
- After his alcohol level dropped and he began to show withdrawal he was treated with CIWA protocol for 2 days with lorazepam, vitamins etc. Lorazepam stopped.
- 3 days after admit he began to become much more anxious, agitated, BP and pulse much increased

# Most likely differential diagnosis of the new agitated state would be

- A. Social Anxiety Disorder
- B. Suicidal intensity
- C. Psychosis/Mania from possible Bipolar
- D. Amphetamine psychosis
- E. Extended Alcohol Withdrawal or Benzodiazepine Withdrawal



**A specific benzo screen was done and showed clonazepam, he was asked about this and reported long term street use of clonazepam- 6-10 mg a day, last used day before admit but no clinician had asked about this.**

- This best demonstrates
  - A. Cup screens often fail to register certain Benzos
  - B. Patients are poor historians
  - C. Bipolar psychosis often mimics Benzo withdrawal
  - D. Suicidal intent in intoxicated persons causes autonomic instability
  - E. Better vital sign technology is needed.

# Best tactic now would be

- A. Start Clonazepam taper
- B. Aggressive use of Antipsychotics
- C. Aggressive use of antihypertensives
- D. Anticonvulsant loading dose with Depakote or Carbamazepine then maintenance
- E. Discharge patient for use of street drugs.

# UW PACC REGISTRATION

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## CASE PRESENTATION - #1

- Patient Information:
  - 21 year old, single, male student, in stable housing with major depressive disorder, Post Traumatic Stress Disorder , anxiety disorder (Panic?)
- Clinical Questions:
  - Choice of psychotropic agent

### Psychiatric History

- Passive SI intermittently, not currently; does not possess firearms; in the past has 'put gun to head,' as a gesture, but no real attempts
- Physical abuse by aunt (primary caregiver) in childhood

### Substance Use

- Primary Drug: MDMA, weekly use
- Also has used Alcohol and Marijuana

### PMH

- Gunshot wound s/p craniectomy 2016

### Current Meds

- Rivaroxiban
- Tylenol
- Melatonin

### Prior Meds

- none

## CASE PRESENTATION - #2

- Patient Information:
  - 62 year old divorced female, in stable housing, on disability
  - PTSD with significant avoidance, isolation, panic symptoms
  - Major Depression
  - Question of dependent/avoidant personality traits
- Clinical Questions:
  - Polypharmacy help
  - Tapering benzo in someone on it for yrs who is in her 60's

### Psychiatric History

- has passive SI, no clear hx of attempts
- PTSD in 1989 after she was held up at gun point when she worked in a bank (prior robberies before 1989)
- Her psychiatrist later killed herself
- Her husband who worked in law enforcement was physically abusive
- Child sexual abuse from step grandfather
- DV abuse including alleged assault that led to ICU trip for splenectomy,

### Substance Use

- Primary Drug: Prescribed Opiates; overuse was w/ prescribed meds
- Benzodiazepines: 0.5mg BID Clonazepam currently for past few yrs; daily use for anxiety. Ataxia Anxiety not improving or functioning (PTSD, agoraphobia, social phobia)
- Current daily nicotine use
- Unknown, but likely stimulant use

### PMH

- Chronic pain (back w/ radiculopathy, shoulder)
- Weakness of Bilateral legs
- Ataxia (since 2015)
- Dizziness
- Vit D deficiency
- HTN
- COPD
- Hyponatremia
- Nicotine Dependence
- Osteoporosis
- Asplenia
- HSV

### Current Meds

- Clonazepam 0.5mg BID
- Duloxetine 60mg daily
- Propranolol 80mg TID
- Trazodone 150mg qhs
- Gabapentin 600mg TID
- Buspirone 30mg TID
- Prazosin 2mg qhs
- Hydrocodone
- Methocarbamol
- QVAR
- Amlodopine
- Nabumetone
- Acyclovir
- ProAir
- Atrovent
- Flonase

### Prior Meds

- Diazepam
- Lorazepam
- Aripiprazole
- Lithium
- Lamotrigine
- Nortriptyline 150mg
- Bupropion
- Sertraline
- Mirtazapine
- Rozerem
- Varenicline
- Adderall 30mg TID (problems w/ memory stopped by previous psych)
- also Baclofen
- Tramadol
- Flexeril