

# Rise of Benzodiazepines

## Dangers & Answers



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# Disclosures

- Consulting for the Avisa Group
- I will be discussing "off label" use of drugs during this presentation

# Objectives

- Review Historical Perspective
- Review Problems associated with benzodiazepine use
- Review Current Standards for detoxification/deprescribing
- Review some new research challenging these standards



- "Kids are different today"
- I hear ev'ry mother say
- Mother needs something today to calm her down
- And though she's not really ill
- There's a little yellow pill
- She goes running for the shelter of a mother's little helper
- And it helps her on her way, gets her through her busy day



- That Little yellow pill that helps Mother get through her day is Valium
- Big Pharma has marketed Benzodiazepine to target women—and it worked
- We're going to review this dark history



Relative to benzodiazepines.....

We May Have Been Mislead by some  
of these “Facts”

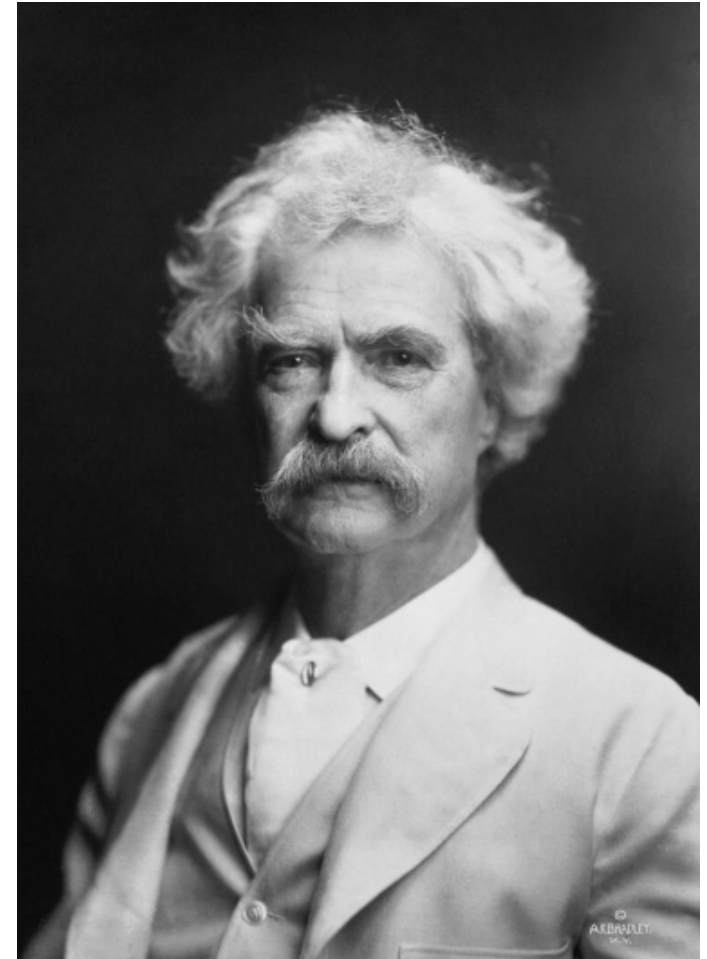
“Facts”

*“It ain't what you don't  
know that gets you into  
trouble.*

*It's what you know for  
sure that just ain't so.”*

*~ Mark Twain*

“Facts”



# What's Happening with Benzodiazepines in the modern Western World

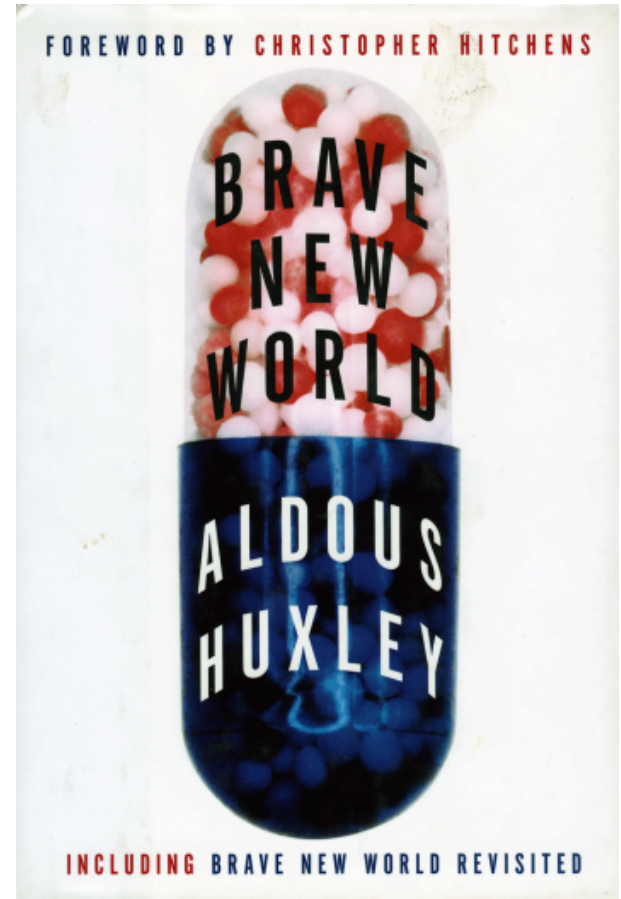
- Reminds me of



# I invite you to remember “Brave New World” – 1932



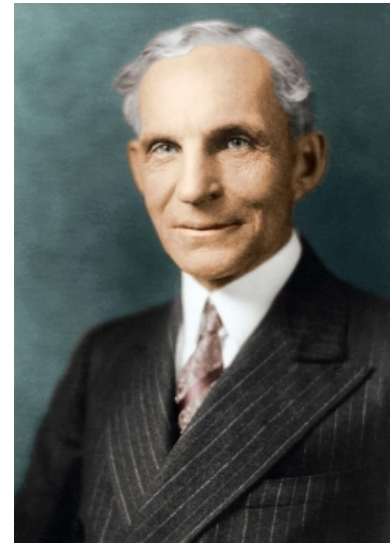
- Ponder if some sort of collective “**Psychic determinism**” has occurred.



# Brave New World- Quick Refresher

## “A Chemical Dystopia”

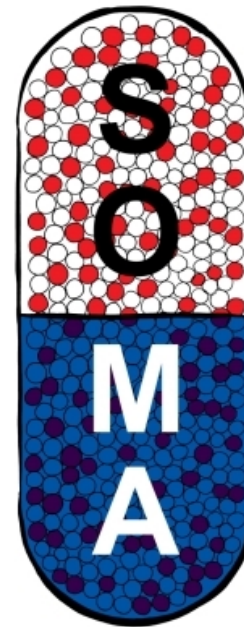
- Henry Ford is  
Worshiped as a prophet
  - Assembly Line Efficiency
  - Homogeneity
  - Predictability
  - **Everyone is Happy**  
because Soma cures all  
**Pain**



Oppression  
though  
Making  
“Happy”

# Brave New World

- Any Individual effort
  - To Create,
  - To Evolve,
  - To Change
- Is Painful
- If anyone experienced this
  - “Painful call to action”
- Given Soma



Comfortably numb

***Soma Makes Everything Acceptable***

But

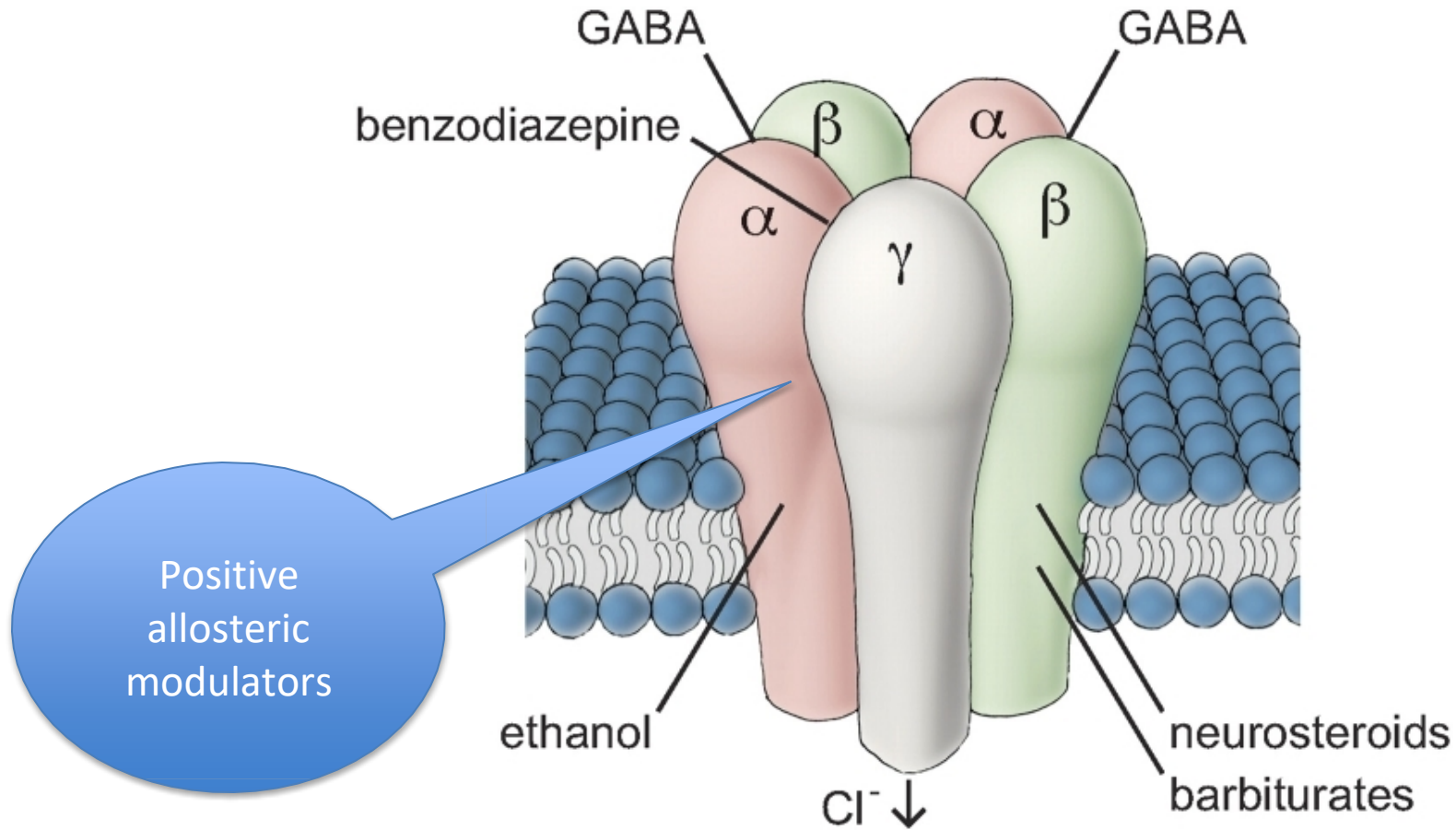
- As we know from the Architect in the Matrix,  
– **Pain has a Purpose**

- It's a Call To Action



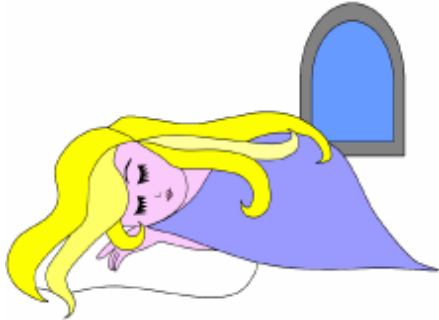


# Benzodiazepines act at the GABA Receptor





**GABA** is the primary inhibitory Neurotransmitter  
**Glutamate** is the primary excitatory neurotransmitter (acts at the NMDA Receptor)



**GABA**

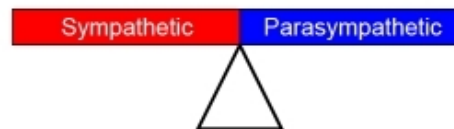
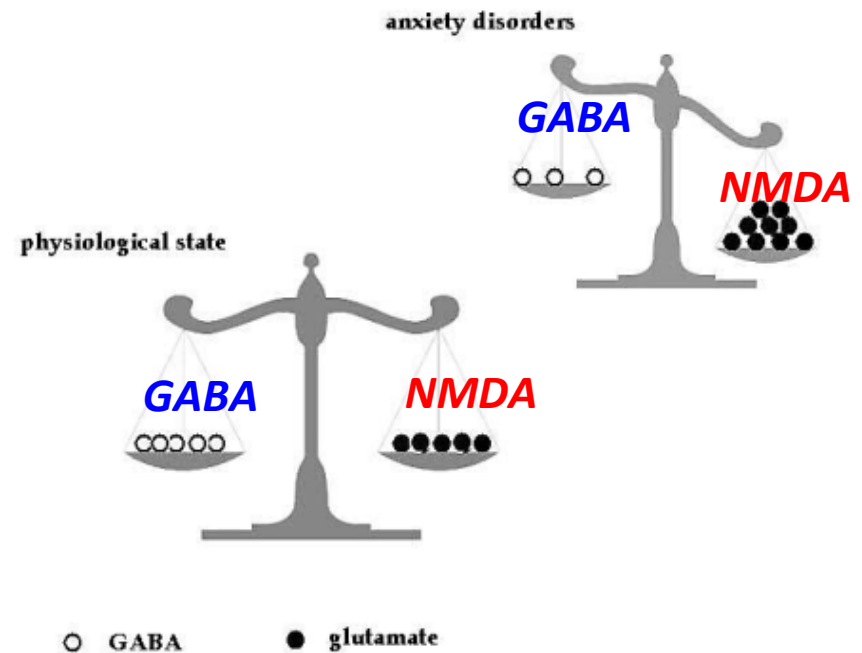


**Glutamate**

# The Balance between the Two is Key

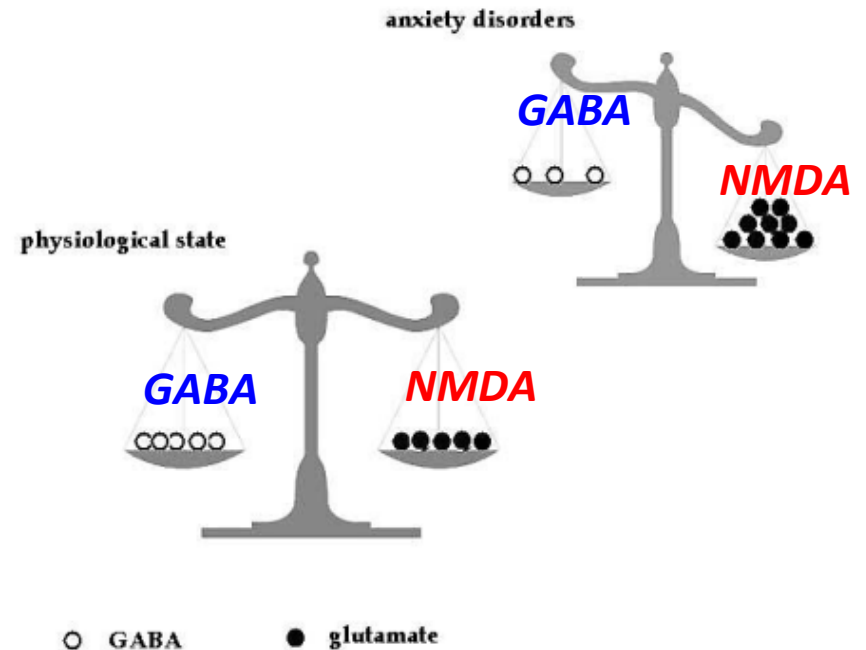
- **GABA = Inhibitory**
  - GABA<sub>A</sub>, GABA<sub>B</sub>
- **Glutamate = Excitatory**
  - AMPA, KA, NMDA

- Proper Function of the CNS depends on physiological homeostasis
  - Maintained by two opposite forces acting independently

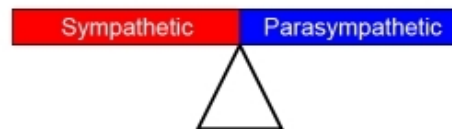


# Why is **GABA** So Important

- “GABA and Glutamate are present in practically all functions in the CNS”
- Together they Make up **90%** of all neurotransmission in the brain



- The Impact of Gabapentin Administration on Brain GABA and Glutamate Concentrations: A 7T 1H-MRS Study, Kejia Cai, Neuropsychopharmacology (2012) 37, 2764–2771



- So No Wonder why things that affect GABA like Benzodiazepines are so powerful



# Let's Face It.....

**Benzo's are powerful--& they really seem to work**

- Benzo's Seem to Dissolve Away Anxiety

Temporarily

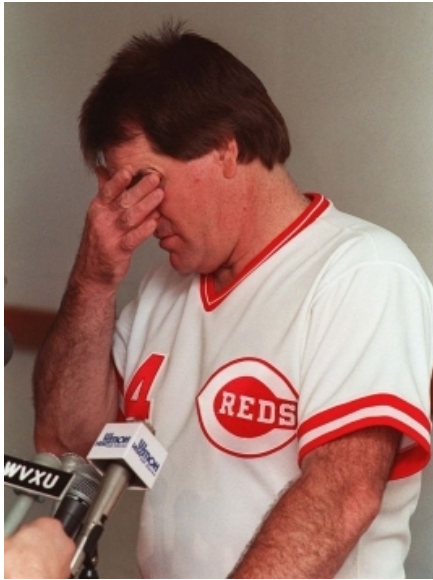
- Benzo's/Z-drugs seem to make you sleep better



**So It Can Seem Very Invalidating When I deny...**

**“It's the only thing that works!!!”**

# There's No Such Thing As A Free Lunch



- At What Cost?

# Benzodiazepines Uses

Immediately make people with **Anxiety** and **Insomnia** feel better

- **Anxiety & Insomnia**

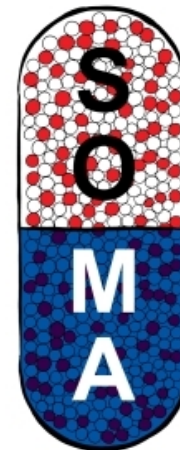
- **Anxiety** is **most** prevalent MH problem in USA

- **19%** 1 yr prevalence in adults
    - National Comorbidity Survey 2017

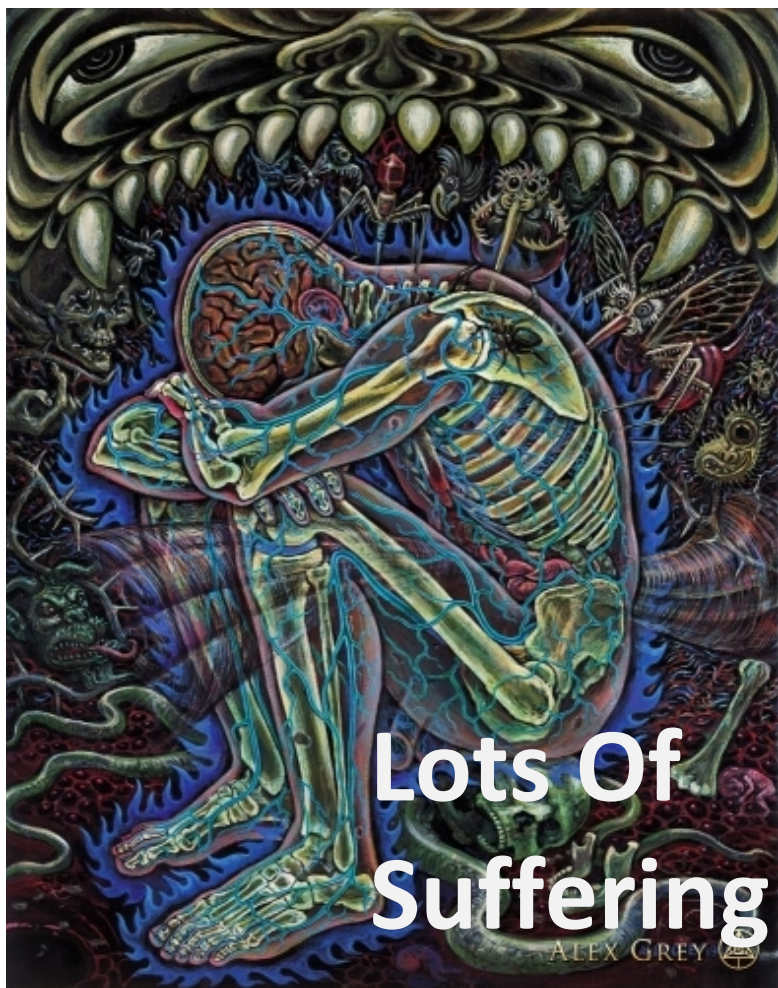
- Anxiolysis
- Muscle Relaxant
- Sedation Hypnotic
- Sleep, Anesthesia
- Anticonvulsant
- Alcohol withdrawal

- **Insomnia**

- **30%** of people report 1 or more symptoms of insomnia
      - [J Clin Sleep Med](#). 2007 Aug 15; 3(5 Suppl): S7–S10.







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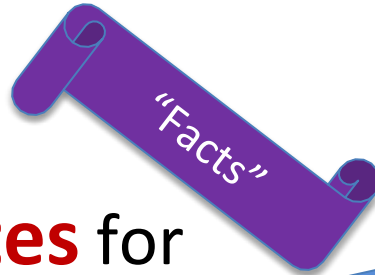


**This Is The Story Of What Happened....**



# It started with Barbiturates

- “New wonder drug **Safer than Opiates** for sleep and anxiety”



The “Facts” we were told and read in the Literature

**WHEN SHE OVERREACTS TO ANY SITUATION**

When the patient tells you that she is too “easily upset,” think of Mebaral. Overreaction to everyday occurrences may be a threat to this patient’s well-being. Mebaral reduces restlessness and irritability; it has a *familiar* sedative effect. But Mebaral has the advantage of “. . . extremely low incidence of toxicity . . .”<sup>9</sup> and does not produce *sedative daze*.<sup>2-8</sup> Often physicians prefer the sedative effects of Mebaral to those of phenobarbital.<sup>2,7-10</sup>

For daytime sedation — ½ grain, ¾ grain, and occasionally 1½ grains three or four times daily.

**MEBARAL®**  
Brand of mephobarbital

**SEDATION WITHOUT SEDATIVE DAZE**

*Bibliography:* 1. Brown, W. T., and Smith, J. A.: *South. M. J.* 46:582, June, 1953. 2. Berris, H.: *Neurology* 4:116, Feb., 1954. 3. Baker, A. B.: Personal communication. 4. Johnston, C.: *North Carolina M. J.* 8:121, March, 1947. 5. Smith, J. A.: *Am. Pract. & Digest Treat.* 4:1, July, 1953. 6. Smith, J. A.: *J.A.M.A.* 152:384, May 30, 1953. 7. Briggs, J. F.: *Minnesota Med.* 34:1082, Nov., 1951. 8. Briggs, J. F., and Bellomo, J.: *Dis. Chest* 34:96, July, 1958. 9. McCullagh, W. H.: *J. Florida M. A.* 41:718, March, 1955. 10. Cohen, B., and Myerson, A.: *New England J. Med.* 227:336, Aug. 27, 1942.

*a moth seems a monster*

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# Barbiturates

- Pharma's Early attempts to convince us we need a pill to cope

"daytime sedative" for everyday situational stress



now  
she can  
cope...

thanks to

**Butisol** SODIUM  
(SODIUM BUTABARBITAL)

"daytime sedative" for everyday situational stress

When stress is situational—environmental pressure, worry over illness—the treatment often calls for an anxiety-allaying agent which has a prompt and predictable calming action and is remarkably well tolerated. Butisol, Sodium (sodium butabarbital) meets this therapeutic need.

After 30 years of clinical use . . . still a first choice among many physicians for dependability and economy in mild to moderate anxiety.

**Contraindications:** Porphyria or sensitivity to barbiturates.

**Precautions:** Exercise caution in moderate to severe hepatic disease. Elderly or debilitated patients may react with marked excitement or depression.

**Adverse Reactions:** Drowsiness at daytime sedative dose levels, skin rashes, "hangover" and systemic disturbances are seldom seen.

**Warning:** May be habit forming.

**Usual Adult Dosage:** As a daytime sedative, 15 mg. (½ gr.) to 30 mg. (¾ gr.) t.i.d. or q.i.d.

Available for daytime sedation: Tablets, 15 mg. (½ gr.), 30 mg. (¾ gr.); Elixir, 30 mg. per 5 cc. (Grainal T-1).

**BUTICAPIN** (Capsules Butisol, Sodium (sodium butabarbital)) 15 mg. (½ gr.), 30 mg. (¾ gr.).

**McNEIL**

McNeil Laboratories, Inc., Fort Washington, Pa.



# But They Weren't Safe

## MARILYN MONROE FOUND DEAD

### Sleeping Pill Overdose Blamed

#### Red Super Bomb Kicks Off Series

High Altitude Test Reported  
as Being in 40-Megaton Range

UPPERCAL, Sweden (AP)—The Soviet Union exploded a big nuclear bomb high in the atmosphere Sunday. Swedish scientists estimated it to be in the 40-megaton range, the highest ever reported for a nuclear test. The bomb was reported to have exploded at a height of 300,000 feet, the highest ever for a nuclear test. The explosion was reported to have been a success, and the test was reported to have been the first of a series of tests. The test was reported to have been the first of a series of tests. The test was reported to have been the first of a series of tests.

#### Nixon Team at Helm of State GOP

BY RICHARD BERGHELD, Staff Political Writer  
WASHINGTON (AP)—Sen. Barry Goldwater, Republican star, has been named to head the GOP's national committee. Goldwater, who was defeated in the 1964 presidential election, will lead the committee. The committee will be responsible for the party's platform and strategy. Goldwater is expected to be a strong voice for the conservative wing of the party.



#### Unclad Body of Star Discovered on Bed; Empty Bottle Near

BY HOWARD HERZEL AND DON KEIF  
Marilyn Monroe, a troubled beauty who failed to find happiness as Hollywood's brightest star, was discovered dead in her Brentwood home of an apparent overdose of sleeping pills Sunday.  
The 36-year-old actress was found lying face down on her bed and clutching a telephone receiver in her hand when a psychiatrist broke into her room at 1:30 a.m.  
She had been dead an estimated six to eight hours. About 3:15 p.m. Saturday she had called the psychiatrist, Dr. Ralph Ginzburg, and was told to go to a hotel where the psychiatrist could see her, police reported.  
Her body was taken to the County Morgue, where Coroner Theodore J. Curphy will hold an autopsy.  
More news and pictures of Marilyn Monroe on page A-8, A-9, and B1, Part 4.  
This article is a "preliminary opinion" that death



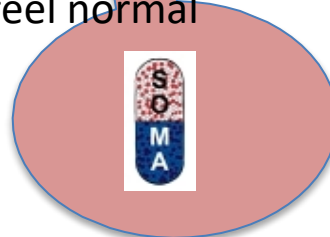
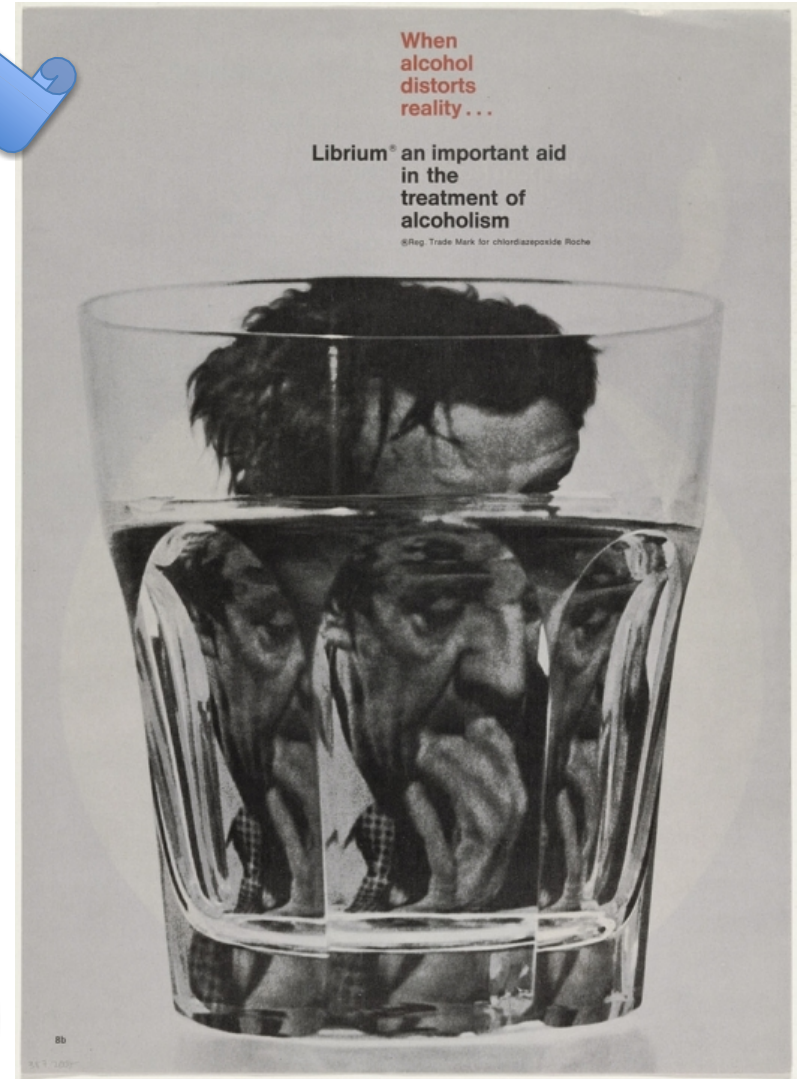
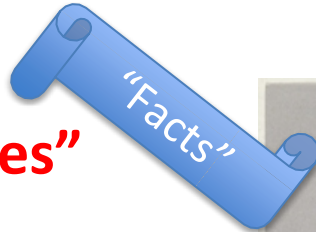
# Then Came Benzodiazepines

- **“Safer than Barbiturates”**

- *Chlordiazepoxide*
- 1954 Leo Sternbach in Austria synthesized 1960 Roche Pharmaceuticals Released in USA

- Heavily marketed

- To treat stressors of life
  - **Like going to college**
  - **Raising kids**
  - **Marriage**
  - **“Getting old”**
  - **Responsibilities**
- Need to take a pill to feel normal





# Mad Marketing

- In a Way, Pharma Created their own demand by pathologizing normal conditions



# Wyeth showed us how Serax can help this poor woman who is Trapped Behind a Cage of Mops



## You can't set her free. But you can help her feel less anxious.

You know this woman.

She's anxious, tense, irritable. She's felt this way for months.

Beset by the seemingly insurmountable problems of raising a young family, and confined to the home most of the time, her symptoms reflect a sense of inadequacy and isolation. Your reassurance and guidance may have helped some, but not enough.

SERAX (oxazepam) cannot change her environment, of course. But it can help relieve anxiety, tension, agitation and irritability, thus strengthening her ability to cope with day-to-day problems. Eventually—as she regains confidence and composure—your counsel may be all the support she needs.

Indicated in anxiety, tension, agitation, irritability, and anxiety associated with depression.

May be used in a broad range of patients, generally with considerable dosage flexibility.

**Contraindications:** History of previous hypersensitivity to oxazepam. Oxazepam is not indicated in psychoses.

**Precautions:** Hypotensive reactions are rare, but use with caution where complications could ensue from a fall in blood pressure, especially in the elderly. One patient exhibiting drug dependency by taking a chronic overdose developed upon cessation questionable withdrawal symptoms. Carefully supervise dose and amounts prescribed, especially for patients prone to overdose; excessive prolonged use in susceptible patients (alcoholics, ex-addicts, etc.) may result in dependence or habituation. Reduce dosage gradually after prolonged excessive dosage to avoid possible epileptiform seizures. Caution patients against driving or operating machinery until absence of drowsiness or dizziness is ascertained. Warn patients of possible reduction in alcohol tolerance. Safety for use in pregnancy has not been established.

Not indicated in children under 6 years; absolute dosage for 6 to 12 year-olds not established.

**Side Effects:** Therapy-interrupting side effects are rare. Transient mild drowsiness is common initially; if persistent, reduce dosage. Dizziness, vertigo and headache have also occurred infrequently; syncope, rarely. Mild paradoxical reactions (excitement, stimulation of affect) are reported in psychiatric patients. Minor diffuse rashes (morbilliform, urticarial and maculopapular) are rare. Nausea, lethargy, edema, slurred speech, tremor and altered libido are rare and generally controllable by dosage reduction. Although rare, leukopenia and hepatic dysfunction including jaundice have been reported during therapy. Periodic blood counts and liver function tests are advised. Ataxia, reported rarely, does not appear related to dose or age.

These side reactions, noted with related compounds, are not yet reported: paradoxical excitation with severe rage reactions, hallucinations, menstrual irregularities, change in EEG pattern, blood dyscrasias (including agranulocytosis), blurred vision, diplopia, incontinence, stupor, disorientation, fever, euphoria and dysmetria.

**Availability:** Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

**Serax**<sup>®</sup>  
(oxazepam)



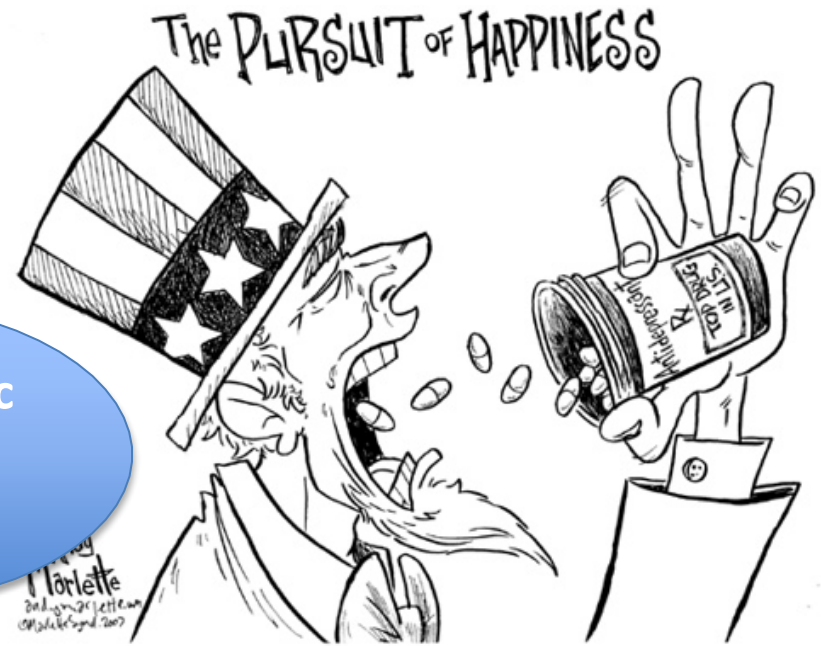
Wyeth Laboratories  
Philadelphia, Pa.

# Grand Success Marketing

- By 1974, **60 million** Americans were prescribed valium

Just like Prozac  
destigmatized  
Depression

- The Marketing
  - Destigmatized Anxiety
  - ***Mostly Directed to Women!!!!!!***



# Then Came **Xanax** (alprazolam)

Our favorite palindrome

- 1981---Pfizer/Upjohn capitalized on the fact valium didn't work for panic attacks
- **-Even Popularized the idea of "the panic attack"**
  - Created demand by Popularizing a disorder
    - Iatrogenic Panic attacks
    - **People were encouraged to interpret episodic anxiety as a panic attack**



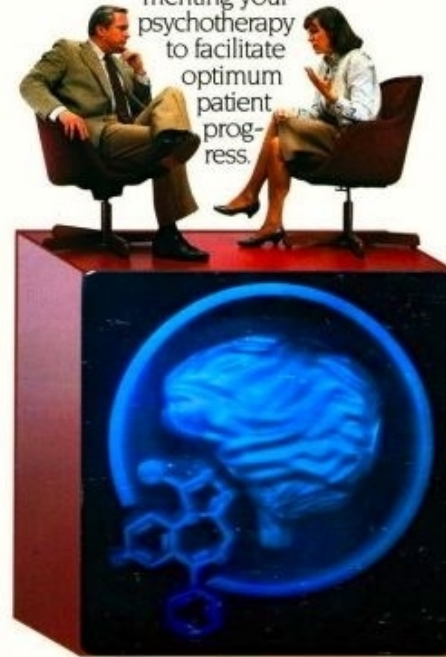
Pharma  
needed to find  
a niche for  
xanax



## A UNIQUE STRUCTURE TO SUPPORT YOUR PSYCHOTHERAPY.

The incorporation of a triazolo ring to the basic benzodiazepine structure clearly differentiates Xanax from other benzodiazepines.

Xanax effectively relieves anxiety associated with depression, complementing your psychotherapy to facilitate optimum patient progress.



**Xanax**<sup>®</sup> 0.5 mg  
Tablets  
alprazolam <sup>®</sup>

COMPLEMENTS AN EFFECTIVE  
THERAPEUTIC ALLIANCE

Pharma found  
another niche  
for xanax


**Xanax**<sup>®</sup> 0.5 mg  
Tablets  
alprazolam <sup>®</sup>

COMPLEMENTS AN EFFECTIVE  
THERAPEUTIC ALLIANCE

Upjohn

# By Now, You get the Idea

IN A WORLD  
WHERE CERTAINTIES  
ARE FEW...



NO WONDER  
**Ativan**<sup>®</sup>  
(lorazepam) or  
IS PRESCRIBED BY SO MANY  
CARING CLINICIANS.

Please see additional page for full summary of prescribing information.

“No Wonder Ativan is prescribed By so many caring clinicians”

# So How effective was all that Marketing?

- *Prevalence of Benzodiazepine use*

- 12.6% in 2018

- Maust 2018



**NSDUH**  
NATIONAL SURVEY ON DRUG USE AND HEALTH

NSDUH 2017—

**-70,000 People surveyed in person**

- **2:1 Female : Male**



I think its higher

- *Prevalence of Benzodiazepine use*

- West 2014

- **High School Seniors**

- **5%** prescribed BZDs

- **8%** Illicit BZDs

- F>M 2:1

- Nielsen 2007

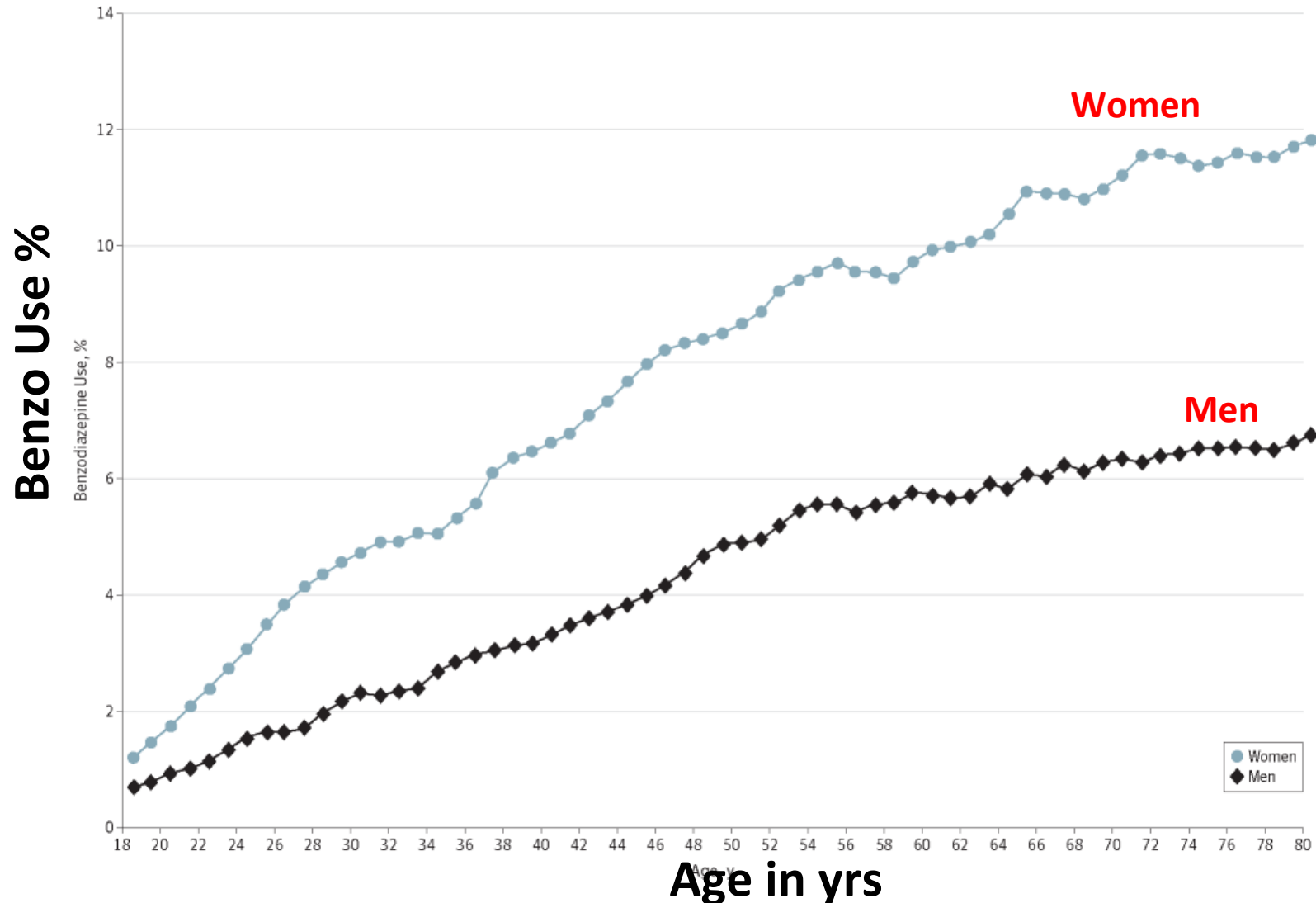
- Disproportionately High in Suboxone/Methadone/Opiate patients

- Up to **25%!!!**



# *Two Disturbing trends*

*JAMA Psychiatry - Olfson 2015*



# Prevalence

Really???

- Chronic daily use also increases with age
  - 14.7 % young adults who use
  - 31.4% elderly
- **Benzodiazepine use in the United States.** [Olson M<sup>1</sup>](#), [King M<sup>2</sup>](#), [Schoenbaum M<sup>3</sup>](#). [AMA Psychiatry](#). 2015 Feb;72(2):136-42. doi: 10.1001/jamapsychiatry.2014.1763.



# Pakistan Study of Resident Physicians

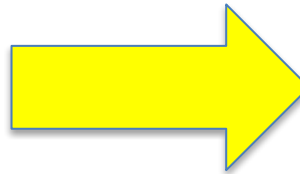
- BENZODIAZEPINE USE AMONG RESIDENT DOCTORS IN TERTIARY CARE HOSPITAL, Aftab Alam Khan, J Ayub Med Coll Abbottabad 2019;31(4)
- 278 Residents in the Study
  - 48.7% use BZD's
  - Primary reasons
    - #1) Insomnia
    - #2) Anxiety

**If we're taking it ourselves, unconsciously we might be less likely to discourage its use in our patients**

# There's More?

But

- It's not just the Drug Companies to blame.....

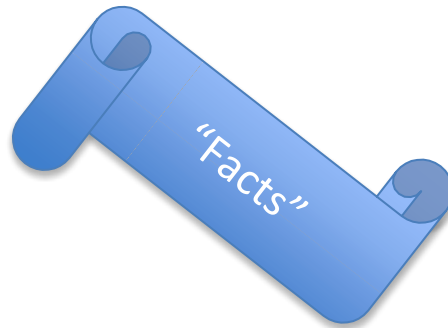


**DEA Schedule ---?**



# DEA Schedule IV

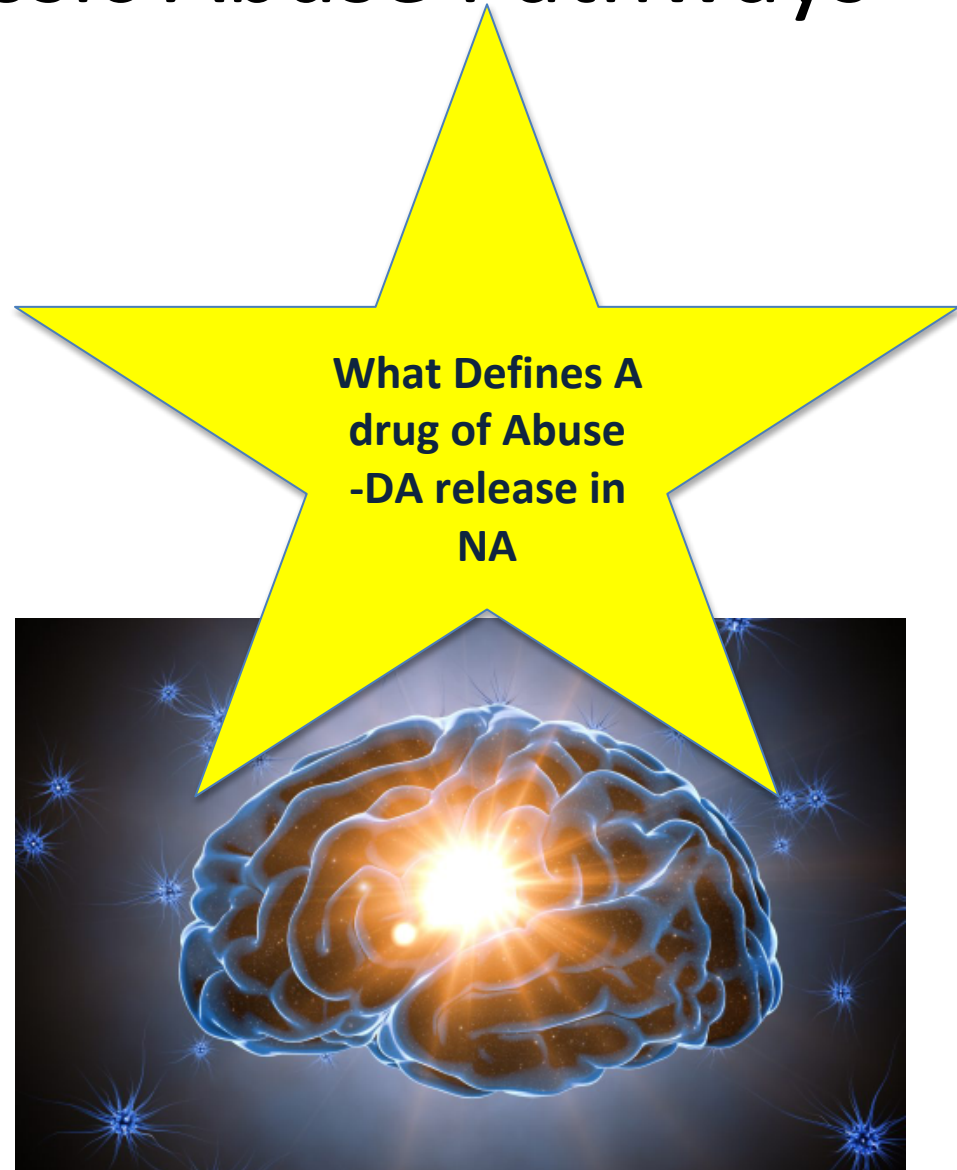
- “ Low potential for abuse and low risk of dependence.”





# BZD's Activate Classic Abuse Pathways



- Tan et al Nature 2010
  - BZD's activate dopaminergic neurons in VTA by modulating GABA<sub>A</sub> receptors in neighboring interneurons.
  - Bottom Line
    - Increase Dopamine levels in Nucleus Accumbens through disinhibition
      - Similar to Opioids, cannabinoids, GHB



# Pay For Performance



# How does this all add up?

- 1) Less stigma—from marketing  
– Cool to be on Xanax 
- 2) Direct dopamine release into reward pathway
- 3) Possible Inappropriate Scheduling by DEA 
- 4) Pay for performance



Incentive  
Salience



– Most prescribed  
Psych medication in  
America

- #1—Xanax
- #2---Ambien



“I need my Xanax just like I  
need my Insulin”

# What else?

- **A lot of people get addicted**
  - 50 % of chronic BZD users met criteria for BZD dependence (DSM4)
    - Guerlais 2015



# Benzodiazepine Addiction

- **And it only takes a month to get addicted**
  - BZD dependence (addiction) Happens in 50% of patients taking for greater than one month

The old DSM 4 definition



My Goodness...

- De la Cuevas  
Psychopharmacology  
2003



# Not all Benzo's are Equal

- Can Buy in the **Tenderloin**
  - Xanax>>Klonopin> Ativan
- Can't Buy in the **Tenderloin**
  - Oxezapam
  - Librium(Chlordiazepoxide)
  - Chlorazepate

"You can  
Have these  
Back"





# So Who Is The Most Evil





# “A Review of Alprazolam Use, Misuse, Withdrawal”

Nassima Ait Daoud J Add Med 1/18

- Great Review Article Describing the idiosyncrasies of Alprazolam
  - **Worse Withdrawal than other benzo’s**
  - **More Misused**
  - **More toxic in overdose**
    - Twice as likely to end up in ICU
  - **Can become dependent in 7 days**



# What's The Deal With Gabapentin?



# Gabapentin/Pregabalin

- Mechanism?
  - Indirectly results in increased GABA activity
    - Halts the formation of new synapses?
    - May increase GABA biosynthesis
    - ***NMDA receptor antagonist Activity***
- Can Buy in the Tenderloin
  - Followed on PDMP



Intriguing

# Is it Addictive

- Probably doesn't cause Dopamine release in Nucleus Accumbans
- Very commonly hear Anecdotally & 2 reference....
  - Enhances the euphoria of opiates
  - “It doubles the High”
  - the use of gabapentin and an opioid together **increased the risk of opioid related deaths by 60%**

[Bonnet U](#)<sup>1</sup>, [Scherbaum N](#)<sup>2</sup> **How addictive are gabapentin and pregabalin? A systematic review.** *Eur Neuropsychopharmacol.* 2017 Dec;27(12):1185-1215. doi: 10.1016/j.euroneuro.2017.08.430. Epub 2017 Oct 5.

Gomes T, Juurlink DN, Antoniou T, et al. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested control study. *PLoS Med.* 2017;





# Z Drugs

## “The Safer Alternative to Benzodiazepines”

- Sleeping Pills
  - Zolpidem, Zopiclone, esZopiclone, zaleplon
  
- Just like Benzo’s Z-drugs are..
  - Positive Allosteric Modulators of GABA receptor



Sound Familiar

# Z drugs

- Growing body of literature establishing their addictive qualities
- Commonly studied together w BZD's
- Rehabs frequently seeing patients addicted solely to zolpidem



# Some Z-Drug Abuse References For Your Records

- [Zolpidem abuse](#)
- Madrak, Leslie N; Rosenberg, Mark. **The American Journal of Psychiatry**; **Washington** Vol. 158, Iss. 8, (Aug 2001): 1330-1.
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- [Repeated Zolpidem Treatment Effects on Sedative Tolerance, Withdrawal, mRNA Levels, and Protein Expression](#)
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- **High-dose zolpidem dependence - Psychostimulant effects? A case report and literature review**
- [Chattopadhyay, Abhijna; Shukla, Lekhansh; Kandasamy, Arun; Benegal, Vivek. \*Industrial Psychiatry Journal\*; Mumbai Vol. 25, Iss. 2, \(Jul/Dec 2016\). DOI:10.4103/ipj.ipj\\_80\\_14](#)
- [Review of Safety and Efficacy of Sleep Medicines in Older Adults](#)
- Schroeck, Jennifer L; Ford, James; Conway, Erin L; Kurtzhalts, Kari E; Gee, Megan E; et al. **Clinical Therapeutics**; **Bridgewater** Vol. 38, Iss. 11, (Nov 2016): 2340-2372
- **ZOLPIDEM: INTRAVENOUS MISUSE IN DRUG ABUSERS** [EMMANUEL BRUNELLE](#) et al *Addiction* Sept 2005
- **Psychiatric Morbidity in Dependent Z-Drugs and Benzodiazepine Users, Yin et al**, *International Journal of Mental Health and Addiction*, 6/2017
- **Cimolai N. 2007.** Zopiclone: is it a pharmacologic agent for abuse?. *Canadian Family Physician Medecin de Famille Canadien* . 2007. **53(12)**: 2124-2129.
- **Nordfjærn T, Bjerkeset O, Bratberg G, Moylan S, Berk M, Gråwe R. 2013.** Socio-demographic, lifestyle and psychological predictors of benzodiazepine and z-hypnotic use patterns. *Nordic Journal of Psychiatry* . 2013. **68(2)**: 107-116.
- Potentially inappropriate use of benzodiazepines and z-drugs in the older population-analysis of associations between long-term use and patient-related factors [Aliaksandra Mokhar, Niklas Tillenborg, Jorg Dirmaier, Silke Kuhn, Martin Harter](#) and [Uwe Verthein](#) *PeerJ*. 6 (May 22, 2018): pe4614.

Not Even Really  
Debatable Any  
More



# Let's Summarize the Bad News?



# Cognitive Impairment

- Cognitive Impairment while taking
  - Vignola 2000,
  - Sakol 1998,
  - Golombok 1998
  - McAndrews 2002



# Dementia

- 10 Recent Studies showed increased risk of dementia with BZD and Z-drug use
  - High Dose
  - Long term use
  - Long acting BZDs
  - **If use > 3yrs—**
    - **highest risk—**
    - **no recovery**
- **Tapainen, 2018**
  - Nationwide case control
  - 350k patients



Billioti de Gage S, Moride Y, Ducruet T, Kurth T, Verdoux H, Tournier M, et al. Benzodiazepine use and risk of Alzheimer's disease: case-control study. *BMJ*. 2014;349:g5205.

Billioti de Gage S, Begaud B, Bazin F, Verdoux H, Dartigues JF, Peres K, et al. Benzodiazepine use and risk of dementia: prospective population based study. *BMJ*. 2012;345:e6231.

Zhong G, Wang Y, Zhang Y, Zhao Y (2015) Association between Benzodiazepine Use and Dementia: A Meta-Analysis. *PLoS ONE* 10(5): e0127836

**The risk of Alzheimer's disease associated with benzodiazepines and related drugs: a nested case-control study**

[V. Tapiainen](#), *Acta Psychiatrica Scandinavica*, 2018

# Dementia – Controversial

- Anticholinergic and benzodiazepine medication use and risk of incident dementia: a UK cohort study, Grossi et al. BMC Geriatrics (2019) 19:276
- In a cohort study with 10-year follow-up (N=8216) we did not find any evidence of an increase in risk of dementia associated with the use benzodiazepines or anticholinergics

# Hot off the Press


## Dementia – Controversial

- **Associations of Benzodiazepines, Z-Drugs, and Other Anxiolytics With Subsequent Dementia in Patients With Affective Disorders: A Nationwide Cohort and Nested Case-Control Study**, [Merete Osler <sup>1</sup>](#), [Martin Balslev Jørgensen <sup>1</sup>](#) · Am J Psychiatry **2020** Jun 1;177(6):497-505.
- 235,465 patients over age 20 in the Danish National Patient Registry between 1996 and 2015.
  - Median f/U 6 yrs
  - Did not reveal associations between use of benzodiazepines or Z-drugs and subsequent dementia, even when exposures were cumulated or divided into long- and short-acting drugs.
  - **Some results were compatible with a protective effect.**
    - Insomnia and anxiety are known risk factors for dementia

# Drug Interactions

- Safe Medications like **Buprenorphine** become dangerous when combined with Benzodiazepines.

- Kintz-“Forensic Science” International 121 2001) 65±69
- Reynaud- “Addiction”,1998
- **Nielsen**, “Drug and Alcohol Dependence”, 2005
- **Lintzeris**, “American Journal on Addictions” 2010
- **Lee**, “Drug and Alcohol Dependence”, 2014
- .....



Ceiling Effect on  
Respiratory  
suppression  
Disappears

Pinray, “Basic & Clinical Pharmacology & Toxicology” 2008



# BZD Z-drugs MVAs

- “Overwhelming evidence both experimental and epidemiological, BZD and Z-drugs being implicated in fatal and non fatal MVA’s”
  - Brandt 2017



# Impairment

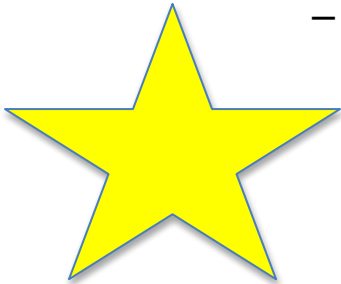
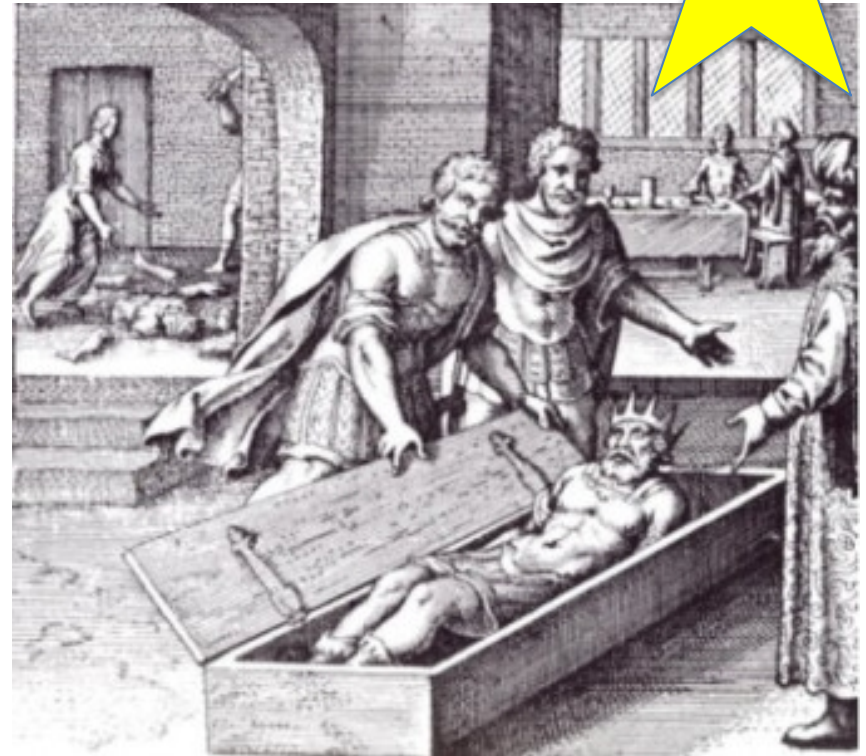
- Z drugs “significantly impaired driving performance, cognitive, memory, and psychomotor performance the morning following bedtime administration”
  - Mets Sleep, 2011





# Benzo's and Z drugs Mortality

- Weich BMJ 2014
  - **34,721** Patients in Primary Care **followed for 7.6 yrs**
  - Age Adjusted hazard ratio all cause mortality
    - **3.46 after adjusting for confounders**
- In other words
  - You're 3 and a half times more likely to die if you're on a benzo or z drug



# Prescribed BZDs Increases risk of Suicide

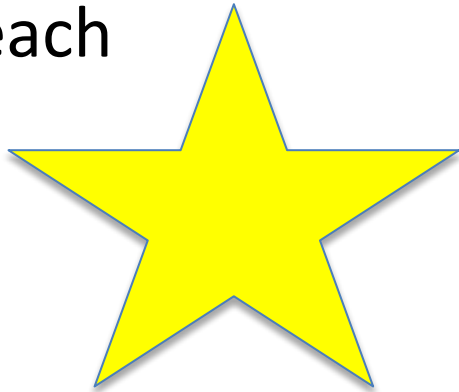
- Dodds 2017
  - Review Article of 17 studies
  - Majority of studies found that benzodiazepine use was associated with increased suicide risk.
- Thought to be mediated by increasing Aggression & Behavioral Disinhibition



**Once I became aware of this, it was striking how often I see this association in practice—esp clonazepam, Esp within the first few months of initiation**

# Zolpidem & Suicide

- **Case control of 2199** pts who attempted or completed suicide b/n 2001 and 2011 in Taiwan and 10 controls for each
- Ambien Use was associated with a **2-fold greater risk of suicide** after adjustment for:
  - age, sex, urbanization, occupation, history of BZD and antidepressant use, various mental disorders, insomnia



# Falls

- Decades of evidence implicating them in Falls
  - Falls are a big deal!!!!



## Article

December 15, 1989

## Benzodiazepines of Long and Short Elimination Half-life and the Risk of Hip Fracture

Wayne A. Ray, PhD; Marie R. Griffin, MD, MPH; Winanne Downey

» [Author Affiliations](#)

*JAMA*. 1989;262(23):3303-3307. doi:10.1001/jama.1989.03430230088031

1. Herings et al., Arch Int Med 1995.
2. Wagner AK et al., Arch Int Med 2004.
2. 3. Wang PS et al., AJP 2001.

# Benzodiazepines and Pneumonia

- Benzodiazepines have been shown to increase the relative risk of pneumonia
- Meta-analysis of 10 studies involving more than 120,000 pneumonia cases were included
  - The odds for developing pneumonia were 1.25-fold higher (odd ratio, OR = 1.25; 95% confidence interval (CI), 1.09-1.44) in BZD users compared with individuals who had not taken BZD.

Benzodiazepines or related drugs and risk of pneumonia:

A systematic review and meta-analysis

Guo-qing Sun, Int J Geriatr Psychiatry. 2019;1–9.

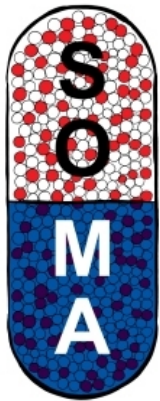
# Prescriptions Increasing in # and Size

- Bachhuber 2016
  - Am J Public Health

**–1996 to 2013**

- BZD scripts increased from **4.1-5.6%** of population in USA

**– Quantities tripled**



Yikes



# There's some scary Data There.... What Do We Do Now?



Sometimes its best to get people off  
these meds



# Options Summary

- #1) Convert to long acting Benzo using equivalency chart
  - Taper over Weeks to months
    - Requires motivated and compliant patient
    - Often challenging in use disordered people
- #2) Prolonged taper on Same Benzo
  - 50% initially
  - 10% per week after
- #3) Convert to Anti-epileptic (Phenobarbital, carbamazepine) then taper that med
  - May be Better If Pt has Use D/O
- #4) Water Taper
  - Dissolve in Water
  - Minimal Daily Decreases in dose

# “Standard of Care” Recommendations for Taper

- “The overall consensus is that BZD’s should be discontinued gradually over a period of several **weeks to avoid Sz’s and severe withdrawal Sx’s**”
  - Soyka NEJM 2017 quoting Cochrane review
- Change to long acting BZD
  - Although never been shown to actually make a difference in final outcomes
    - Lader BMJ 2014
    - Soyka Medikamentabhängigkeit 2015
- Taper over 4-12 weeks
  - 10-50% reductions at a time



Standard of Care



# “Standard of Care” Recommendations for Taper

- **Controversy**
- **Paucity of Data**

Two Most Quoted Reviews Used to Justify The use of Benzodiazepines as Tapering agent in Helping People Detox from BZD's

**Not even about tapering from benzodiazepines!!!**

- Amato Cochrane Review 2010 is relative to BZD safety in Tx of **Alcohol Withdrawl**



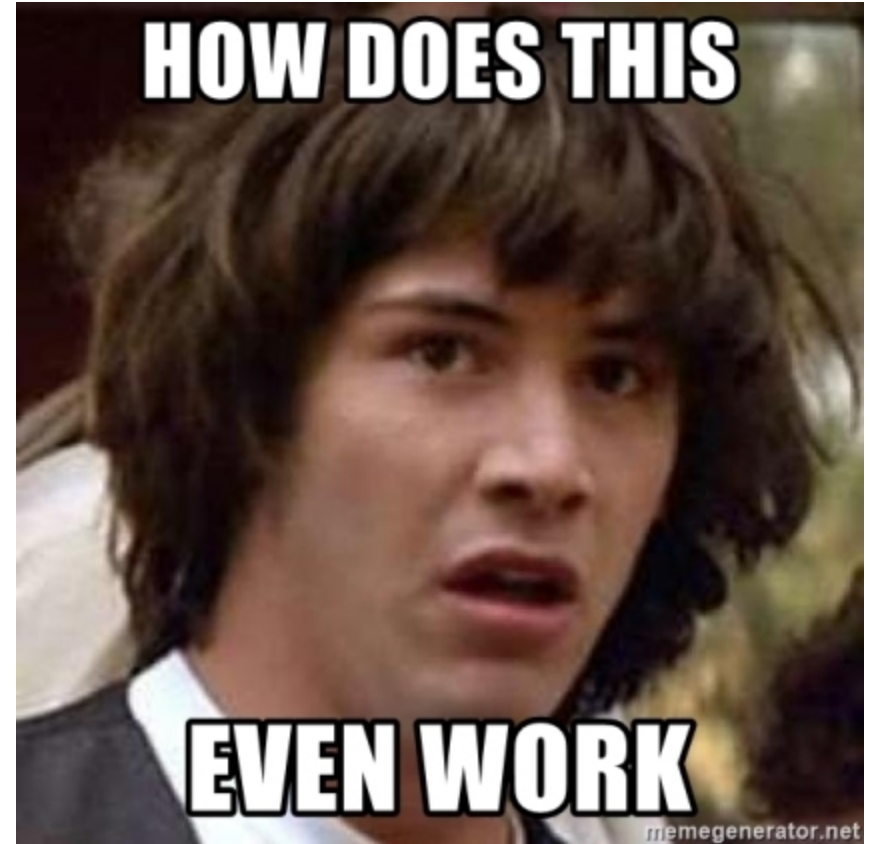
- Darker Cochrane Review 2015 Meta analysis of CBT + taper vs taper alone for **BZD withdrawal**

- CBT + taper was better

“Facts”

# Long Tapers are Effective?

- I Invite you to question this?
- Is this consistent with your experience?
- Not Mine





# Don't Forget Long Tapers are a marathon

- **Tapering patients, most often, will be uncomfortable throughout the entire taper..& long after**
- **Supportive measures Throughout taper & PAWS**

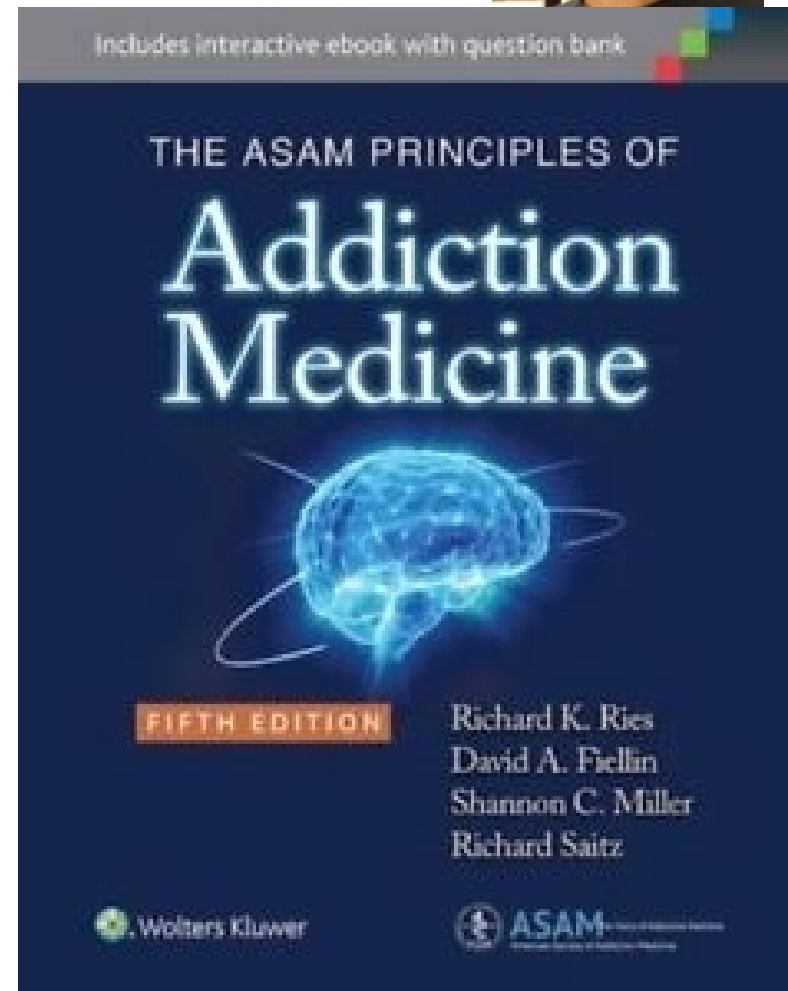




# Alternative Discontinuation

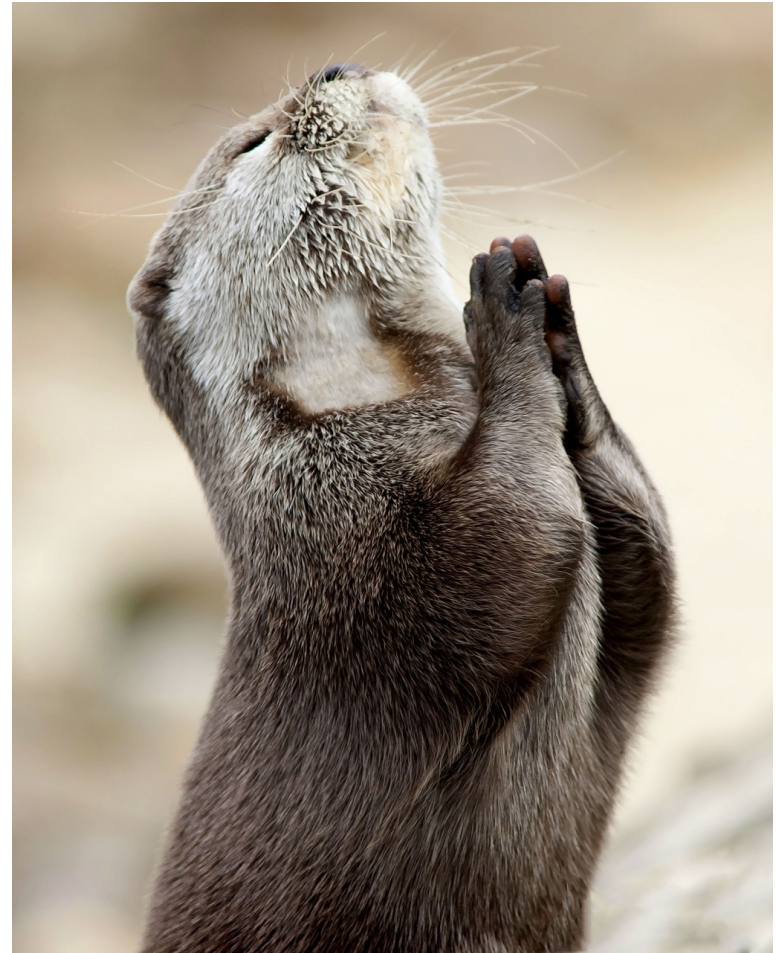


- Rapid taper of Benzo over 3 days
  - 1/3—1/3—0
    - **Usually Inpatient**
- Cross Titrating
  - Depakote 500tid or
  - Carbamazepine 200tid or
  - Gabapentin 800tid
- Continue Antiepileptic for at least 1 month
- Start SSRI's for rebound anxiety
  - Ries J. Psychoactive Drugs 1998
  - Garcia-Borreguero, Eu Arch Psych 1990



# Controversy

- Nothing comparing slow “standard of care” taper to the “Ries” style rapid taper-Cross Titration to anti-epileptic Meds



Please somebody do this study!

# Hospitalization?

- **If it were my family member.....**
- Recommended for people on suprathreshold doses
  - National Center for PTSD
    - **Ptsd.va.gov 2013**



# Inpatient Barbiturate Taper For BZD detox.

Very  
Simple  
Safe &  
Effective

- Johns Hopkins  
Reviewed 300 inpatient  
rapid Detox from Only  
BZD's using 3 day Fixed  
dose Phenobarbital  
taper
  - Kawasaki J. Sub. Ab Tr  
2012



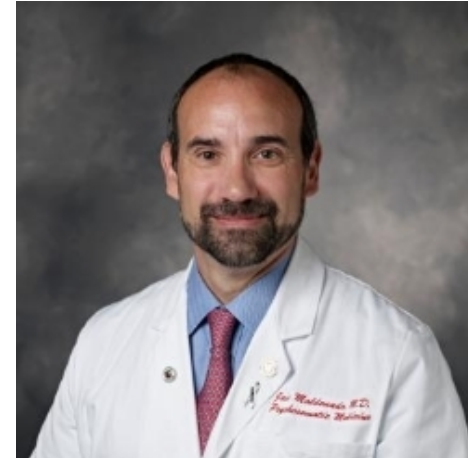
Table 2  
Phenobarbital protocol and percentage of doses held

Dose/Interval	No. of doses in protocol	Percentage who received all doses <sup>a</sup>	Percentage of doses held because of sedation <sup>a</sup>
200 mg once	1	86	14
100 mg every 4 hours	5	58	17
60 mg every 4 hours	4	70	14
60 mg every 8 hours	3	56	25

<sup>a</sup> Patients who were discharged against medical advice were not included.

# Add some Alpha 2 Agonist

- Maldonado Article 2017
  - Emphasizes the use of Alpha 2 agonists combined with antiepileptics to treat **alcohol** withdrawal (Similar pathophys to benzo withdrawal)
- **Elegantly describes how antiepileptics & alpha 2 agonists more closely address the underlying pathophysiological derangements that underlie withdrawal syndromes than do benzos**
  - **Elevated NE & glutaminergic state**



# I use a Modified Maldonado

Pheno's can be dangerous used for Outpt detox

- Residential/Inpatient
  - Immediate discontinue Benzo
  - **Phenobarbital**
    - Fixed dose 32-64mg qid + additional doses prn based on CIWA-B protocol
    - 4-10 days
  - **Clonidine Patch 0.1-0.2**
    - 7-14 days
    - 0.1 oral tid prn
  - PAWS – when necessary
    - Gabapentin 100-300 tid for 1-6 months
    - Oxcarbazepine 150 bid for 1-6 months
- Outpatient
  - **Clonidine Patch**
    - 0.1-0.2 for 7 or 14 days
  - **Oxcarbazepine**
    - 150 bid
  - Rapid 3-7 day taper of benzo
  - PAWS – when necessary
    - Gabapentin 100-300 tid for 1-6 months
    - Oxcarbazepine 150 bid for 1-6 months



# How Do We Chose?

## Will a taper be successful

- **Discontinuation Factors**

- Duration of use
- Dose
- **MOTIVATION**
- **Addiction**
- DOC- Is it their Primary Addiction
- Number of Withdrawal episodes in past
- **Coach-partner**





# Why All This Debate?

- Withdrawal is Bad News!



# Benzodiazepine Withdrawal is Dangerous

- No controversy Here
  - Hollister,  
Psychopharmacologia, 1961
    - Sudden Withdrawal of  
BZD's causes:
      - Seizures
      - Psychosis
      - Delirium
  - Dangerous and  
miserable



**Does BZD Withdrawal  
cause DT'S?**

# Benzodiazepine Withdrawal

- Pathophysiologically similar to Alcohol withdrawal but variable in length
- More likely to cause Seizures
- Rebound Anxiety/insomnia




# BZD Withdrawal

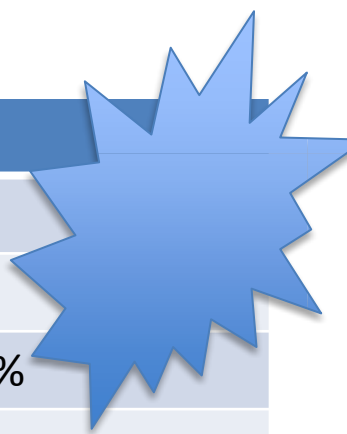
- 1<sup>st</sup> and most reliably
  - Recurrence of Sx's initially treated for
    - Anxiety
    - Insomnia
  - Back with vengeance
- Starts in 48-72 hrs from short acting BZD's
- **May be 5-10 days to notice symptoms for the longer ones**



# Withdrawal Symptoms

Non Specific Sx's	Frequency %
Insomnia	71%
Anxiety	56%
Mood Swings	49%
Myalgia/Twitching	49%
Headache, Tremor	38%
N/V, Anorexia	36%
Sweating, Blurred Vision	22%
<b>Complications</b>	
Psychosis 	7%
Seizures	4%

Hypersensitivity	
Noise	38%
Light	24%
Smell/Touch	15%/7%
Hyposensitivity	
	15%/4%
Smells/Taste	
<b>Qualitative Changes</b>	
Movement	24%
Vision, Taste	13%
Derealization	24%

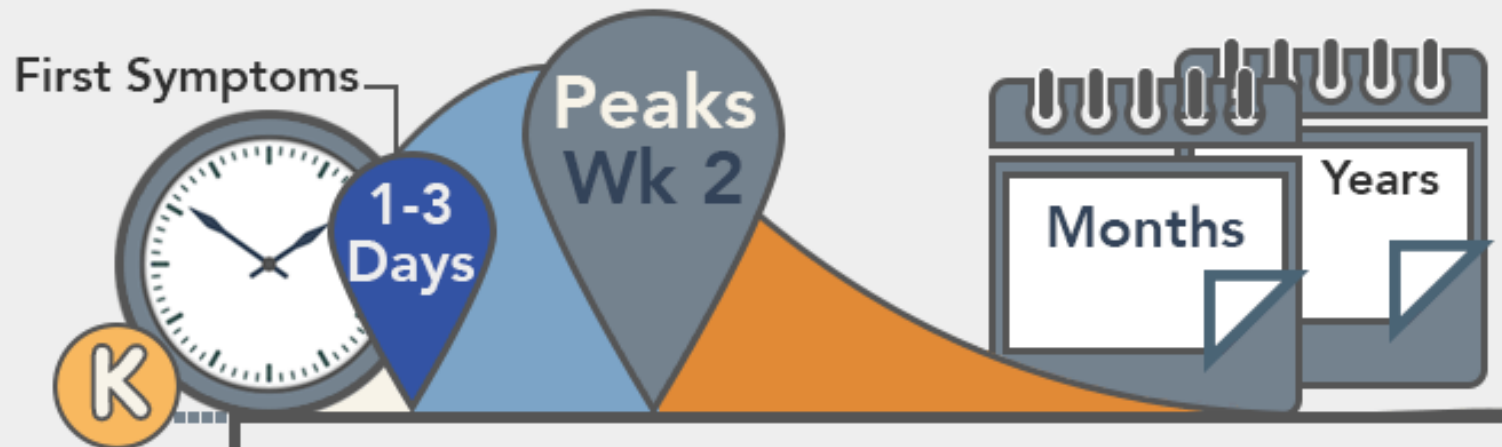


# Kindling Effect

- Not “Largely theoretical”
- Sensitization
  - Multiple withdrawals lead to more severe withdrawals
- Inpatients who get Psychotic



# Klonopin Withdrawal Timeline



**General:** Symptoms last 2-4 days

**Acute:** Symptoms peak around week 2 and then begin to subside

Symptoms can last a few days up to several months or even years if not addressed professionally.

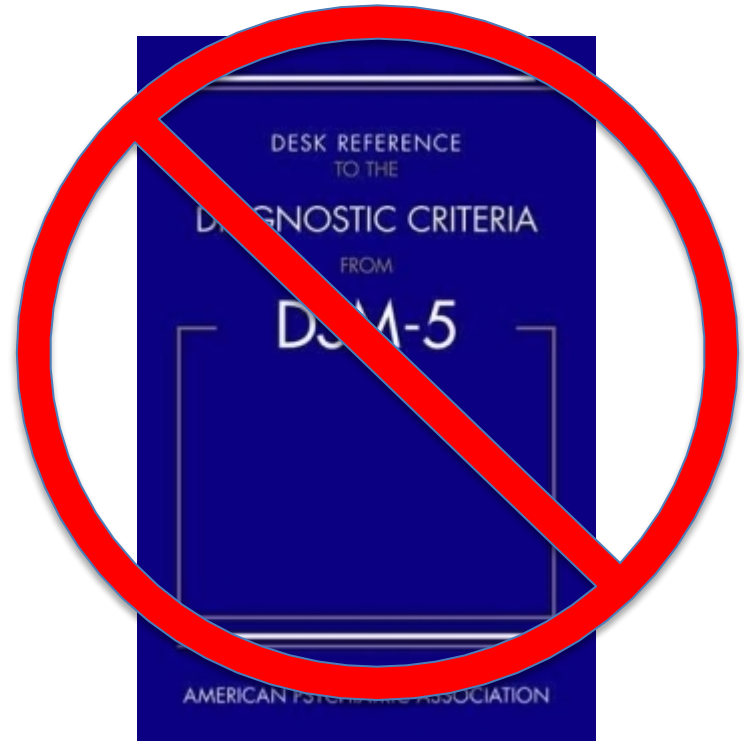


# PAWS

- Post-Acute-Withdrawal Syndrome (PAWS) is a set of [impairments](#) that can persist for weeks, months, or years after the abstaining from a substance of abuse.
- Also known as:
  - post-withdrawal syndrome
  - prolonged withdrawal syndrome
  - protracted withdrawal syndrome.

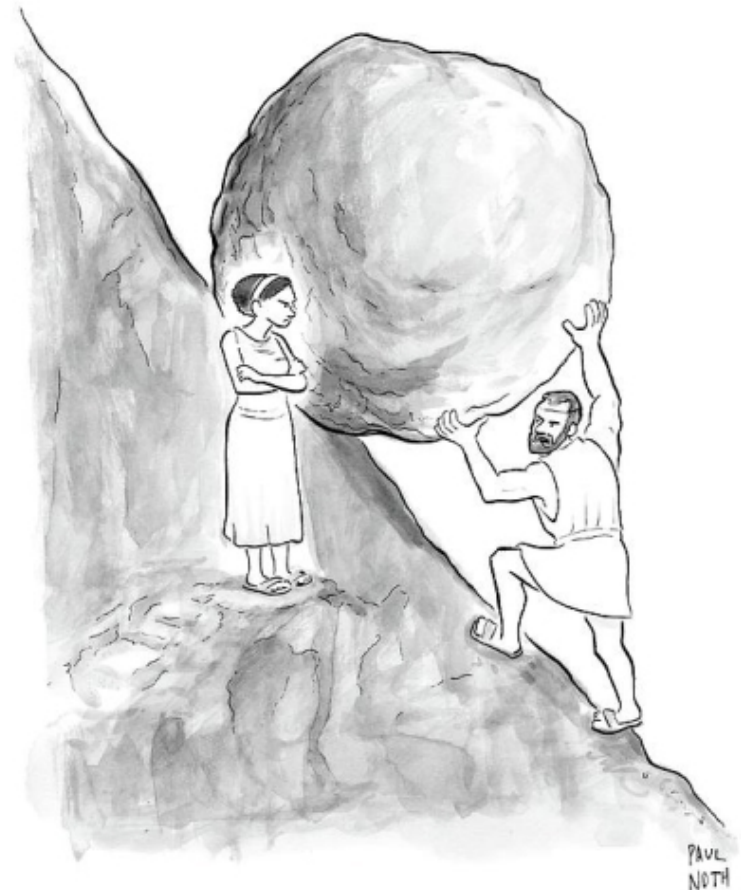
# PAWS

- Not DSM 5 Diagnosis
  - Very small amount of Literature
  - More Literature (Old) for Protracted withdrawal from Alcohol
    - Miller FT (Mar–Apr 1994). "Protracted alcohol withdrawal delirium". *J Subst Abuse Treat.* **11** (2): 127–30.
    - Satel SL (May 1993). "Should protracted withdrawal from drugs be included in DSM-IV?". *American Journal of Psychiatry.* **150** (5): 695–704.



# Benzodiazepine PAWS references

- “Benzodiazepine withdrawal—An unfinished Story”
  - “**Complete recovery may take a year or more**”
    - Ashton BMJ 1984
  - Coming off Tranquilizers: A **Sisyphean** Toil
    - Lader Addiction 2009
- Post acute withdrawal syndrome, More than just return of pre-treatment Sx’s
  - Higgit, Fonagy 1990



*“I am not having this conversation again.”*

# PAWS

- Estimated that 90% of people recovering from Drugs of Abuse experience this
- Wax and Wane in Severity
  - may disappear altogether only to reappear at a later time

# Sx's Are Many --- & often Non-Specific

- **Difficulty with cognitive tasks**
  - learning, problem solving, or memory

- **Irritability**

- Feelings of anxiety or panic
- Depression
- Psychosis
- Obsessive-compulsive behaviors
- Difficulty maintaining social relationships
- Craving originally abused substances
- **Apathy or pessimism**
- **Disturbances in sleep patterns**
- **Increased sensitivity to stress**



Benzo Brain

- Fatigue
- Decreased energy
- Lack of motivation
- **Hypersensitivity**
  - Pain
  - Anxiety
  - Sound
- Anhedonia
- Autonomic Disturbances

# PAWS

- These symptoms tend to increase in severity when triggered by stressful situations, but might flare up even without any clear stimulus.
  - Looks like emotional Dysregulation
  - Personality disorder
- Can Lead to Mis-diagnosis

# PAWS- Treatment

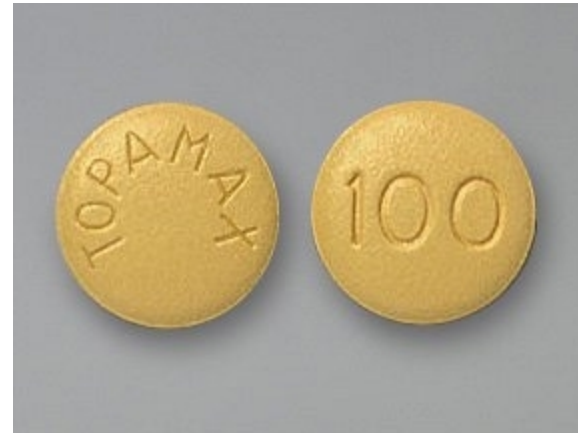
Most research  
is in Alcohol  
PAWS

- Medications
  - Strongest Evidence is for anti-epileptic meds
    - Carbamezapine,  
**Oxcarbamezapine,**  
Topiramate
    - Trileptal/gabapentin
  - Some limited evidence
    - Baclofen
    - Acamprosate
    - Atomoxetine
- How long?
  - Not much guidance from literature
  - I often do 6 months



# Antiepileptics for PAWS

- “Well suited for managing the symptoms of altered hedonic function, stress reactivity, and cravings “ present in PAWS
- Anticonvulsants may facilitate homeostasis and restorative changes (in the GABA/glutamate) system once a subject has obtained sobriety
  - Hammond et al 2015



# PAWS Treatment

- Keep Lots of tools in the toolbox
- Slow and Steady
  - Medications of course
- But don't forget – Treat the anxiety/insomnia that they took the Benzo's for in the first place
  - SSRI's etc...
  - Psychotherapy
    - CBT-I
  - Behavioral therapy
  - Group Therapy/12 Step
  - Alternative

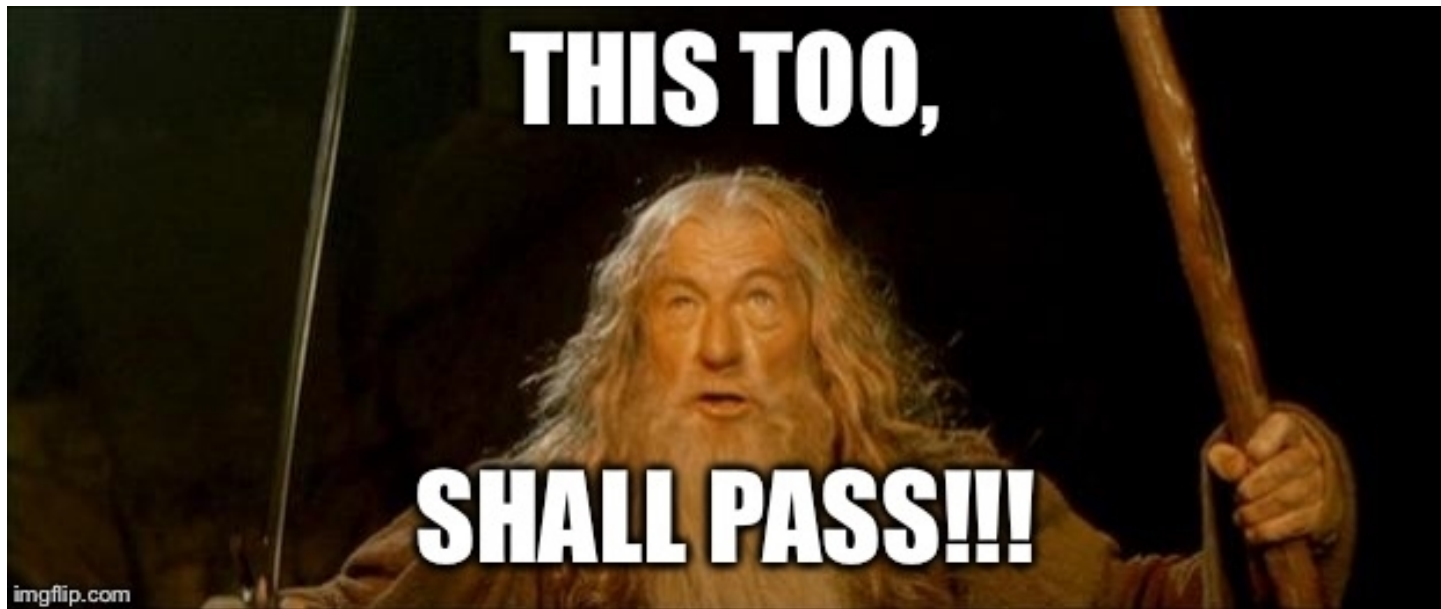


# Attention to PAWS

- Why?



# PAWS causes Relapses



# PAWS Treatment-- Future

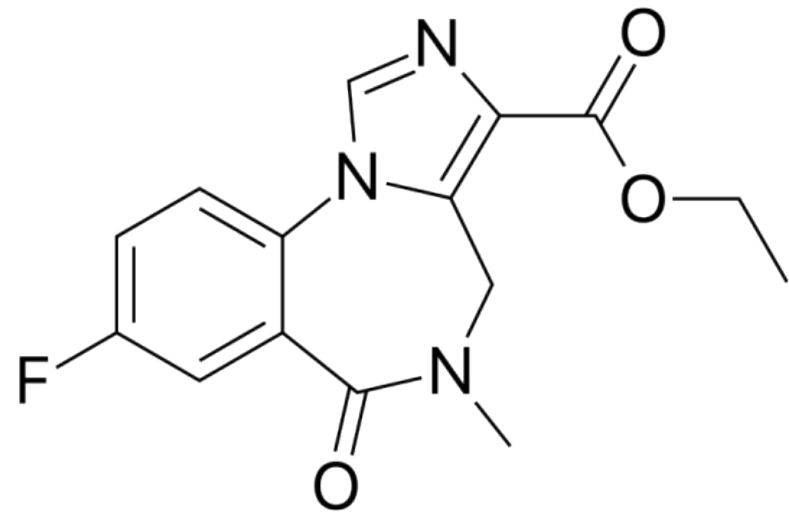
- Flumazenil

- Selective GABA<sub>A</sub> Antagonist

- Speeds up the process

- L. Saxon; S. Borg & A. J. Hiltunen (August 2010). "Reduction of aggression during benzodiazepine withdrawal: effects of flumazenil". [Pharmacology Biochemistry and Behavior](#). **96** (2): 148–151.
    - Sean David Hood, Benzodiazepine dependence and its treatment with low dose flumazenil, *Br J Clin Pharmacol*. 2014 Feb; 77(2): 285–294.

**Danger**



# Future



- Big Fail
  - Oude 2006
    - **88% recommenced use after taper within 15 months**
    - --Likely PAWS
  - We're Doing Something Wrong
    - Much More research needed
    - Have to do Better

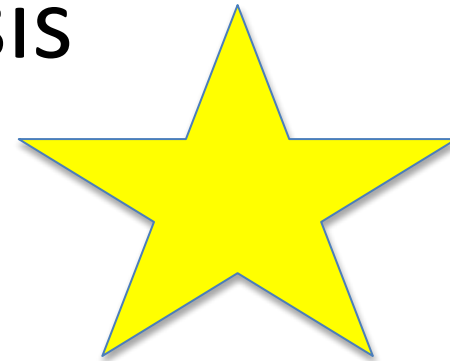


Opinion  
alert

# Pollman BMC Pharma & Tox 2015

## Meta-analysis

- Our review revealed that benzodiazepine and Z drug deprescribing interventions are numerous, largely heterogeneous and poorly described. The pace of publication annually remains stable, indicating maintained interest in the field. Generalizability is problematic.



**First Honest Acknowledgement I've seen  
Of the state of affairs**



# Summary

- Benzodiazepines were heavily marketed esp. to treat Women.
  - The marketing was quite successful
- Benzodiazepines use leads to collateral damage
  - Falls, mortality, drug interactions
  - Dementia?, Cognitive impairment
  - Suicide, Pneumonia, MVA's
- De-prescribing is necessary for some and is problematic for many when attempted
  - Limited guidance from the literature on best practices
  - May be worth reconsidering the standard of care taper
  - Cross titration to antiepileptic with alpha 2 agonists
- PAWS is very real and managing this can help limit relapses



# The End



"BUT I DON'T WANT  
COMFORT.  
I WANT GOD,  
I WANT POETRY,  
I WANT REAL DANGER,  
I WANT FREEDOM,  
I WANT GOODNESS.  
I WANT SIN."

- ALDOUS HUXLEY, BRAVE  
NEW WORLD