**UW PACC**

Psychiatry and Addictions Case Conference

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# BENZODIAZEPINES:

# THE HIDDEN EPIDEMIC


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UW Medicine
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Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

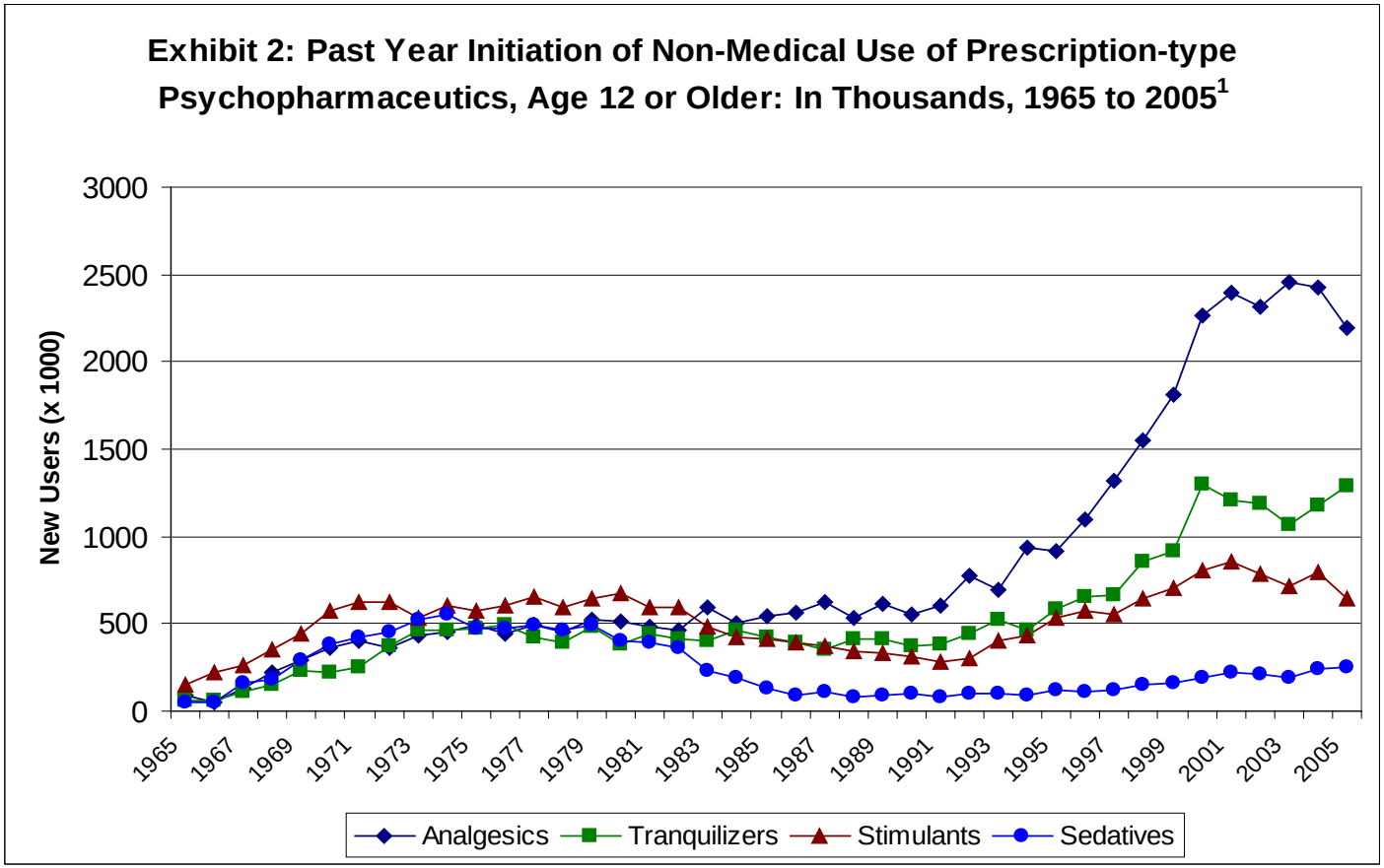
# EDUCATIONAL OBJECTIVES

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

# MEDICAL INDICATIONS FOR USE

- Anxiolytic – chronic / phobic anxiety & panic attacks
- Sedative and hypnotic – sleep disturbance & anaesthesia / premed
- Anticonvulsant – status epilepticus, myoclonic & photic epilepsy
- Muscle relaxant – muscle spasm / spasticity
- Alcohol withdrawal.




# While Opiates have grown fastest, Benzos are not far behind

**Source: SAMHSA, OAS, NSDUH data , July 2007**

Journal of Analytical Toxicology, Volume 27, Number 2 March 2003

# Oxycodone Involvement in Drug Abuse Deaths: A DAWN-Based Classification Scheme Applied to an Oxycodone Postmortem Database Containing Over 1000 Cases*

**Authors:** Cone E.J.[1]; Fant R.V.[1]; Rohay J.M.[1]; Caplan Y.H.[2]; Ballina M.[3]; Reder R.F.[3]; Spyker D.[3]; Haddox J.D.

Of 1014 cases:

- 30 (3.3%) involved oxycodone as the single reported chemical entity; of these,

- The vast majority (N = 889**, 96.7%)** were multiple drug abuse deaths

The most prevalent drug combinations were oxycodone in combination **with benzodiazepines**, alcohol, cocaine, other narcotics, marijuana, or antidepressants.

# Table 1. ED visits involving nonmedical use of selected pharmaceuticals

| Drug | Estimated visits | | 95% CI | |
|---|---|---|---|---|
| | Number | Percentage | Lower bound | Upper bound |
| **Opiates/opioids** | 172,726 | 32.2% | 136,497 | 208,956 |
| Oxycodone/combinations | 41,701 | | 28,915 | 54,487 |
| Hydrocodone/combinations | 39,844 | | 30,154 | 49,535 |
| Methadone | 38,806 | | 28,151 | 45,461 |
| **Benzodiazepines** | 143,546 | **26.8%** | 110,329 | 176,764 |
| Alprazolam | 46,526 | | 33,960 | 59,091 |
| Clonazepam | 28,178 | | 21,721 | 34,635 |
| **Muscle relaxants** | 25,934 | 4.8% | 19,647 | 32,221 |
| Carisoprodol | 14,736 | | 10,047 | 19,426 |
| Cyclobenzaprine | 6,183 | | 4,430 | 7,935 |
| All ED visits involving nonmedical use of pharmaceuticals | 536,247 | 100.0% | 448,688 | 623,806 |

Note: CI = confidence interval.
Source: Office of Applied Studies, SAMHSA, Drug Abuse Warning Network, 2004 (03/2008 update).



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Original Investigation | December 17, 2014

# Benzodiazepine Use in the United States

Mark Olfson, MD, MPH[1,2]; Marissa King, PhD[3]; Michael Schoenbaum, PhD[4]

**Design, Setting, and Participants** A retrospective descriptive analysis of benzodiazepine prescriptions was performed with the 2008 LifeLink LRx Longitudinal Prescription database (IMS Health Inc), which includes approximately 60% of all retail pharmacies in the United States. Denominators were adjusted to generalize estimates to the US population.

## Results

**In 2008, approximately 5.2% adults 18 to 80 years used benzodiazepines.**

The percentage increased with age from 2.6% (18-35 years) to 5.4% (36-50 years) to 7.4% (51-64 years) to 8.7% (65-80 years).

Benzodiazepine use was nearly twice as prevalent in women as men.

The proportion of benzodiazepine use that was long term increased with age from 14.7% (18-35 years) to 31.4% (65-80 years).

BMJ. 2014 Mar 19;348:g1996. doi: 10.1136/bmj.g1996.

# Effect of Anxiolytic and Hypnotic drug prescriptions on Mortality Hazards: retrospective cohort study.

Weich S[1], Pearce HL, Croft P, Singh S, Crome I, Bashford J, Frisher M.

## PARTICIPANTS:

34 727 patients aged 16 years and older first prescribed anxiolytic or hypnotic drugs, or both, between 1998 and 2001, and 69 418 patients with no prescriptions for such drugs (controls) matched by age, sex, and practice. Patients were followed-up for a mean of 7.6 years (range 0.1-13.4 years).

## RESULTS:

**The age adjusted hazard ratio for mortality = 3.46**

(95% confidence interval 3.34 to 3.59) and 3.32 (3.19 to 3.45) after adjusting for other potential confounders.

**Dose-response associations with mortality found for all three classes of study drugs**

(benzodiazepines, Z drugs (zaleplon, zolpidem, and zopiclone), and other drugs).

## CONCLUSIONS:

In this large cohort of patients attending UK primary care, anxiolytic and hypnotic drugs were associated with significantly increased risk of mortality over a seven year period, after adjusting for a range of potential confounders.

BMJ Open. 2012 Feb 27;2(1):e000850. doi: 10.1136/bmjopen-2012-000850. Print 2012.

# Hypnotics' association with Mortality or Cancer: a matched cohort study.

Kripke DF[1], Langer RD, Kline LE.

**SETTING:**
A large integrated health system in the **USA.**

**DESIGN:**
Subjects (mean age 54 years) were 10,529 patients who received hypnotic prescriptions and 23,676 matched controls with no hypnotic prescriptions, followed for an average of 2.5 years between January 2002 and January 2007.

**RESULTS:**
For groups prescribed

1. **0.4-18 doses/year, HRs were 3.60 increased mortality**

2. **>132 doses/year = 5.32 increased mortaliuy**

demonstrating a dose-response association

J Clin Psychiatry. 2016 May;77(5):661-7. doi: 10.4088/JCP.15m10271.

# Benzodiazepine Use and Risk of Mortality among Patients with Schizophrenia: a retrospective longitudinal study.

Fontanella CA[1], et al;

**METHODS:**

A retrospective longitudinal analysis was performed using Medicaid claims data.
18,953 patients with schizophrenia,
13,741 (72.5%) antipsychotic only
3,476 (18.3%) BZP + NO antipsychotic medication,
1,736 (9.2%) BZP plus antipsychotic
Controlling for a wide array of demographic and clinical variables, the increased

**Mortality Hazard was**

**^208% BZP without an antipsychotic (HR = 3.08 P < .001)**
**^48% higher BZP combined with antipsychotics (HR = 1.48; P = .002).**

Benzodiazepine-prescribed patients were at greater risk of death by suicide and accidental poisoning as well as from natural causes.

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J Toxicol Clin Toxicol. 2003;41(7):975-80.

# 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, 39 involved hypnosedatives, and zopiclone was involved in 12.

CONCLUSIONS: **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**. Hypnosedatives are contributory factors rather than primary substances in poisoning deaths.

# 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 are also increasing dramatically
- **Simple Tox screens often miss Clonazepam- Lor- and Alprazolam**
- **Benzo withdrawal is among the most dangerous, and can occur behind or on top of other drugs and can be missed**

PAIN PHYSICIAN. 2010 JAN;13(1):71-8.

# COMPARISON OF CLONAZEPAM COMPLIANCE BY MEASUREMENT OF URINARY CONCENTRATION BY IMMUNOASSAY AND LC-MS/MS IN PAIN MANAGEMENT POPULATION.

WEST R, PESCE A, WEST C, CREWS B, MIKEL C, ALMAZAN P, ROSENTHAL M, LATYSHEV S.

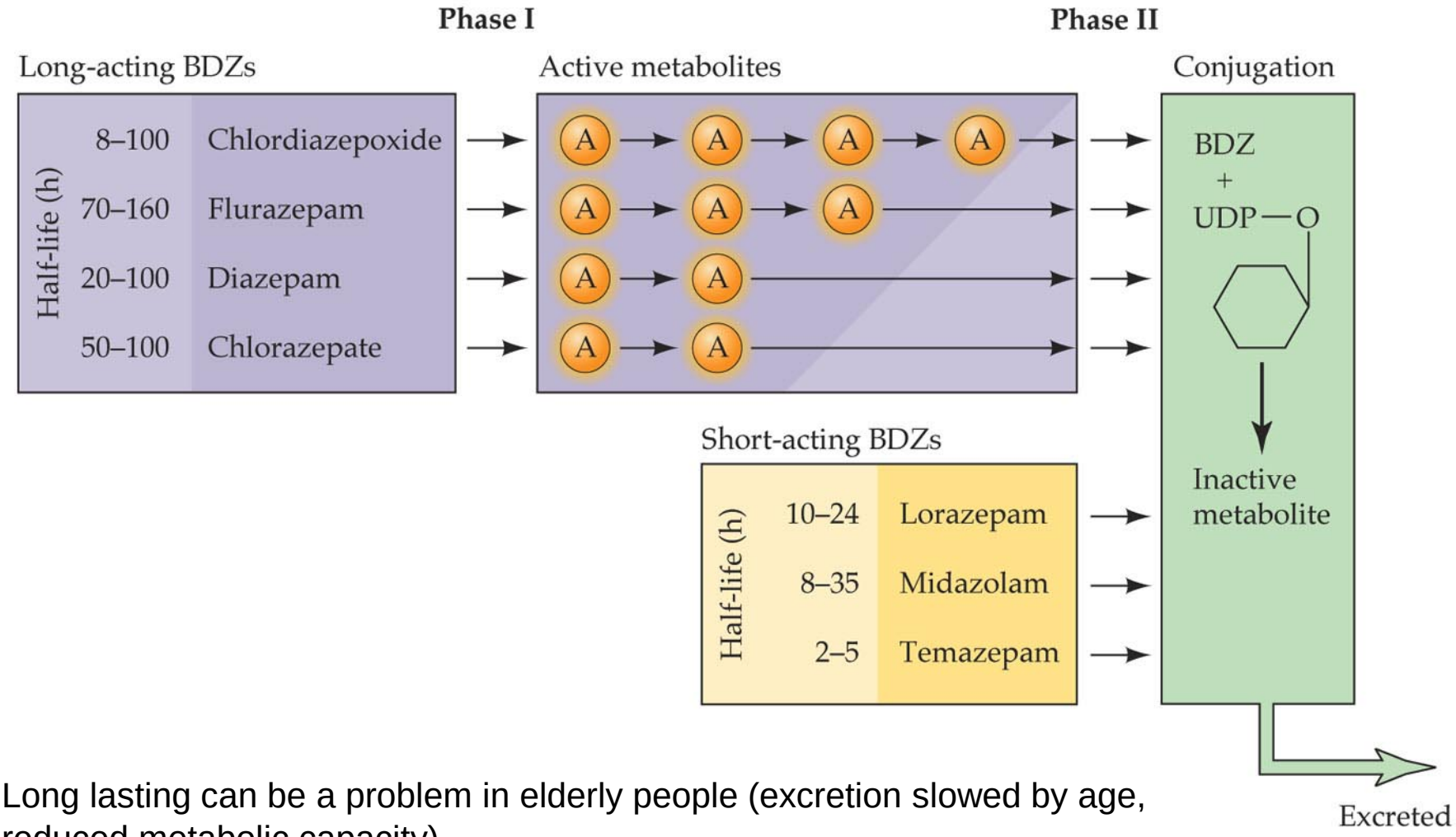
Samples from 180 patients taking clonazepam met these medication criteria

> Positivity rates were 21% (38 samples) by immunoassay ( cups) .

>The positivity rate was 70% (126 samples) if the LC-MS/MS cutoff was set at 200 ng/mL. (chromatography)

>Positivity rate was 87% (157 samples) if the LC-MS/MS was set at 40 ng/mL.

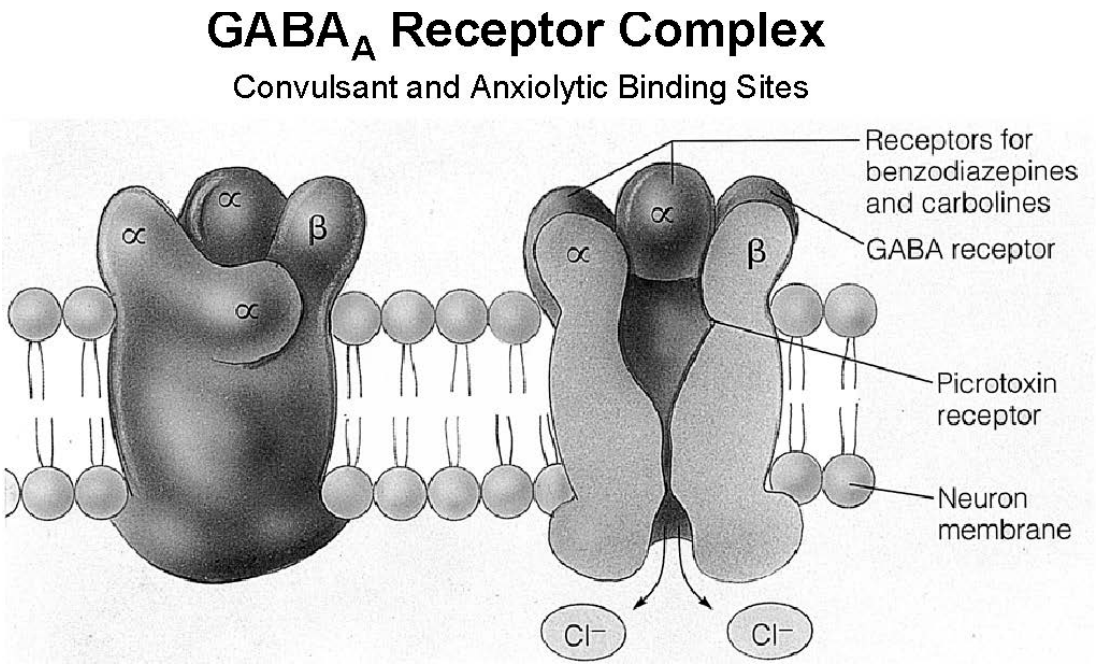
# BENZODIAZEPINE METABOLISM




Long lasting can be a problem in elderly people (excretion slowed by age, reduced metabolic capacity)

# $GABA_A$ RECEPTOR

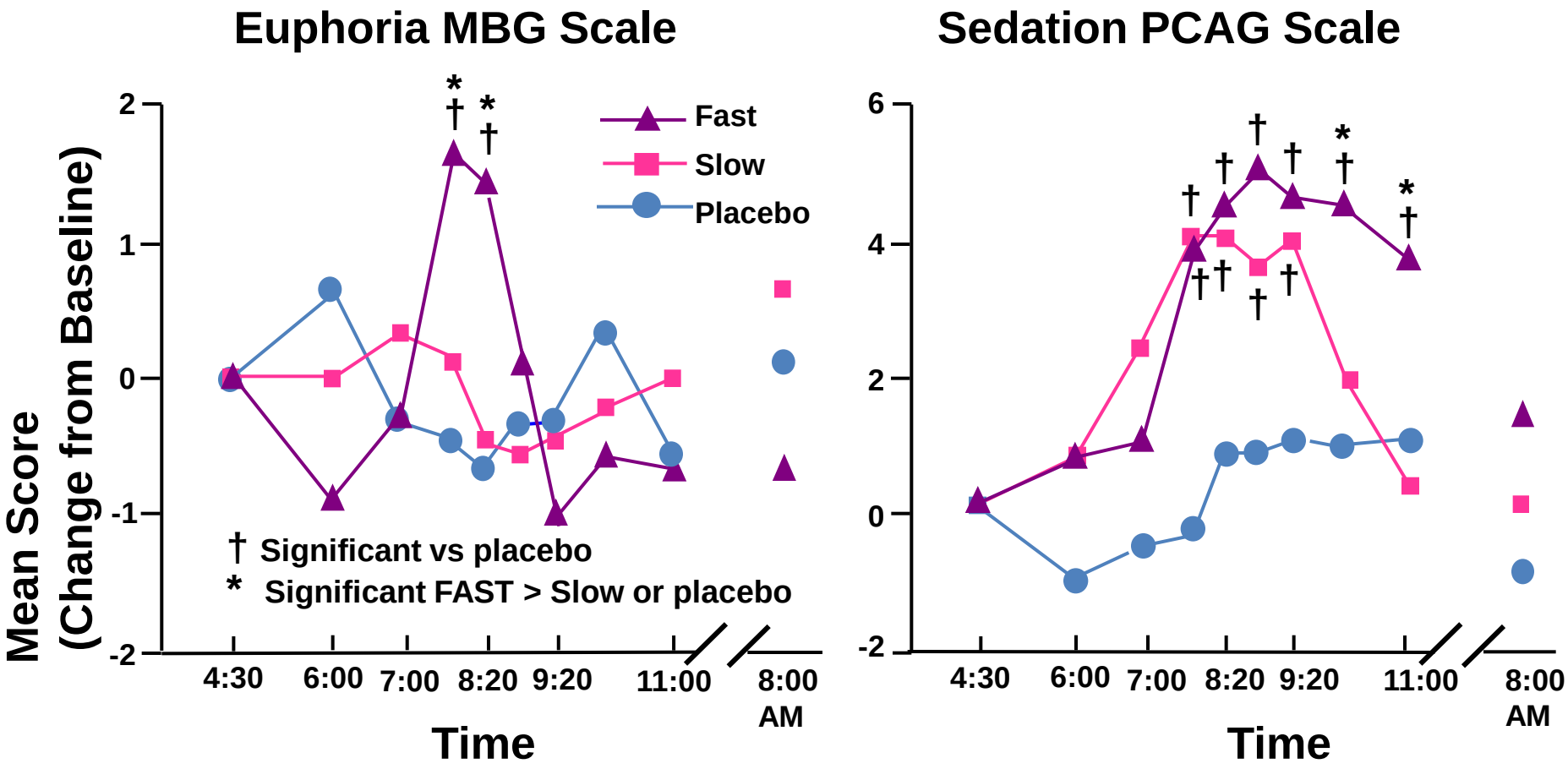
- Transmembrane pentamer composed of 2 $\alpha$, 2 $\beta$, and 1 $\gamma$ or $\delta$ subunits
  - Each has a binding site for GABA
- Benzodiazepines
  - Bind a cleft of $\alpha$ and $\gamma$ subunits
  - Increases frequency of channel opening
- Barbiturates, (propofol)
  - Bind $\alpha$ subunit
  - Increase duration of channel opening
- Agonist: muscimol
- Antagonist: bicuculine



# BENZODIAZEPINES: MAJOR ADVERSE EFFECTS

- Abuse liability
- Sedation
- Psychomotor impairment
- Cognitive impairment (retrograde amnesia)
- Physiologic dependence/withdrawal
- **Increased Death- alone or combo**

# BZD SEDATIVE AND EUPHORIC EFFECTS: DEPEND ON RATE OF PLASMA LEVEL RISE




MBG=Morphine-benzedrine group; PCAG=Phenobarbital-chlorpromazine-alcohol group.

De Wit et al. *Psychopharmacologia*. 1993;112:324-330.

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