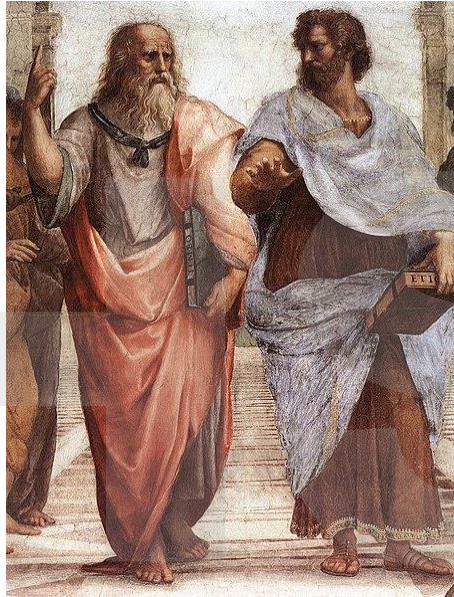


Rise of Benzodiazepines

The Hidden Epidemic



Christopher Blazes, MD
OHSU Addiction Psychiatry Fellowship Director
Assistant Professor Dept of Psychiatry OHSU

Disclosures

- I will be discussing "off label" use of drugs during this presentation

OHSU



- "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”

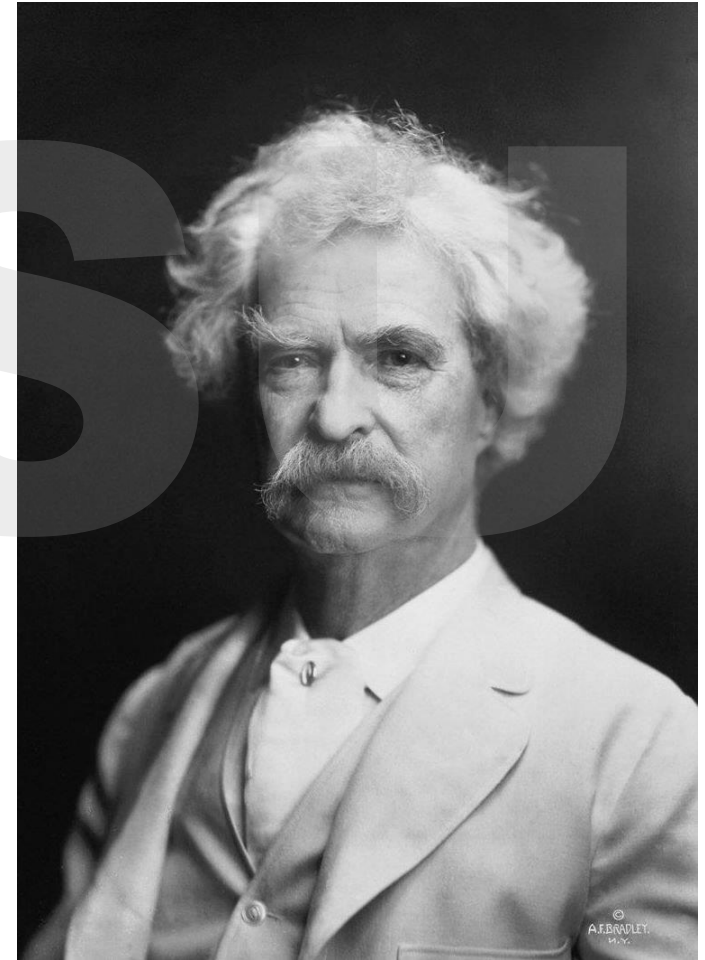
“Facts”

*“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

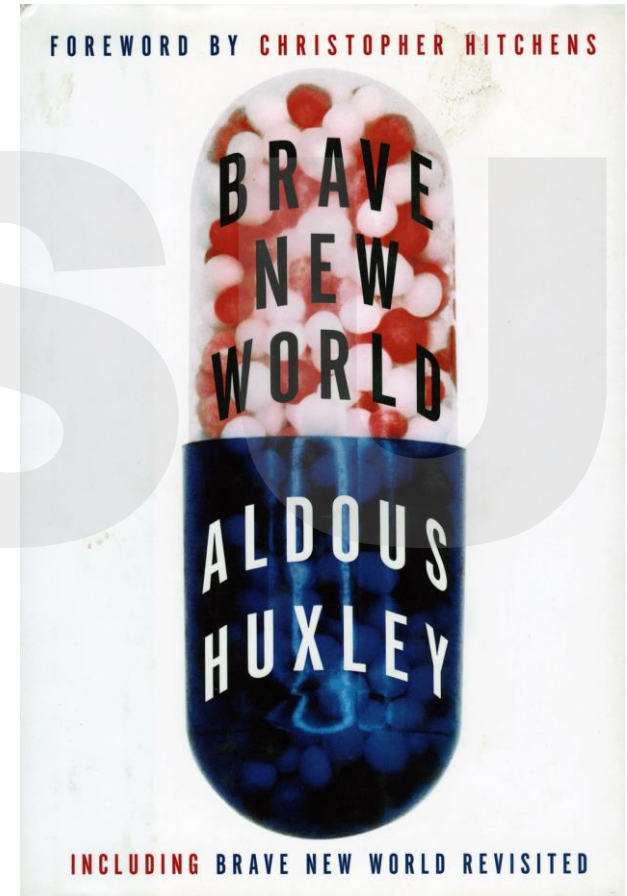
- Reminds me of



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



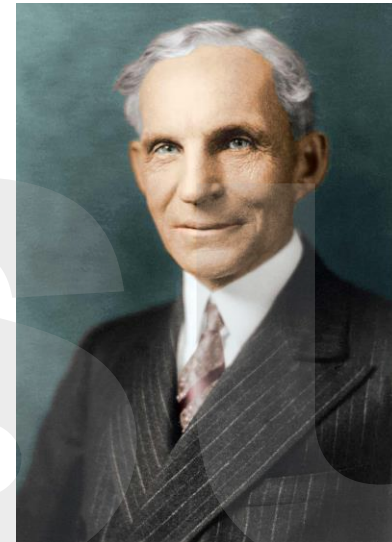
- Ponder if some sort of collective **“Psychic determinism”** has occurred.



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

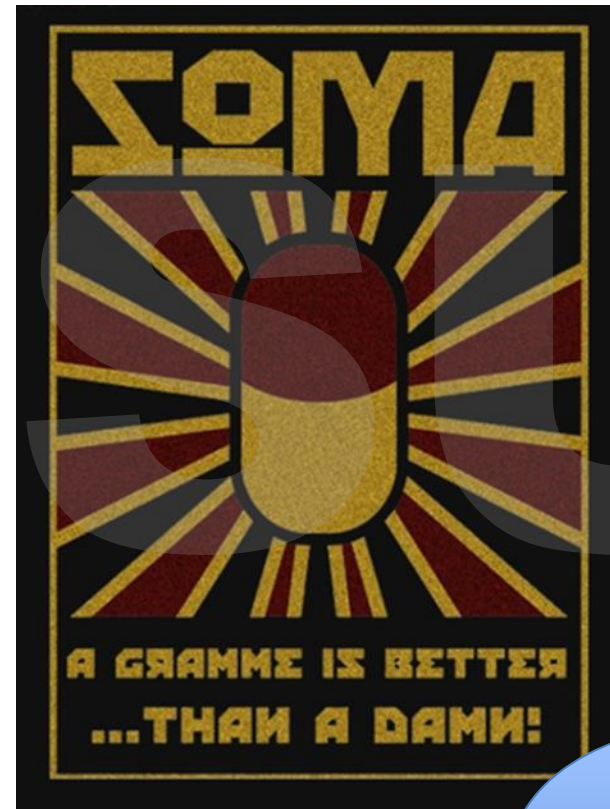


Oppression
though
Making
“Happy”

Brave New World



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



Soma Makes Everything Acceptable

Comfortably numb

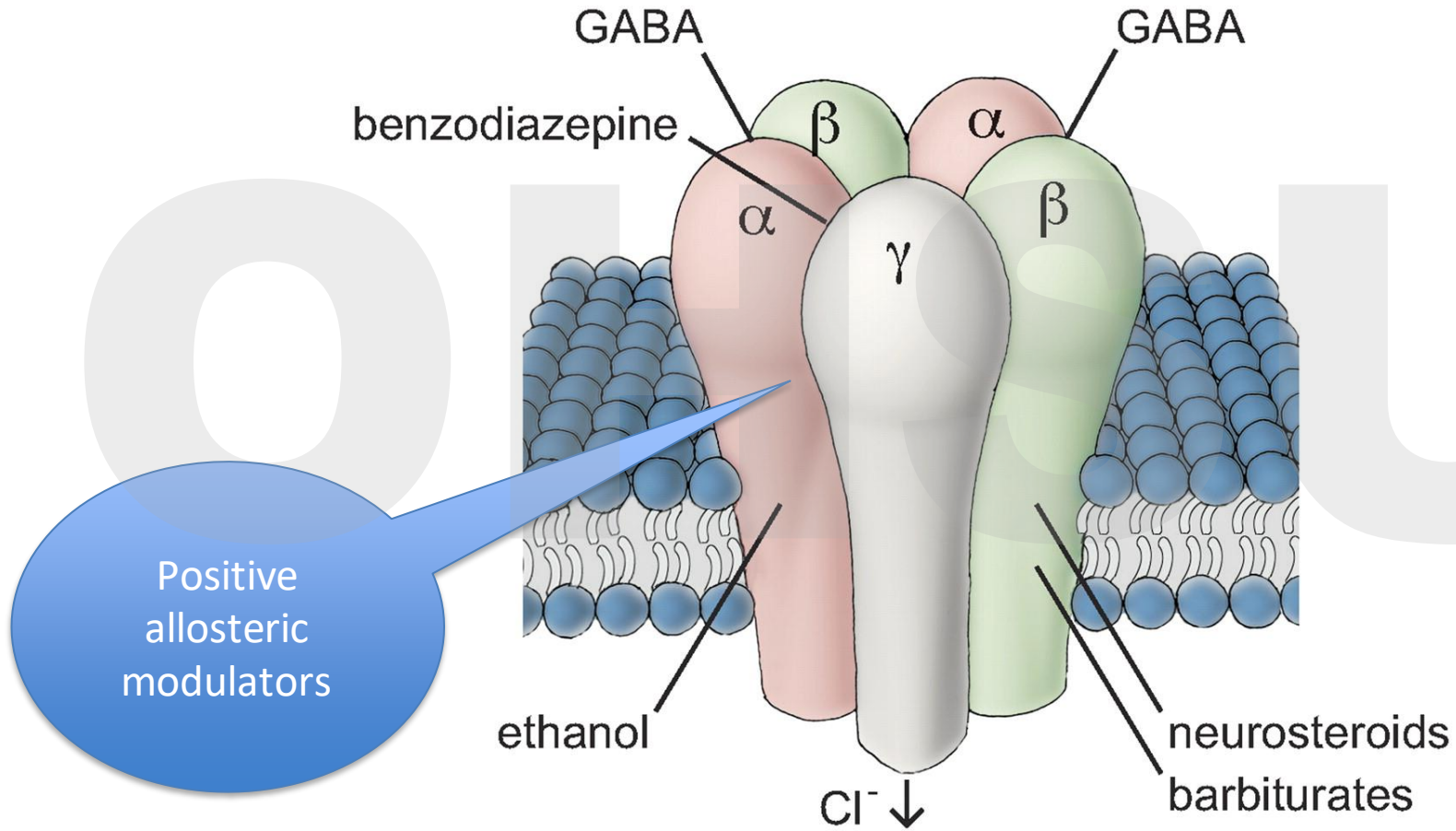
But

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

- It's a Call To Action

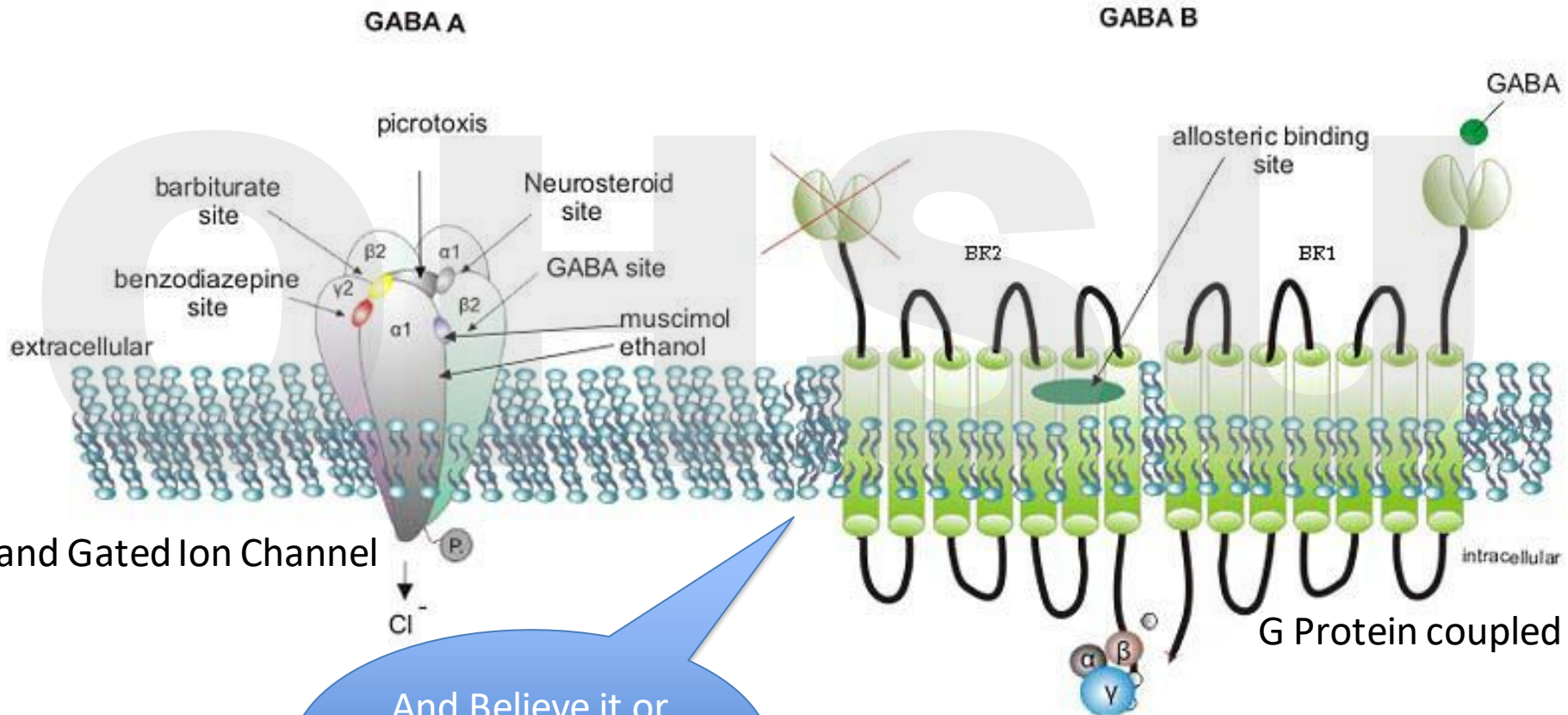


Benzodiazepines act at the GABA Receptor

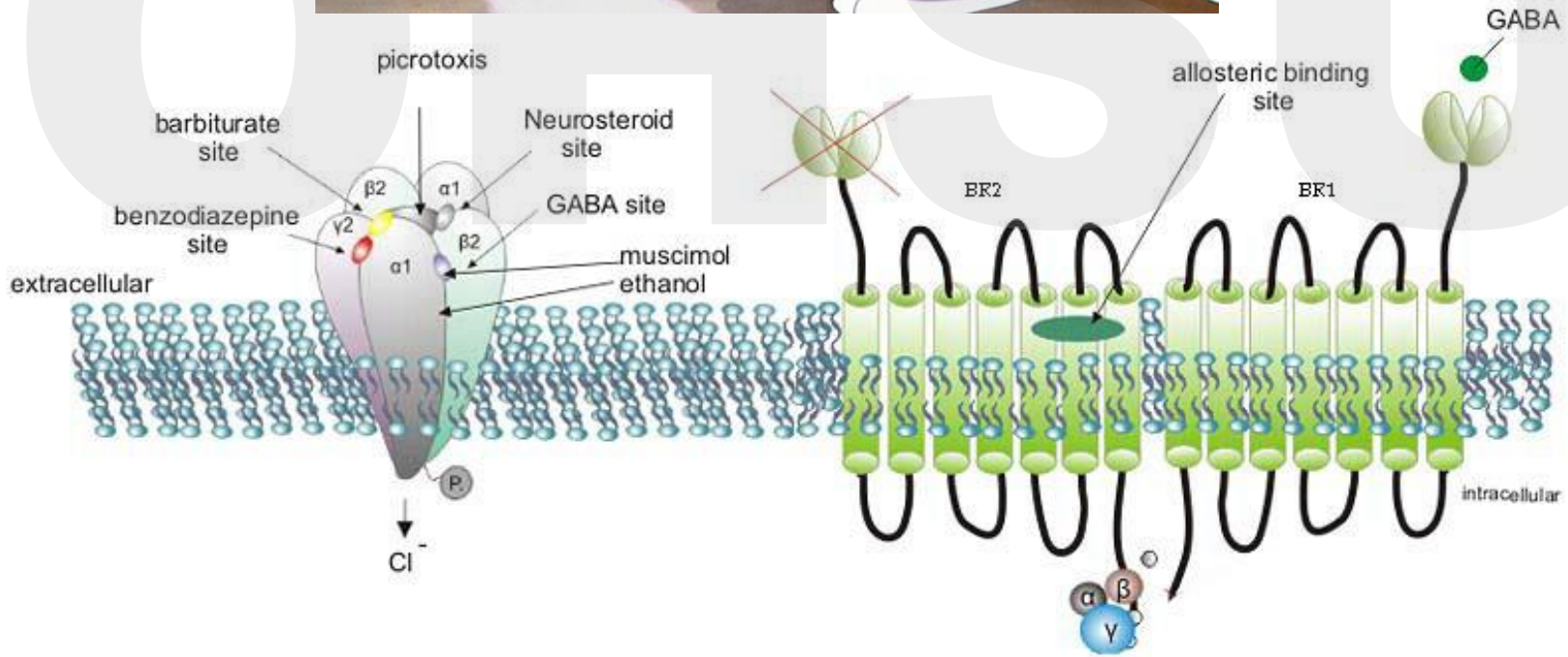
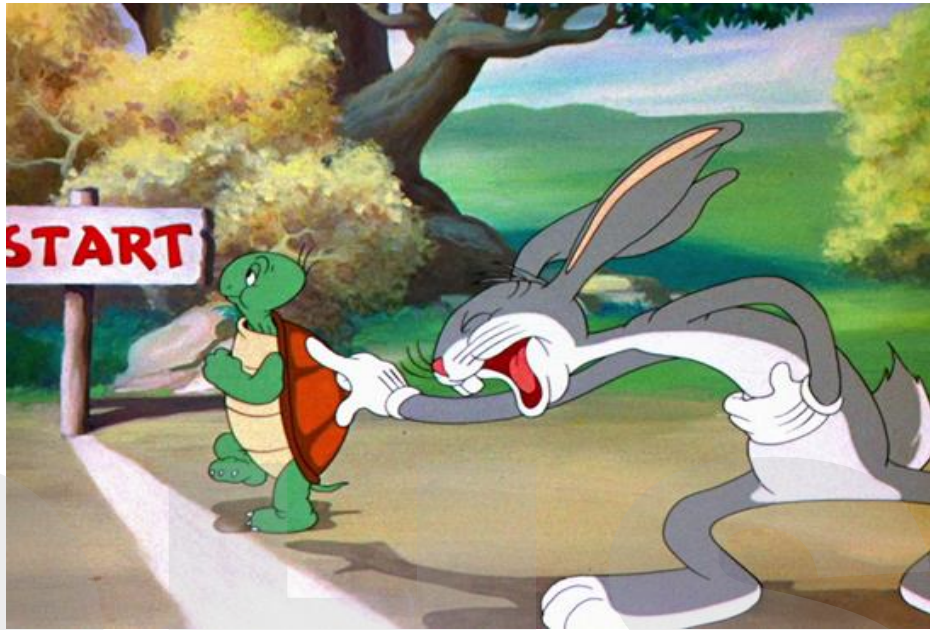


It Gets Much More Complicated

Two Different receptors – Multiple Ligands at multiple Subunits



And Believe it or not..This is clinically relevant!



The Tortoise & the Hare



• GABA_A

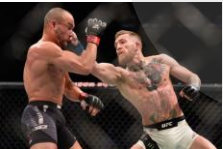


- Ligand gated ion channel that mediate **large and rapid increases** neuronal inhibition

- McDonald and Olsen 1994

– All The Usual Suspects

- Benzodiazepines
- Z-Drugs
- Barbiturates
- Alcohol



• GABA_B



- G-Protein coupled Receptor (GPCR)
- **Slowly maintains the inhibitory tone**

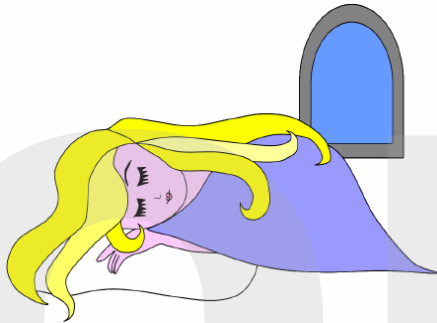
- Bettler et al 2004
- Bowery et al 2002

– Not the Usual Suspects

- GHB
- Baclofen
- Phenibut
- Etoh



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

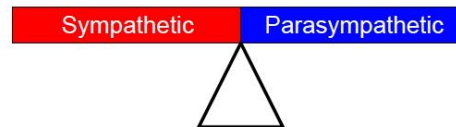
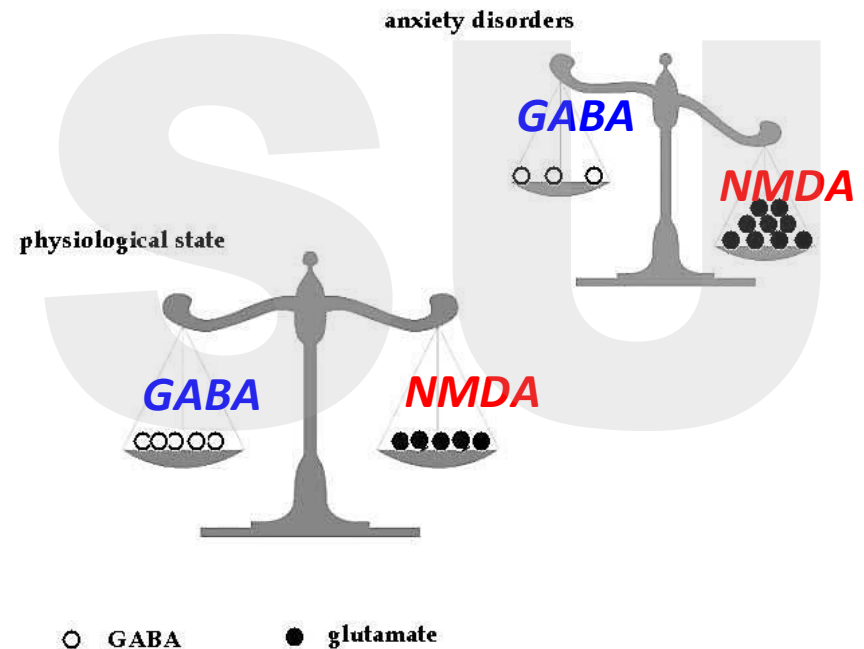


GABA

Glutamate

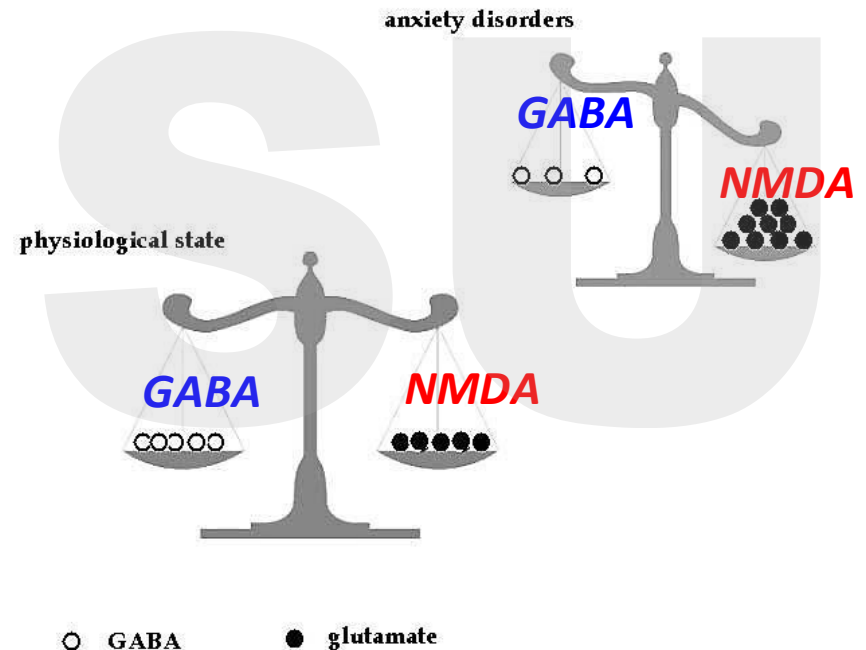
The Balance between the Two is Key

- **GABA = Inhibitory**
 - GABA_A, GABA_B
- **Glutamate = Excitatory**
 - AMPA, KA, NMDA
- Proper Function of the CNS depends on physiological homeostasis
 - Maintained by two opposite forces acting independently

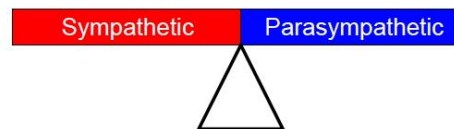


Why is **GABA** So Important

- “GABA and Glutamate are present in practically all functions in the CNS”
- Together they are involved in **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



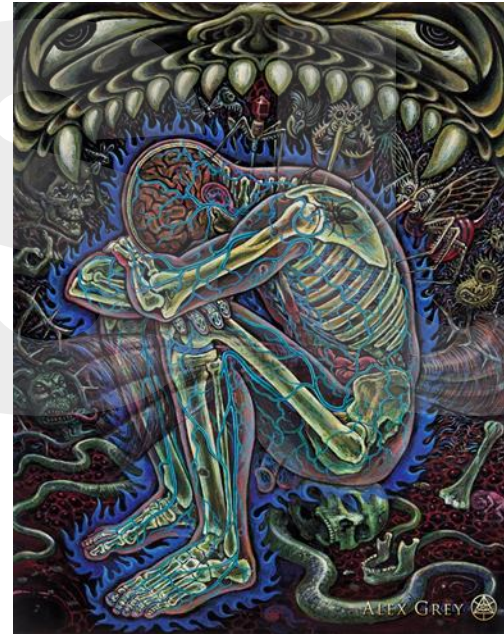
Let's Face It.....

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

- Benzo's Seem to Dissolve Away Anxiety

Temporarily

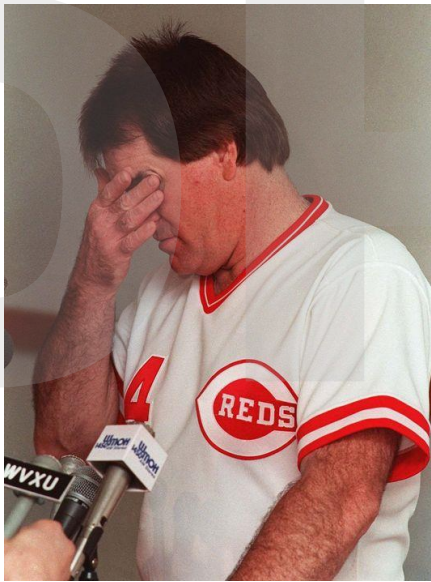
- Benzo's/Z-drugs seem to make you sleep better



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**

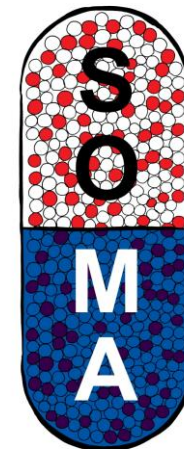
- **Anxiety** is **most** prevalent MH problem in USA

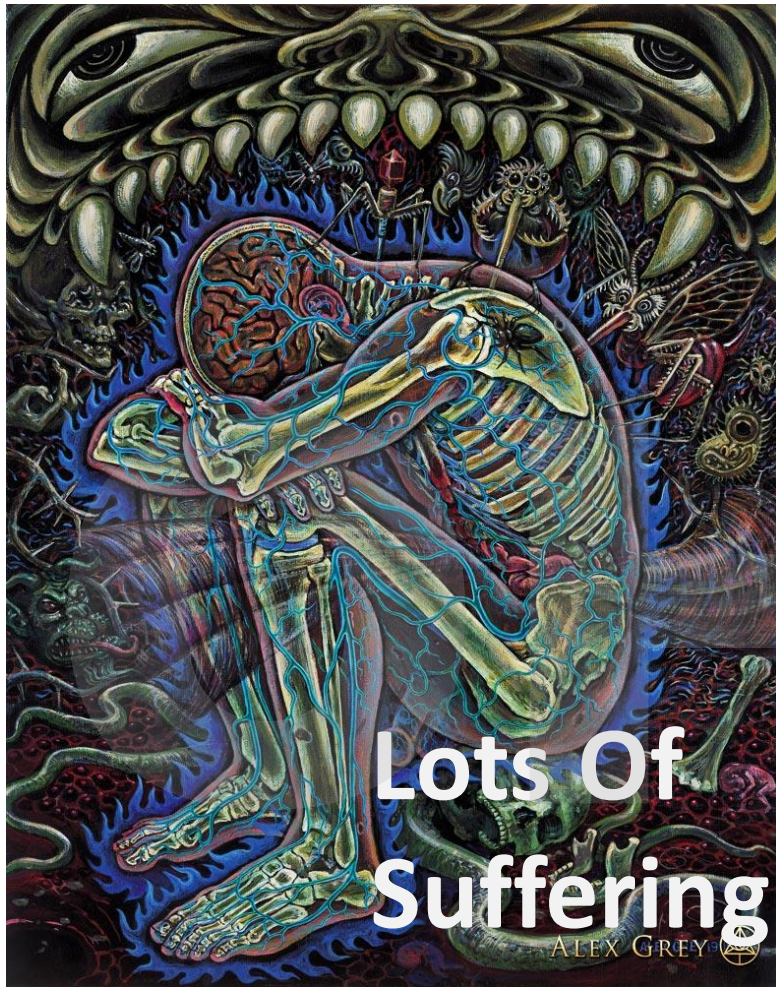
- **19%** 1 yr prevalence in adults
 - National Comorbidity Survey 2017

- 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.



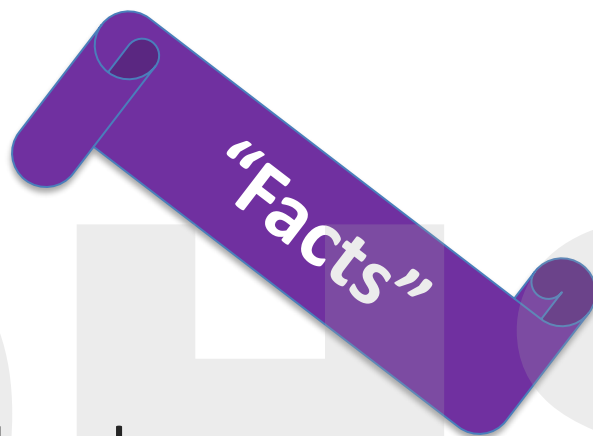


+

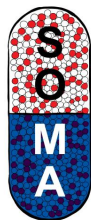


This Is The Story Of What Happened....

Barbiturates Arrived on the Scene



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



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

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. (¼ gr.) to 30 mg. (½ gr.) t.i.d. or q.i.d.

Available for daytime sedation: Tablets, 15 mg. (¼ gr.),

30 mg. (½ gr.); Elixir, 30 mg. per 5 cc. (alcohol 7%);

BUTICAPS® (Capsules **BUTISOL SODIUM** (sodium butabarbital))

15 mg. (¼ gr.), 30 mg. (½ gr.).

McNEIL

McNeil Laboratories, Inc., Fort Washington, Pa.



Barbiturates

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;¹ it has a *familiar sedative* effect. But Mebaral has the advantage of ". . . extremely low incidence of toxicity . . ." and does not produce *sedative daze*.²⁻⁴ Often physicians prefer the sedative effects of Mebaral to those of phenobarbital.^{2,5-10}

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;¹ it has a *familiar sedative* effect. But Mebaral has the advantage of ". . . extremely low incidence of toxicity . . ." and does not produce *sedative daze*.²⁻⁴ Often physicians prefer the sedative effects of Mebaral to those of phenobarbital.^{2,5-10}

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

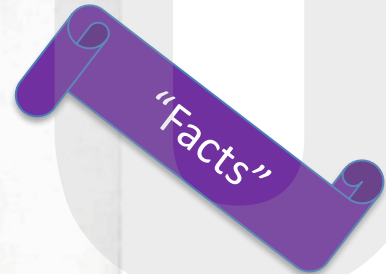
MEBARAL®

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.* 154:1082, May 30, 1953. 7. Briggs, J. F.: *Minnesota Med.* 34:1082, Nov., 1953. 8. Briggs, J. F., and Bellomo, J.: *Dis. Chest* 34:96, July, 1958. 9. Briggs, J. F.: *J. Florida M. A.* 41:718, March, 1955. 10. Cohen, B.: *New England J. Med.* 227:336, Aug. 27, 1942.

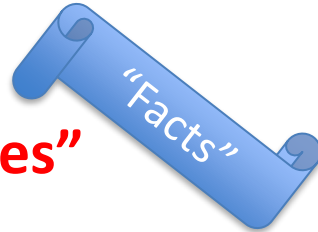
a moth seems a monster



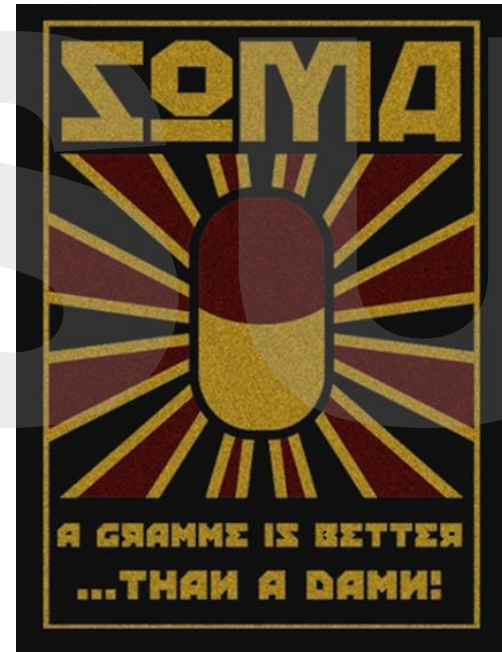
Winthrop LABORATORIES
New York 18th St. & New England Journal of Medicine

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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



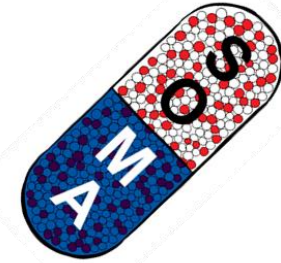
You know this woman.

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.



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.

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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.

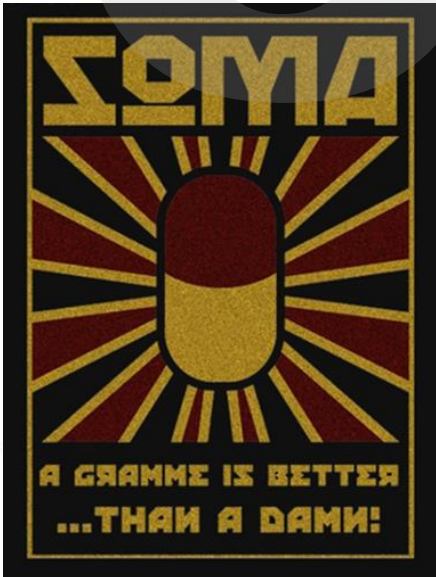
Availability: Capsules of 10, 15 and 30 mg. oxazepam.

To help you relieve anxiety and tension

Serax[®]
(oxazepam)



Wyeth Laboratories
Philadelphia, Pa.



Grand Success Marketing

- The Marketing Destigmatized Anxiety

- Mostly Directed to Women!!!!!!!

- Between 1969 and 1982, diazepam was the most prescribed drug in America
 - over 2.3 billion doses sold in 1978

Just like Prozac destigmatized Depression



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**

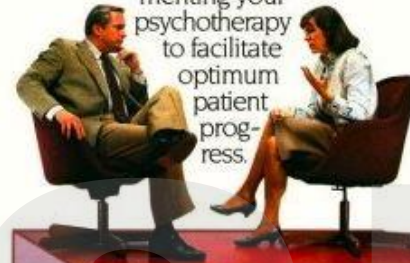


Pharma
needed to find
a niche for
xanax

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 0.5 mg Tablets
alprazolam ©

COMPLEMENTS AN EFFECTIVE THERAPEUTIC ALLIANCE

Pharma found another niche for xanax

Xanax 0.5 mg Tablets
alprazolam ©

COMPLEMENTS AN EFFECTIVE THERAPEUTIC ALLIANCE

Upjohn

© 1987 The Upjohn Company. Please see next page for brief summary of prescribing information.

275/500 patients inherited from a psychoanalytic center were on BZD's

By Now, You get the Idea

IN A WORLD
WHERE CERTAINITIES
ARE FEW...

NO WONDER
Ativan
(lorazepam)
IS PRESCRIBED BY SO MANY
CARING CLINICIANS.

“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%!!!



Corroborative Data

Recent Study from Spain 2020

- The dispensing prevalence of BZDs use in 2015 was:
 - 14.2% overall
 - 18.8% in women
 - 9.6% in men
 - 36% in those over 65 years.

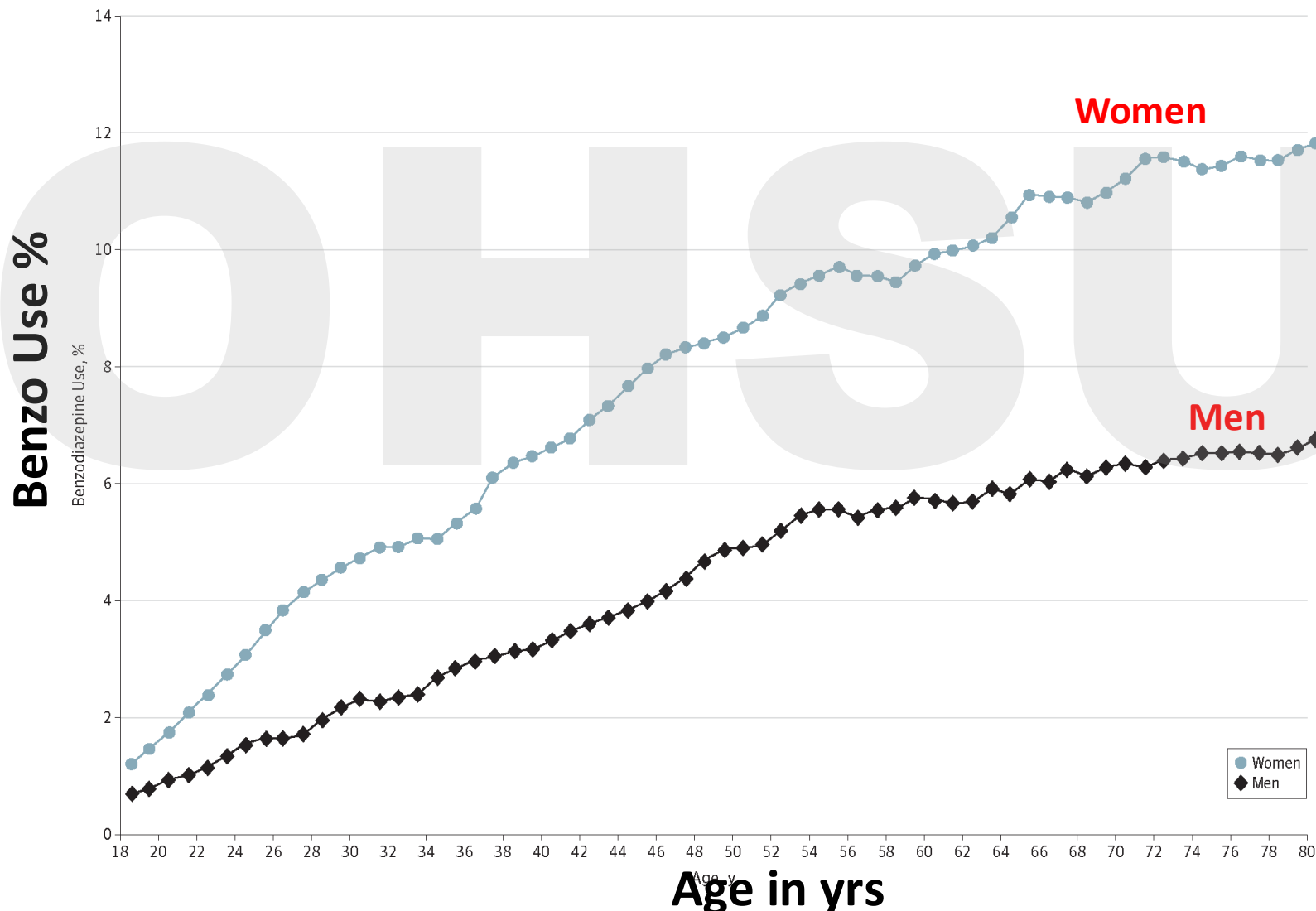


Lleida

Trends in the consumption rates of benzodiazepines and benzodiazepine-related drugs in the health region of Lleida from 2002 to 2015 F. Torres-Bondia, J. de Batlle, L. Galván, M. Buti, F. Barbé & G. Piñol-Ripoll BMC Public Health volume 20, Article number: 818 (2020)

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.** [Olfson M¹, King M², Schoenbaum M³. *AMA Psychiatry*. 2015 Feb;72\(2\):136-42. doi: 10.1001/jamapsychiatry.2014.1763.](#)

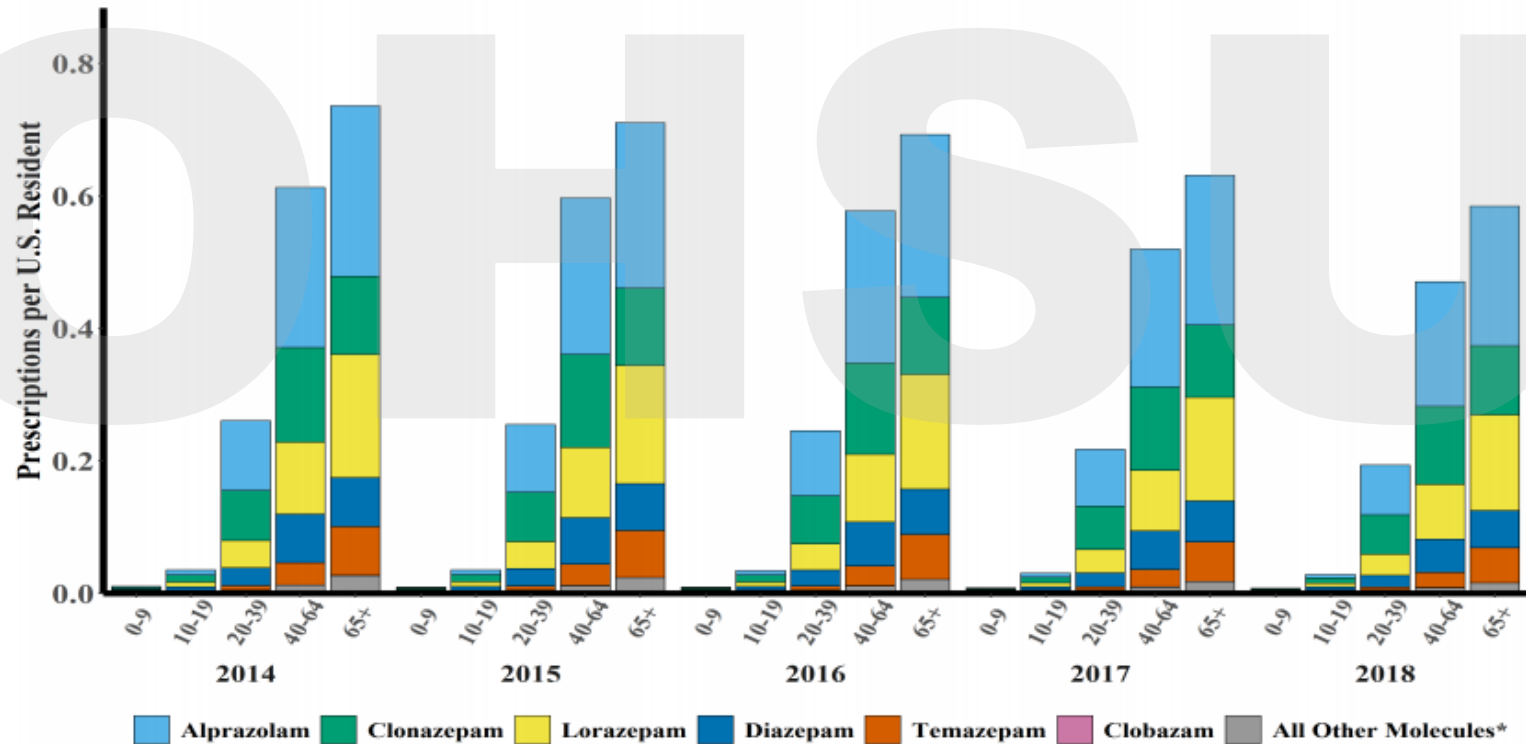


Its slowly getting a little Better

IQVIA National Prescription Audit (Private Data science Co)

Benzodiazepine Prescribing, by Patient Age Group

Benzodiazepine prescriptions dispensed from outpatient retail pharmacies per U.S. resident, by patient age group



December 2019. File: 2019-800 Benzo PI TRx 1-27-2019.csv. NVSS Census Files. (2019). U.S. Census Populations With Bridged Race Categories. Retrieved from https://www.cdc.gov/nchs/nvss/bridged_race.htm. *All Other Molecules include: chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, quazepam, and triazolam

Source: IQVIA, National Prescription Audit™ New To Brand (NPA NTB). January 2014 - December 2018. Data Extracted

We Continue to Prescribe Inappropriately

- 2017 Article evaluating the home prescriptions of 1308 hospitalized patients
- Only 20–30% of prescription of BZDs prescriptions were judged to be appropriate.
 - Wrong Diagnosis
 - Wrong duration



Pek EA, Remfry A, Pendrith C, Fan-Lun C, Bhatia RS, Soong C. High prevalence of inappropriate benzodiazepine and sedative hypnotic prescriptions among hospitalized older adults. *J Hosp Med.* 2017;12:310–6.

Batty G, Hooper R, Osborne C, Jackson S. Investigating intervention strategies to increase the appropriate use of benzodiazepines in elderly medical in-patients. *Br J Clin Gov.* 2001;6:252–8.

Pakistan Study of Resident Physicians

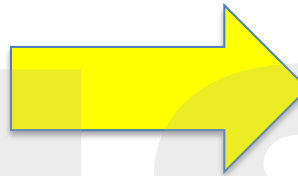
- BENZODIAZEPINE USE AMONG RESIDENT DOCTORS IN TERTIARY CARE HOSPITAL, Aftab Alam Khan, J Ayub Med Coll Abbottabad 2019;31(4)
- 278 Residents in the Study
 - 48.7% use BZD's
 - Primary reasons
 - #1) Insomnia
 - #2) Anxiety

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

There's More?

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

But

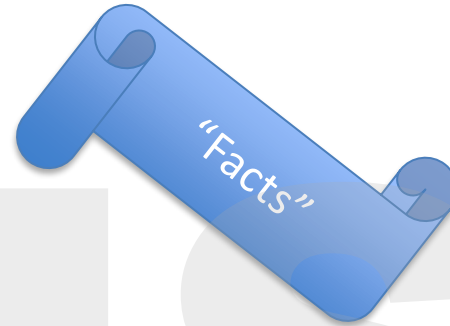


DEA Schedule ---?



DEA Schedule IV

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



BZD's Activate Classic Abuse Pathways

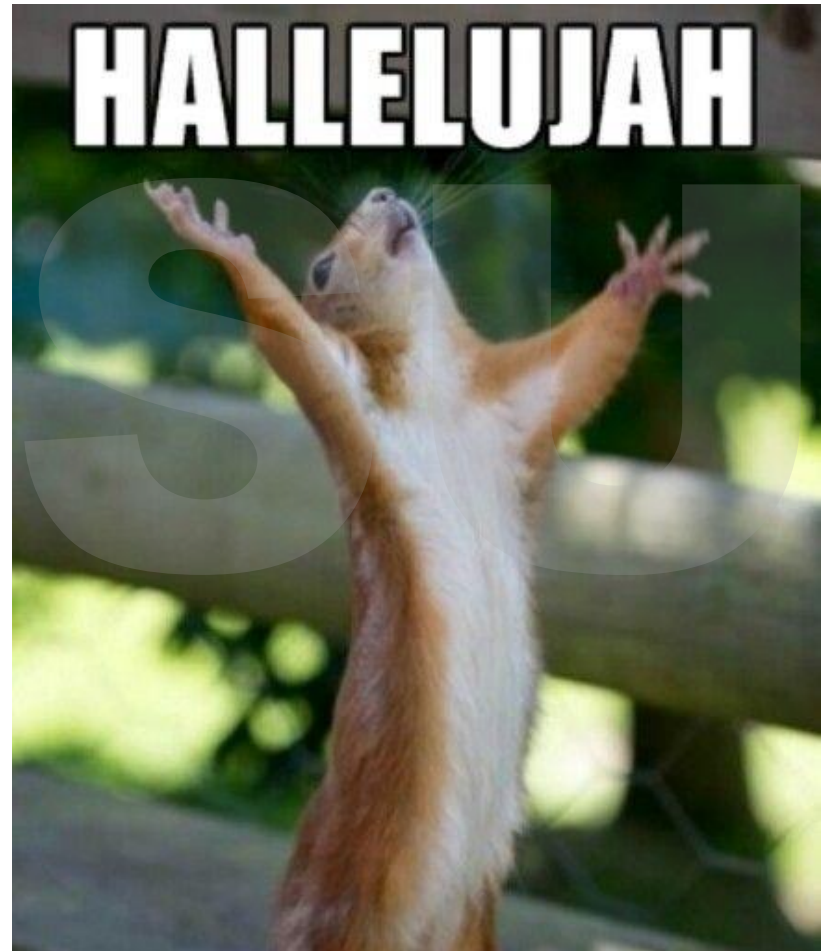
- Tan et al Nature 2010
 - BZD's activate dopaminergic neurons in VTA by modulating GABA_A receptors in neighboring interneurons.
- Bottom Line
 - VTA is where the cell bodies originate that release Dopamine in the Nucleus Accumbans
 - Which is what defines a drug of abuse

**What Defines A
drug of Abuse
-DA release in
NA**



New Black Box Warning

- FDA Drug Safety Communication, Sept 23, 2020
 - Forced all benzodiazepine package inserts to include a boxed warning:
 - "serious risks of abuse, addiction, physical dependence, and withdrawal reactions"





Pay For Performance



PRESS GANEY®



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





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

- 2nd Most prescribed Psych medication in America
 - #1—Zoloft
 - #2---Xanax
 - 39,916,469 prescriptions



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**
 - Oxzapam
 - 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**



Alprazolam-----Why So BAD?

- Low Lipophilic and not Protein Bound
 - Doesn't stay around long
 - Short Half Life
- High Potency
 - Previous slide- more DA release
 - Just plain works
- Rapid onset Withdrawal
 - No metabolites to ease the withdrawal
 - People need more sooner just to feel normal
- Withdrawal More severe (Idiosyncratic)
 - Browne and Hauge 1986, Kantor 1986
 - Psychosis-- Zipursky et al 1985
 - Suicidal-- Risse et al 1990
 - **Alprazolam Activates Alpha 2 receptors (other benzos don't)-- Erikson et al 1986**
- ***Can Become Physiologically dependent in one week***
 - Galpern et al 1991—animal study
- More Likely to Cause BZD induced hyperanxiety
 - Fyer et al 1987
 - Pecknold et al 1988



Built in
clonidine



What??

What's The Deal With Gabapentin?

WHAT'S THE DEAL



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 & 3 references....
 - **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% - (Gomes 2017)**

[-Bonnet U¹, Scherbaum N²](#) **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;

-Gabapentinoid Abuse in order to Potentiate the effects of methadone: A survey amongst substance Misusers. Colin Baird Eur Addict Res 2014;20:115-118

2020 JAMA

- Cohort study of 5,547,667 US surgical admissions:
 - adding gabapentinoids to opioids was associated with an increased risk of opioid overdose and other opioid related adverse events



Association of Gabapentinoids With the Risk of Opioid-Related Adverse Events in Surgical Patients in the United States

Katsiaryna Bykov, PharmD, JAMA Network Open. 2020;3(12):e2031647.

Gabapentin

- Overall...I think its gotten a bad rap
 - I use it all the time

OH S U

O



SU



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
- More and more often I'm seeing patients addicted solely to zolpidem
 - Several per year



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.
- Victorri-Vigneau C, Dailly E, Veyrac G, et al. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) networks survey. *Br J Clin Pharmacol* 2007;64:198-209.
- Cubala WJ, Landowski J. Seizure following sudden zolpidem withdrawal. *Prog Neuropsychopharmacol Biol Psychiatry* 2007;31:539-540
- Freudenreich O, Menza M. Zolpidem-related delirium: a case-report. *J Clin Psychiatry* 2000;61:449-450.
- Aragona M. Abuse, dependence and epileptic seizures after zolpidem-withdrawal: review and case-report. *Clin Neuropharmacol* 2000;23:281-283.
- [Repeated Zolpidem Treatment Effects on Sedative Tolerance, Withdrawal, mRNA Levels, and Protein Expression](#)
- Wright, Brittany T.. The University of Tennessee Health Science Center, ProQuest Dissertations Publishing, 2016. 10131840
- 2. Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: A review of case reports and epidemiological data. *Addiction* 2003;98:1371-8.
- 5. Licata SC, Mashhoon Y, Maclean RR, Lukas SE. Modest abuse-related subjective effects of zolpidem in drug-naive volunteers. *Behav Pharmacol* 2011;22:160-6.
- 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; Kurtzhals, 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

- Not many would argue against the fact that there can be **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 acting BZDs
- Long term use
 - **Highest risk If use > 3yrs—**
 - **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 Scandinavia*, 2018

2020 Paper

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 Osler¹](#), [Martin Balslev Jørgensen¹](#), 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
 - **Some results were compatible with a protective effect.**
 - Insomnia and anxiety are known risk factors for dementia

Dementia – Controversial

2019 Paper

- 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”

Review of Reviews 8/2021


- To conduct a systematic review, appraise and summarize published synthesis studies on the association between the use of benzodiazepines (BZDs) and related drugs (BZRDs) and the risk of dementia development.
 - Included 15 review articles
- “Data suggest an association between the use of BZDs and increased risk of cognitive decline and dementia **in older adults**”

Is there a link between the use of benzodiazepines and related drugs and dementia? A systematic review of reviews. Patrícia Ferreira, European Geriatric Medicine 1 April 2021 / Accepted: 6 August 2021

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

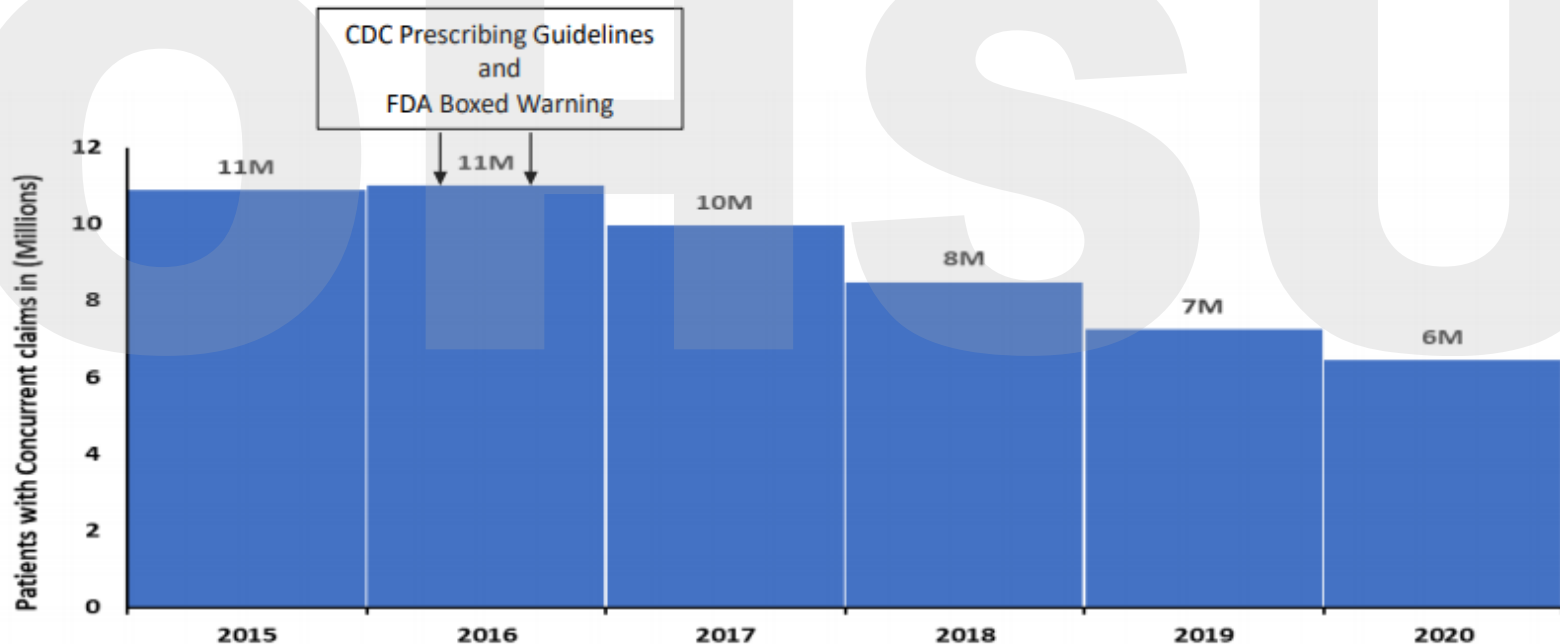
Pinray, “Basic & Clinical Pharmacology & Toxicology” 2008



We're Getting Better But its still happening a lot

Concurrent Dispensing of Benzodiazepines and Opioid Analgesics

Estimated number of patients with concurrent prescriptions for opioid analgesics and oral benzodiazepines from U.S. outpatient retail pharmacies



Opioid analgesics included oral, transdermal, and transmucosal formulations and excluded cough/cold products, migraine products, and buprenorphine-containing medications for opioid use disorder (MOUD). Based on dispensed prescription data, estimated number of patients captured with an episode of concurrency defined as an overlap of at least 1 day supply of an opioid analgesic prescription and an oral benzodiazepine prescription.

Source: Symphony Health Solutions' IDV® (Integrated Dataverse). Data extracted June 2021.

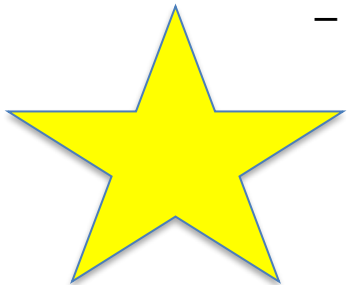
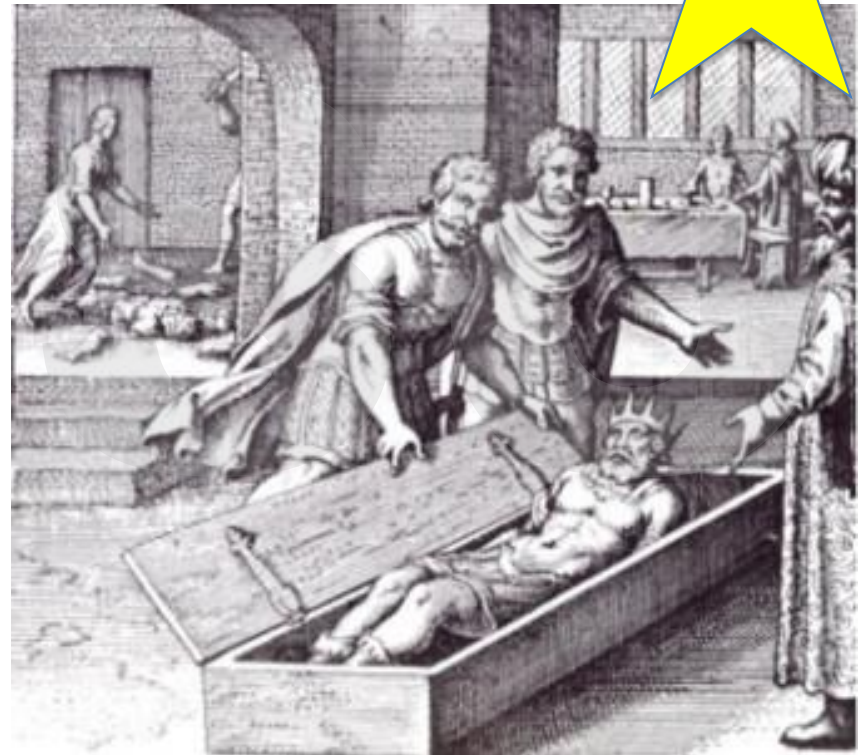
BZD Z-drugs MVAs

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



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



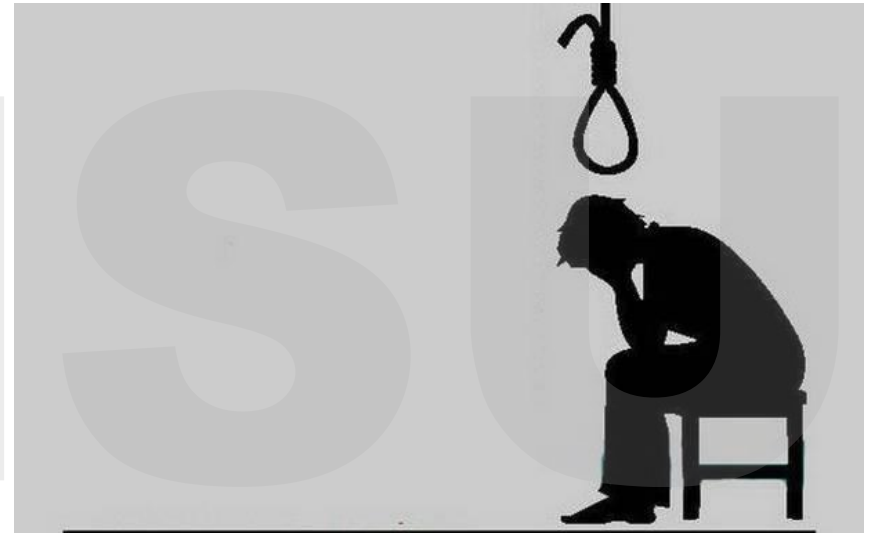
JAMA Dec 2020

- This retrospective cohort study used a large, nationally representative US data set (the National Health and Nutrition Examination Surveys [NHANES]) from 1999 to 2015.
- 5212 participants followed up for a median of 6.7 years
- a significant increase in all-cause mortality was associated with benzodiazepine and opioid cotreatment (hazard ratio, 2.04 [95%CI, 1.65-2.52]) and **benzodiazepines without opioids** (hazard ratio, 1.60 [95%CI, 1.33-1.92]).

Association Between Benzodiazepine Use With or Without Opioid Use and All-Cause Mortality in the United States, 1999-2015, Kevin Y. Xu, MD et al JAMA Network Open.2020;3(12):e2028557.

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

2019 Meta-analysis

- 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.

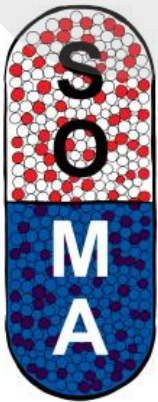
Prescriptions Increasing in # and Size

- Bachhuber 2016
 - Am J Public Health

–1996 to 2013

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

– Quantities tripled



Yikes

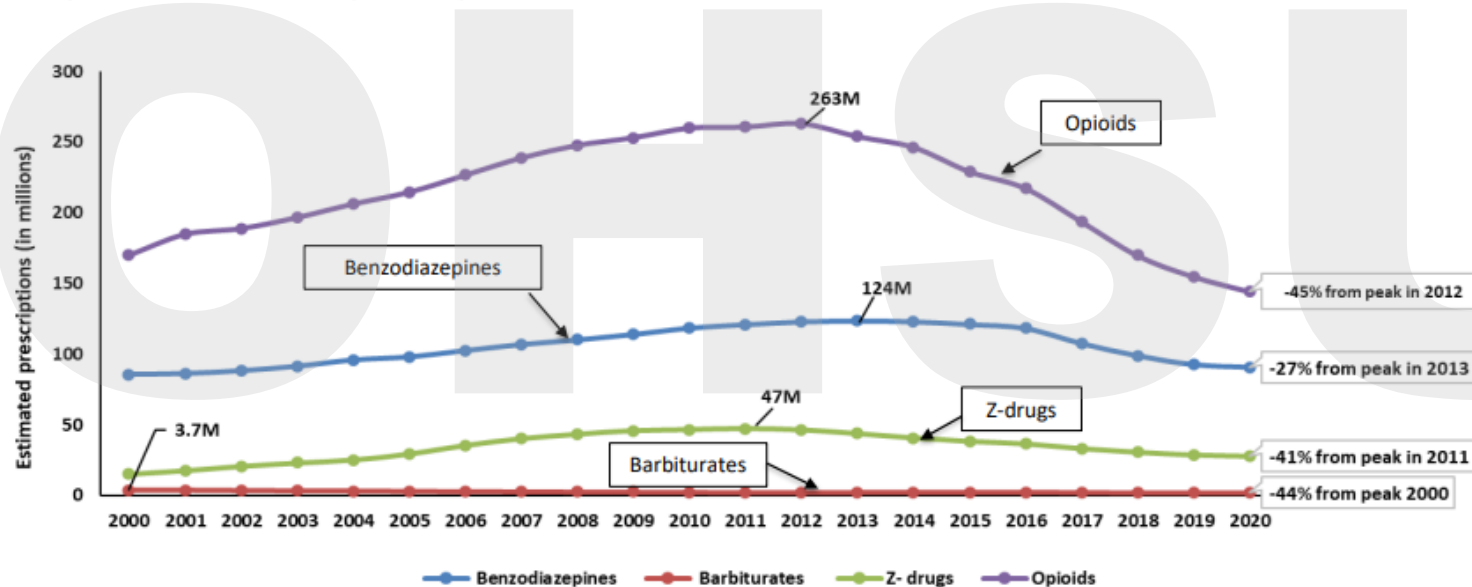
National Prescription Audit Data extracted 6/2021

Shows it is getting a little better



U.S. Benzodiazepine Prescribing Trends, in Context

Estimated prescriptions dispensed for Benzodiazepines, Barbiturates, Z- drugs and opioid analgesics (excluding injectables) from U.S. outpatient* pharmacies



Source: IQVIA, National Prescription Audit (NPA). January 2000 - December 2020. Data Extracted June 2021.

*Data includes outpatient retail and mail-order pharmacies. Excludes injectables.

**Opioid analgesics included all non-injectable formulations and excluded cough/cold products and buprenorphine-containing medications for opioid use disorder (MOUD) products

***There was a change in the underlying data and methodology of the proprietary database, IQVIA NPA, to manage prescription claims that are voided and/or reversed starting in 2017. Benzodiazepine estimates using this new methodology were approximately 3% lower compared to legacy estimates. Changes in the projection methodology do not affect prescription volumes dispensed from the mail-order/specialty pharmacies. Retail channel comprised 84% and mail channel 3% of total market, non-retail was not included in this analysis.

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



Sometimes its best to get people off
these meds



Options Summary

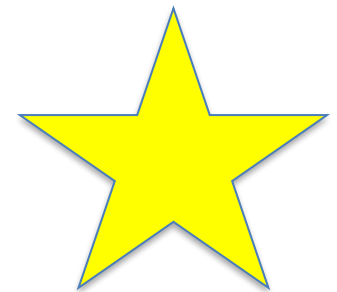
- #1) Convert to long acting Benzo using equivalency chart
 - Taper over Weeks to months (or even years)
 - Requires motivated and compliant patient
 - Often challenging in use disordered people
- #2) Prolonged taper on Same Benzo
 - Very variable guidance
 - Ex. 50% initially
 - Ex. 10% per week after
 - **Some require VERY long tapers**
- #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
- Specific Recs are pretty non specific
 - 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**



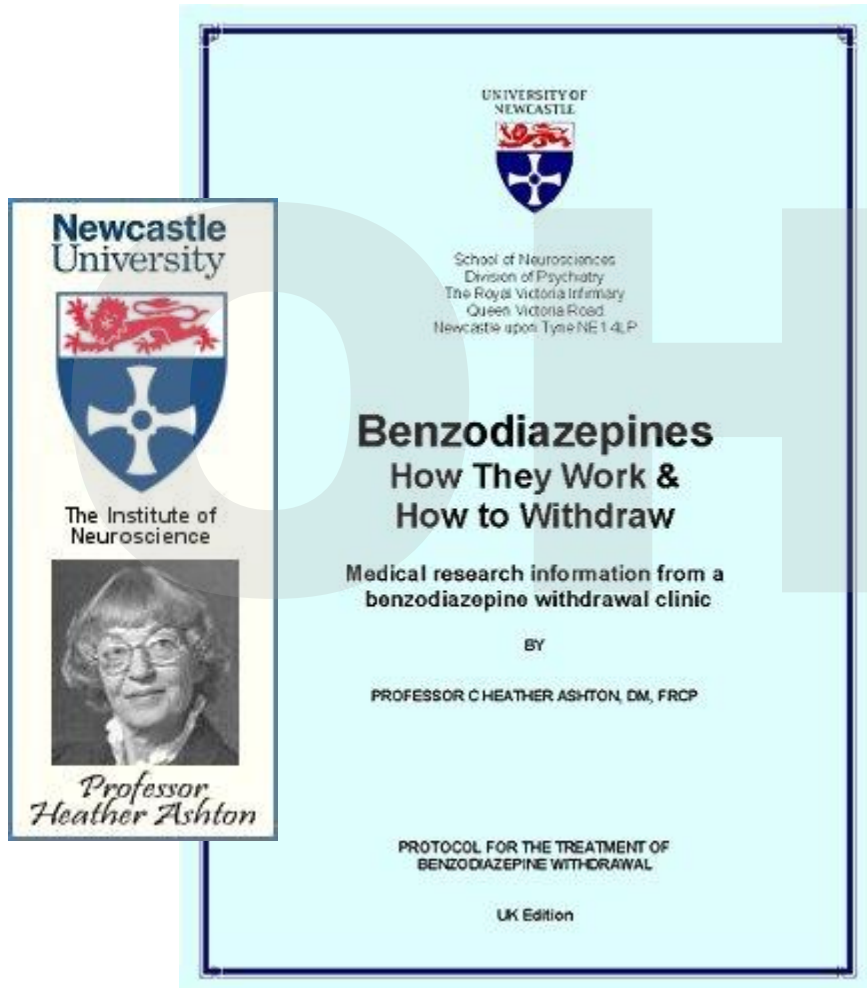
– Darker Cochrane Review 2015 Meta analysis of CBT + taper vs taper alone for **BZD withdrawal**

- CBT + taper was better

“Facts”

Where did this culture come from?

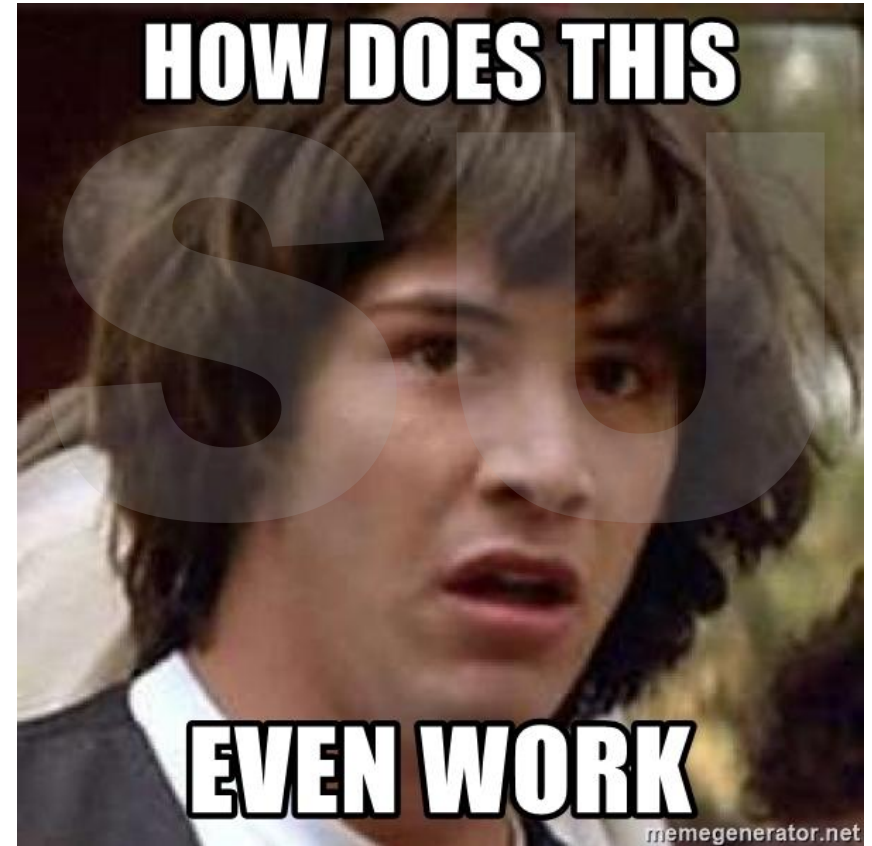
Heather Ashton



- First to argue switch to long acting and slow taper for months
- Years of clinical experience
- **No Studies done**
- Best for non Use-disordered patients

Long Tapers are Effective?

- I Invite you to question this?
- Is this consistent with your experience?
- In my opinion- often not successful



Don't Forget Long Tapers are a marathon

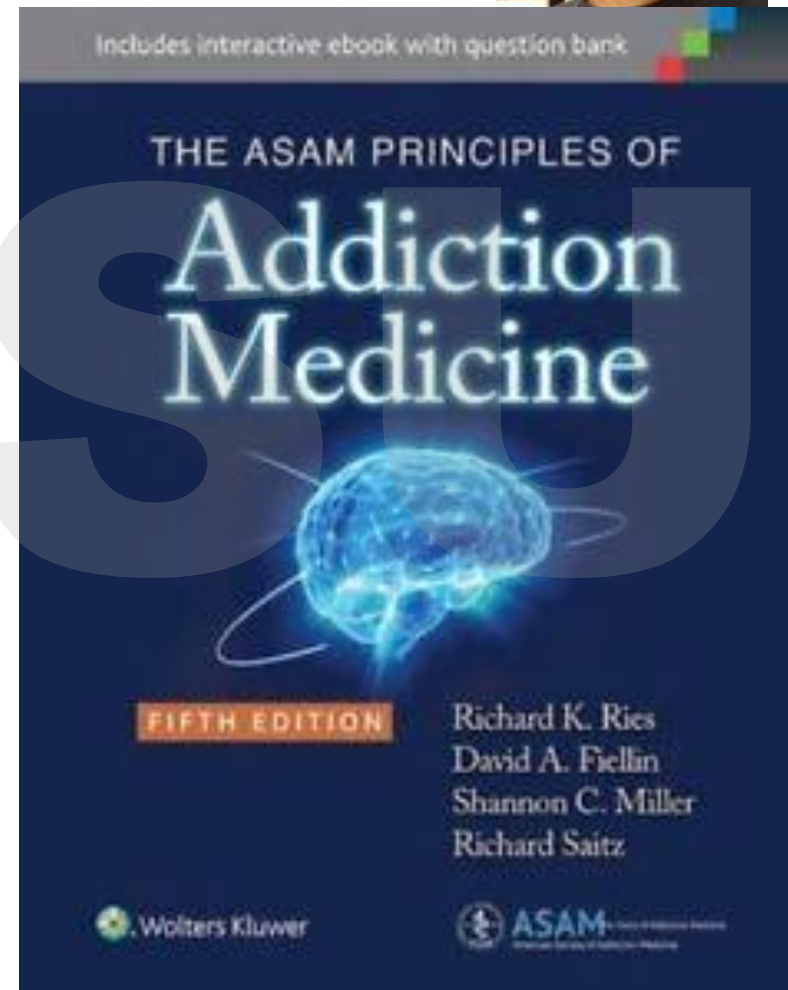
- **Tapering patients, most often, will be uncomfortable throughout the entire taper....& long after**
- **Supportive measures Throughout taper & PAWS**



Alternative Discontinuation

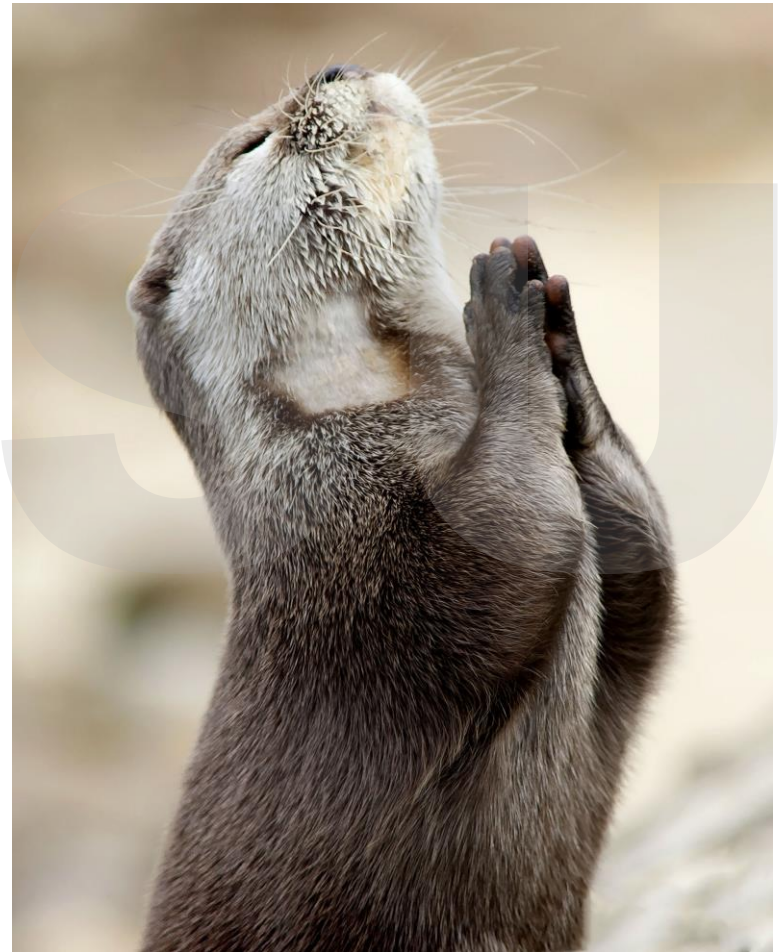


- Rapid taper of Benzo over 3 days
 - 1/3—1/3—0
 - **Usually Inpatient**
- Cross Titrating
 - Depakote 500mg tid or
 - Carbamazepine 200mg tid or
 - Gabapentin 800mg tid
- Continue Antiepileptic for at least 1 month (I think longer)
- Start SSRI's for rebound anxiety
 - Ries J. Psychoactive Drugs 1998
 - 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 supratherapeutic doses
 - National Center for PTSD
 - **Ptsd.va.gov 2013**
- **Soyka NEJM 2017**
 - **Recommends hospitalization for Diazepam dose >100mg/day**



Max recommended Dose Xanax-4mg
Klonopin-4mg
Ativan-10 mg
Diazepam-40mg

From My experience...

- What's the best choice?

OHSU

- Phenobarbital with
Alpha 2 agonists

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

- Been used at Bayview for 20 years
- Maintain doses of methadone/bup
 - Might have to hold doses for sedation

Table 2
Phenobarbital protocol and percentage of doses held

Dose/Interval	No. of doses in protocol	Percentage who received all doses ^a	Percentage of doses held because of sedation ^a
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

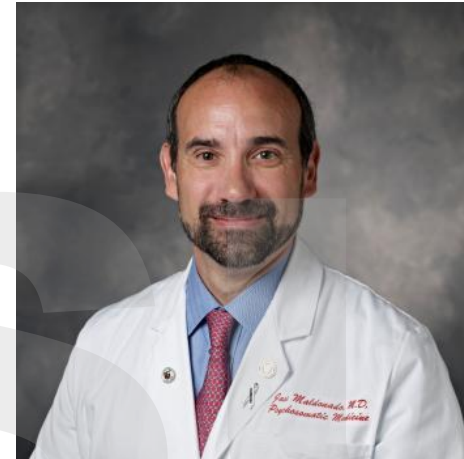
^a Patients who were discharged against medical advice were not included.

Main outcomes

Seizures	0 (0%)
Delirium	3 (1.0%)
Falls	0 (0%)
Sedation	84 (27.1%)
Left against medical advice	53 (17.1%)
ED visits within 30 days	22 (7.1%)
Readmission with 30 days	19 (6.1%)

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**



Alpha 2 Agonists

- I Don't consider these adjunct meds
- Necessary to include



Opinion Alert

I use a Modified Maldonado

Pheno's can be dangerous used for Outpt detox

- Residential/Inpatient
 - Immediate discontinue Benzo
 - **Phenobarbitol**
 - Loading dose 64-192mg
 - Age, weight comorbidity
 - 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**
 - Start 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**



Bottom Line

- For the sick, addicted, or elderly, or those having been on high doses or for long duration
 - Go really fast- Inpatient
 - Or
 - Go really really slow – outpatient (6 months 2years)
- Stable, healthy patients with no use disorder... can likely tolerate more rapid home tapers



Rapid home tapers often lead to functional and psychiatric destabilization – risk of suicide – recent law suits

Why All This Debate?

- Withdrawal is Bad News!



Withdrawal Review

- Benzo Withdrawal is widely variable and unpredictable!
- We often underestimate how bad it can be



Kindling Effect

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



Klonopin Withdrawal Timeline

First Symptoms



Last dose



1-3 Days

General: Symptoms last 2-4 days



Peaks Wk 2

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



Months

Years

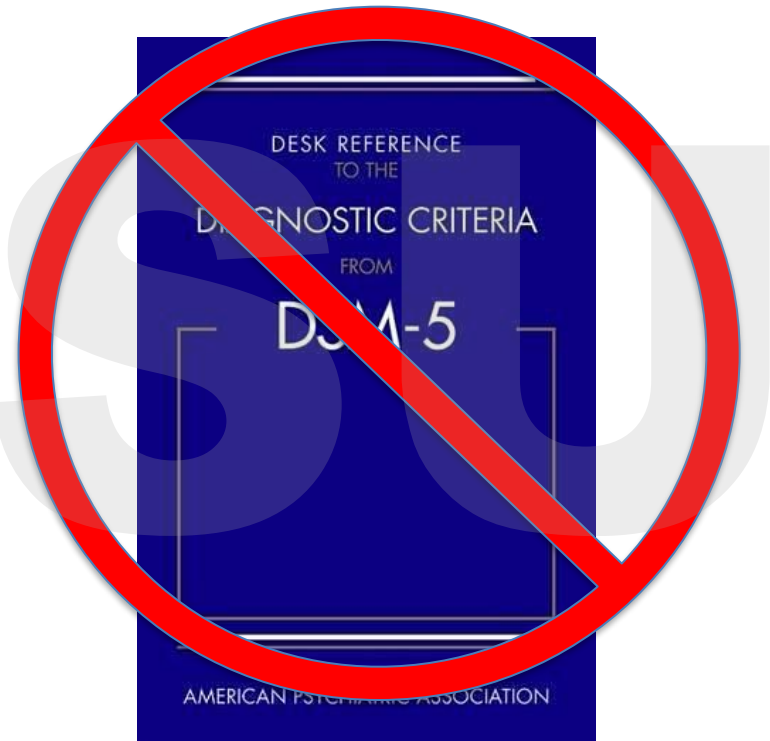
Symptoms can last a few days up to several months or even years if not addressed professionally.

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.

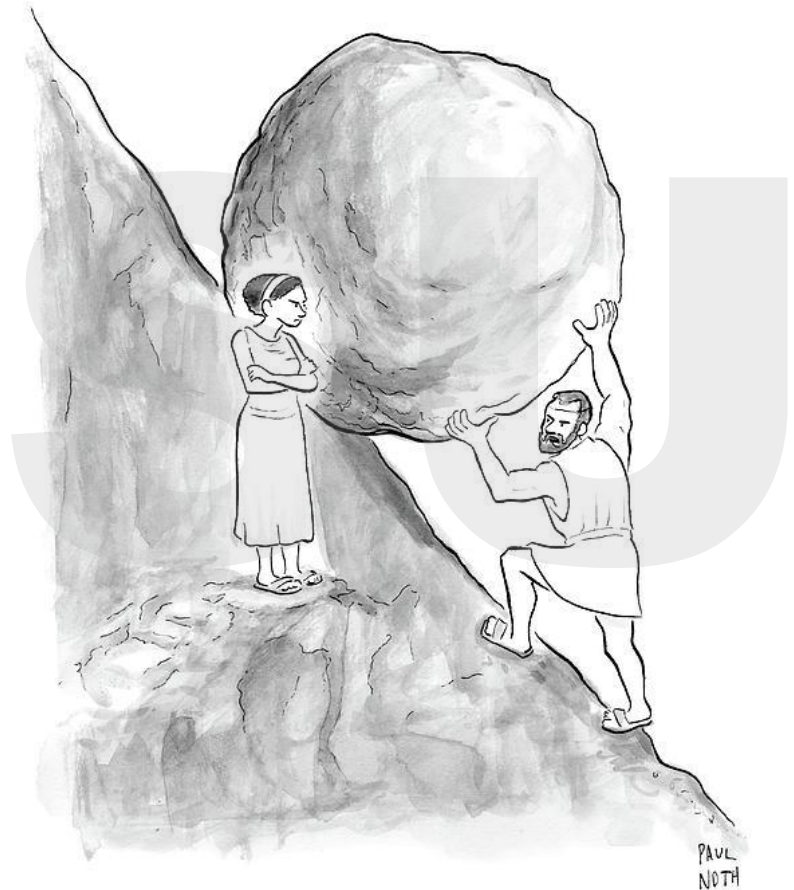
PAWS

- 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

- Carbamazepine,
Oxcarbazepine,
Topiramate

- Trileptal/gabapentin

- Some limited evidence

- **Baclofen**
 - Acamprosate
 - Atomoxetine

- How long?

- Not much guidance from literature
 - I often do 6 months

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**
 - **CBT/DBT**
 - Behavioral therapy
 - Group Therapy/12 Step
 - Alternative



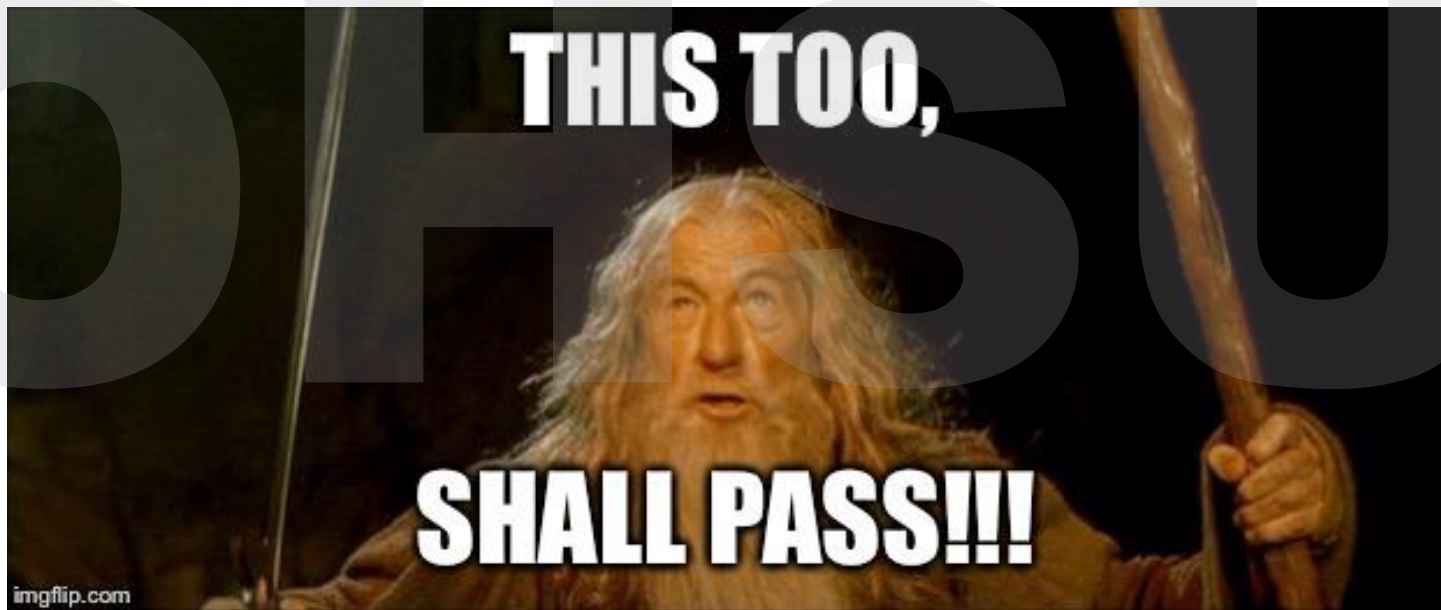
Attention to PAWS

- Why?



SUPER
DUPER
IMPORTANT

PAWS causes Relapses

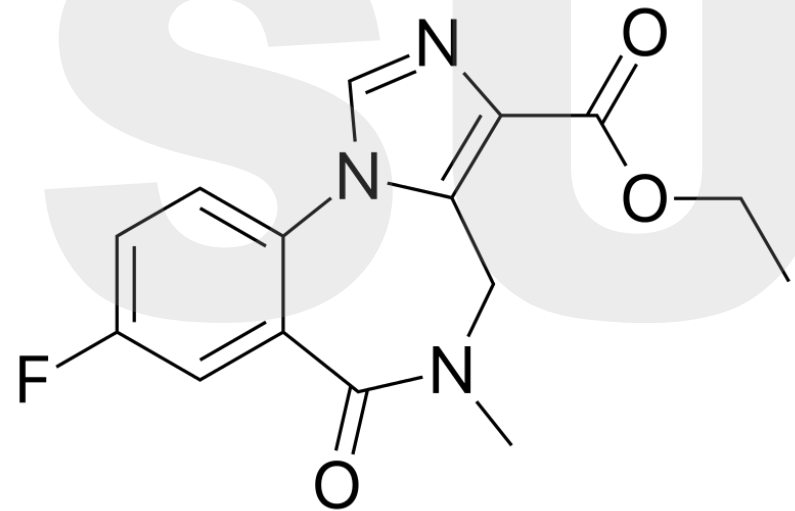


PAWS Treatment-- Future

- Flumazenil

- Selective GABA_A 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.



Complex Persistent Opioid Dependence

Review > [J Gen Intern Med. 2020 Dec;35\(Suppl 3\):964-971. doi: 10.1007/s11606-020-06251-w.](#)

Epub 2020 Nov 6.

Complex Persistent Opioid Dependence with Long-term Opioids: a Gray Area That Needs Definition, Better Understanding, Treatment Guidance, and Policy Changes

Ajay Manhapra^{1 2 3 4}, Mark D Sullivan⁵, Jane C Ballantyne⁵, R Ross MacLean^{6 7},
William C Becker⁷

- People on Long term Prescription opioids
 - Forced taper for safety
 - Worsening pain
 - Declining function
 - Clinical instability
 - Aberrant behaviors

Future



- **Big Fail**

- Couvee 2002, Holton 1992

- **82-86% recommenced use after successful taper within 15 months**

- --Likely PAWS

- We're Doing Something Wrong

- Much More research needed
- Have to do Better



Opinion

Couvee, J. E., Timmermans, E. A. & Zitman, F. G. (2002) The long-term outcome of a benzodiazepine discontinuation program in depressed outpatients. *Journal of Affective Disorders*, 70, 133-141

Holton, A., Riley, P. & Tyrer, P. (1992) Factors predicting long-term outcome after chronic benzodiazepine therapy. *Journal of Affective Disorders*, 24, 245-252.

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
 - If they have a use disorder-tapers often don't work
- PAWS is very real and managing this can help limit relapses
- Complex Persistent Benzodiazepine Dependence
 - Declining function, clinical instability, behavioral dysregulation during tapers or after discontinuation that was not present while on stable dose.



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

Paradoxical Reaction

- 1%-2% (Tae 2014)
 - Talkative
 - Disinhibited
 - Hostility & **rage**
 - Rainbows and unicorns
 - Emotional release
 - Excitement
 - Excessive movement
 - **Mania**
- **Very young and old are susceptible**
 - And the **Disagreeable**
- Autistic, Intellectual Disabled, S/P CVA, TBI

I Think It's
More



Paradoxical Reaction

- More Likely to Happen:
 - High dose,
 - Short half life
 - High potency
- **Patient unaware**
- Mechanism
 - **?Inhibition of cortical restraint**
 - Effect is similar to and enhanced by alcohol consumption in some
 - Inhibit 5-HT transmission
 - Low %-HT is assoc w aggression
 - Genetic?
 - Identical twins both had them
 - **Short 1987**



Oddity

- Strangely Powerful
- Nightmare office Visits



Oddity # 2



+



or

=



Maldonado

There's pretty good data for Alpha 2 Ag use in Alcohol W/D

- Alpha 2 Agonists

- Clonidine
- Guanfacine
- Dexmedetomidine



- The severity of AWS correlates positively with the amount of released NE
- Activated alpha 2-adrenergic receptors inhibit the presynaptic release of GLU, aspartate, and NE
- Good literature on effectiveness in AWS

– 7 studies

Lakhlani PP, Lovinger DM, Limbird LE. Genetic evidence for involvement of multiple effector systems in alpha 2A-adrenergic receptor inhibition of stimulussecretion coupling. Mol Pharmacol 1996;50(1):96–103.

Maldonado

Targeting the Tigers

- Carbamazepine
- Mechanisms of action include
 - (1) its ability to stabilize the Na channels, reducing firing frequency
 - (2) its potentiation of GABA receptors
 - (3) its inhibition of **GLUTAMATE** release
- Valproic Acid
 - GABA transaminase inhibitor/[GABA
 - Inhibits voltage-sensitive Na_v1 channels
 - **Inhibition of cortical GLUTAMATE release**



Maldonado

Targeting the Tigers

- Gabapentin
 - Voltage-gated Ca_v1 channel blockade
 - Decreases cortical GLU release
 - NMDA antagonism
 - Activation of spinal alpha-2 adrenergic receptors
 - Attenuation of Na⁺-dependent action potential
- oxcarbazepine
 - reduces high-voltage-dependent Ca channels of striatal and cortical neurons, thus reducing NMDA glutamatergic transmission associated with alcohol withdrawal



Maldonado

Oversimplified summary == Alpha 2 Agonists + Antiepileptic

- a. Alpha-2 agents
 - i. Clonidine transdermal 0.1 mg (2 patches)
 - ii. Plus, administer clonidine 0.1 mg by mouth or IV every 8 hours (3 doses)
- iii. Alternatively, may use GUA 0.5, 1 mg by mouth twice a day; GUA has better anxiolytic effect and is less hypotensive than clonidine
- b. If patient's VS unable to tolerate alpha-2 effect may instead use GAB
 - i. Day 0: 1200 mg loading dose + 800 mg 3 times a day
 - ii. Day 1 to 3: 800 mg by mouth 3 times a day
 - iii. Day 4 to 5: 600 mg by mouth 3 times a day
 - iv. Day 5 to 7: 300 mg by mouth 3 times a day
 - v. Day 8: D/C
- **ii. VPA by mouth or IV**
 - 1. Start VPA 250 mg by mouth or IV bid plus 500 mg every HS (can increase to 500 BID)
 - 2. Cases of late severe AWS may require up to 1.5 gm in first 24 hours
 - 3. If Sx's escalate after 12 hours, increase total dose to 2 gm in divided doses
 - 4. If Sx's of AWS continue or worsen, add GAB
- **Vitamin supplementation**
 - a. Thiamine 500 mg IV, intramuscular (IM), or by mouth 3 times a day 5 days
 - Followed by thiamine 100 mg IV, IM, or by mouth for rest of hospital stay (or up to 14 d)
 - b. Folate 1 mg by mouth daily
 - c. Multivitamin, 1 tab by mouth daily
 - d. B complex vitamin 2 tabs by mouth daily
 - e. Vitamin K 5 to 10 mg subcutaneously 1 (if international normalized ratio is >1.3)

Maldonado Rescue protocol

- 1. Alpha-2 agents
 - a. Initiate DEX at 0.4 mg/kg/h (no loading)
 - b. Titrate dose by 0.1 mg/kg/h every 20 minutes to effect or in response to an elevated assessment score (AWAS >10)
 - c. There is no maximum dose, yet clinical experience suggests the maximum required DEX dose for alcohol withdrawal management is approximately 2.4 mg/kg/h
- 2. Valproic acid by mouth, or valproate sodium by IV
 - a. Add VPA 250 mg by mouth or IV twice a day plus 500 mg every HS (if the patient is not already on it)
 - b. It may be necessary to increase the dose to 500 mg twice a day plus 1000 mg every HS if the patient continues to be symptomatic after 12 to 24 hours
 - c. If Sx's of AWS continue or worsen, **add GAB**
- 3. GAB schedule
 - a. Day 0: 1200 mg loading dose plus 800 mg 3 times a day
 - b. Day 1 to 3: 800 mg by mouth 3 times a day
 - c. Day 4 to 5: 600 mg by mouth 3 times a day
 - d. Day 5 to 7: 300 mg by mouth 3 times a day
 - e. Day 8: D/C
- Doesn't give recommendations for dosing of Carbamazepine, oxcarbazepine

Moldonado Efficacy

- “To date (4 years of use of the protocol), there have been no significant adverse side effects requiring discontinuation of the protocol, no fatalities, no progression to alcohol withdrawal seizures, and no breakthrough DTs. Despite this positive experience, the author acknowledges that large, randomized studies are needed to confirm these findings.”

OH SU

Urine Drug Screens

- 28 yo Man gave an admission UDS which was positive for Benzodiazepines.
 - He swears he hasn't taken any in a month!
 - Is he lying????




2 Ways he's telling the truth?

Medications Reported to Cause a False Positive Urine Drug Screens by Medication
Copyright Pharmacology Weekly, Inc.

Medication	Brand Names	Drug Class (Use)	Causes False + Reaction	Reference:
Brompheniramine	Brovex, Bromax, Dimetapp	Antihistamine	Amphetamine or Methamphetamine	J Food Drug Anal 1995;34:259-68. Clin Chem 1992;38:611-2.
Bupropion	Aplenzin, Forfivo XL, Wellbutrin, Zyban	Antidepressant; Dopamine Reuptake Inhibitor	Amphetamine or Methamphetamine	Depress Anxiety 2000;12:53-4. Clin Chem 1995;41:955-6.
Chlorpromazine	Thorazine	Typical Antipsychotic; Phenothiazine	Amphetamine or Methamphetamine, Methadone	Clin Chem 2005;51:2176-7. J Food Drug Anal 1999;7:259-68.
Clomipramine	Anafranil	Tricyclic Antidepressant	Methadone	Clin Chem 2005;51:2176-7.
Dextromethorphan	Robitussin DM	Cough Suppressant	Phencyclidine (PCP)	J Emerg Med 2000;18:379-81. Ther Drug Monit 2007;29:671-3.
Diphenhydramine	Benadryl	Antihistamine	Methadone	J Food Drug Anal 1999;7:259-68. Clin Chem 1984;30:1430.
Doxylamine	Aldex, Doxytec	Antihistamine	Methadone	J Clin Chem Clin Biochem 1983;21:599-600.
Efavirenz	Sustiva	NNRI	Tetrahydrocannabinol (THC)	Ther Drug Monit 2006;28:286. Clin Chem 2006;52:896-7.
Ibuprofen	Advil, Motrin	Non-steroidal Anti-inflammatory Drugs (NSAID)	Opiates, Tetrahydrocannabinol, Barbiturates	Ther Drug Monit 2007;29:671-3.
Naproxen	Naprosyn	Non-steroidal Anti-inflammatory Drugs (NSAID)	Tetrahydrocannabinol, Barbiturates	Clin Chem 1990;36:602-6.
Promethazine	Phenergan	Typical Antipsychotic; Phenothiazine	Amphetamine or Methamphetamine	Arch Pathol Lab Med 2006;130:1834-8.
Quetiapine	Seroquel	Atypical Antipsychotic	Methadone	J Am Acad Child Adolesc Psychiatry 2007;46:435-6. J Clin Psychopharmacol 2007;27:273-8.
Ranitidine	Zantac	H2 Receptor Antagonist	Amphetamine or Methamphetamine	Clin Chem 1990;36:1391-2. J Anal Toxicol 1991;15:101-3.
Sertraline	Zoloft	Selective Serotonin Reuptake Inhibitor (SSRI)	Benzodiazepines	J Am Acad Child Adolesc Psychiatry 1996;35:1571-2. Psychiatry 2009;6:36-9.
Fentanyl	Nucynta	Opioid Analgesic	Methadone	J Analyt Toxicol 2012;36:582-587.
Thioridazine	Mellaril	Typical Antipsychotic; Phenothiazine	Methadone	Clin Chem 2005;51:2176-7.
Trazodone	Oleptro	Antidepressant; Serotonin Reuptake Inhibitor (SSRI)	Amphetamine or Methamphetamine	Br J Psychiatry 1996;169:669-70.
Venlafaxine	Effexor	Antidepressant; Serotonin/Norepinephrine Reuptake Inhibitor (SNRI)	Amphetamine and Phencyclidine (PCP)	J Toxicol Clin Toxicol 2003;41:999-1002. Clin Chem 2002;48:676-7.
Verapamil	Calan, Covera HS, Verelan	Calcium Channel Blocker (Non-dihydropyridine)	Methadone	Clin Chem 1998;44:1039-41.

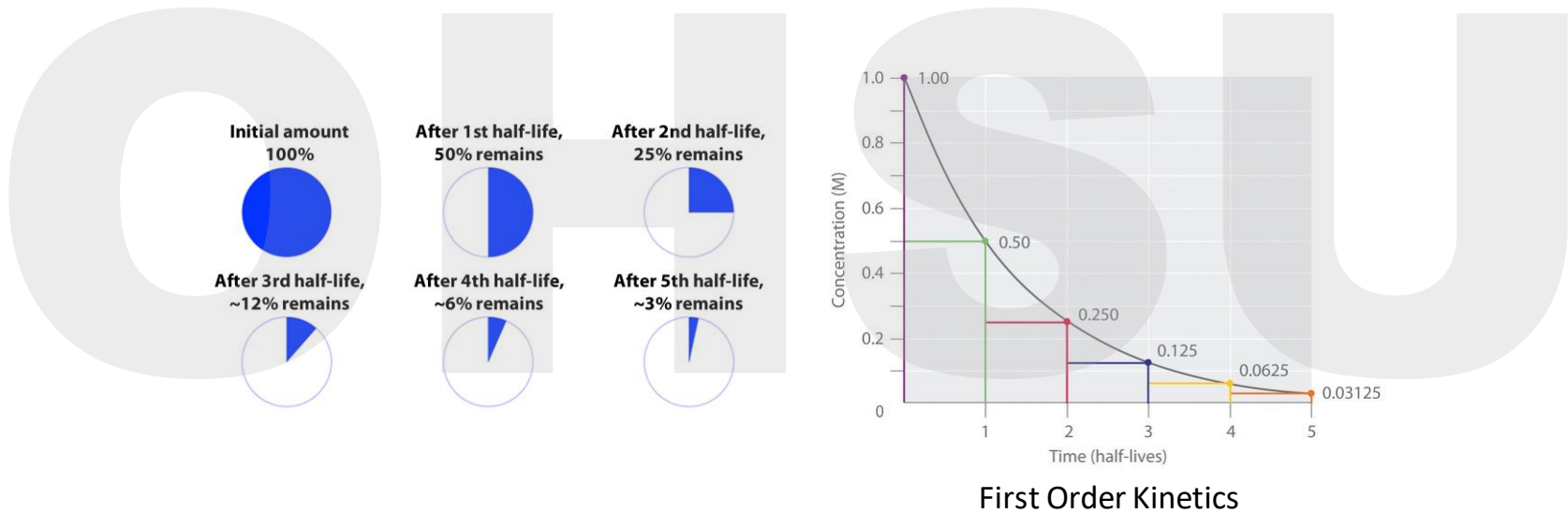
Benzodiazepines Commonly Used for Treatment Of Alcohol Withdrawal

Benzodiazepine	Half-life Parent in hours	Half-life Metabolite in hours	Comparative oral dose	Peak activity
Chlordiazepoxide (Librium) IM	5-30	3-100	25 mg	60-120minutes
Diazepam (Valium) IM/IV	20-50	3-100	5 mg	20-40minutes
Lorazepam (Ativan) IM/IV	10-20	<i>none</i>	1 mg	5-20 minutes
Oxazepam (Serax) Only PO	3-21	<i>none</i>	15 mg	90-120minutes
Chlorazepate (Tranxene)	48	50-180	7.5mg	60-120minutes



Why So Much Variability

What Does a half life Really Mean?



How Long will Valium Stay in Your System?

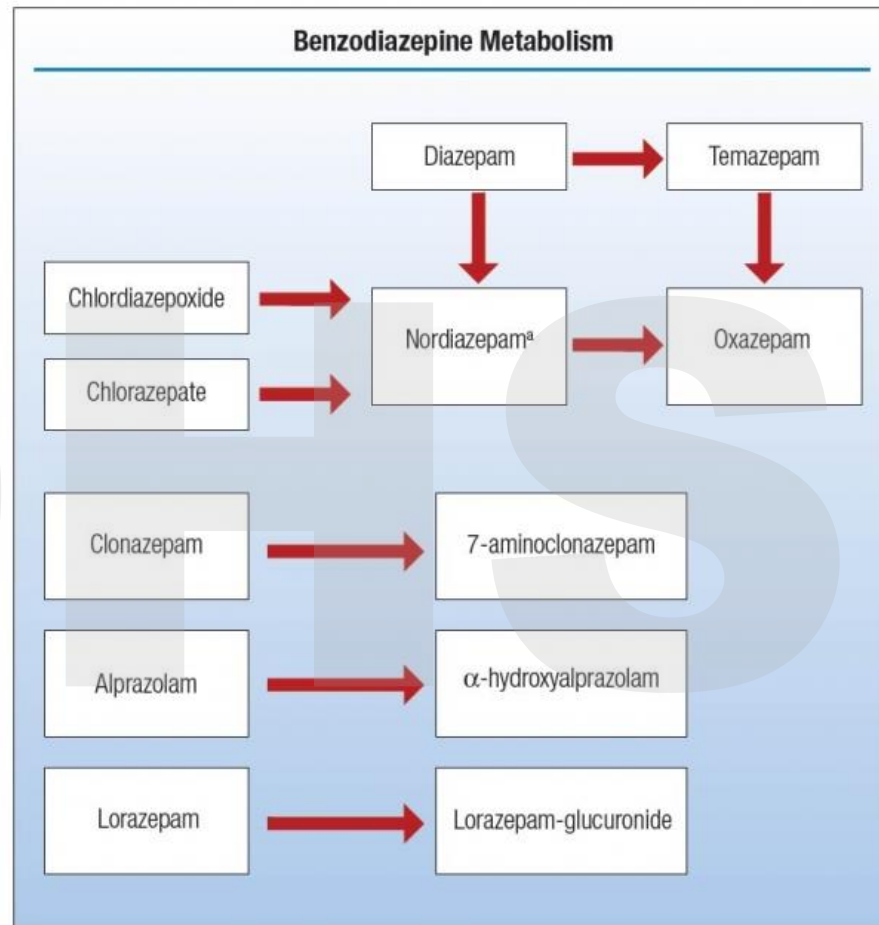


Figure 1: Illustrations of benzodiazepine metabolism.

Arrows indicate metabolic pathways

*Nordiazepam is also a metabolite of halazepam, medazepam, prazepam, and tetrazepam

Benzodiazepine ELISA Screen

Is Problematic to
interpret

- **False Positives**

- Are Quite Rare
 - Daypro (Oxaprozin)
 - **One Other????**
 - 27-32% of patients on this med will Have Positive ELISA
 - » Lum 2008
 - » Nasky 2009

Higher Cut-Off levels miss them

- **False Negatives**

- Mostly with higher potency BZD's (the ones with low therapeutic doses)
 - **Clonazepam**
 - At low to moderate dosing
 - **Alprazolam**
 - Sometimes & Unpredictable
 - **Lorazepam**
 - Sometimes & Unpredictable
- Also Thought to be related to not detecting glucuronidated form

GCMS will clarify if you Your lab will do one on a Negative screen?!

Assess Benzo Withdrawal

- CIWA-B
 - Includes Vital signs
 - Unlike CIWA
- BWSQ
 - BZD withdrawal Symptom Questionnaire
 - Validated
- Scales miss some severe withdrawal



**We CAN be
Benzo Free!**

BENZODIAZEPINE WITHDRAWAL SCALE (CIWA-B) 2

CLINICIAN SHEET

Clinician observations

18. Observe behaviour for sweating, restlessness and agitation	
0	None, normal activity
1	
2	Restless
3	
4	Paces back and forth, unable to sit still

19. Observe tremor	
0	No tremor
1	Not visible, can be felt in fingers
2	Visible but mild
3	Moderate with arms extended
4	Severe, with arms not extended

20. Observe feet palms	
0	No sweating visible
1	Barely perceptible sweating, palms moist
2	Palms and forehead moist, reports armpit sweating
3	Beads of sweat on forehead
4	Severe drenching sweats

Surname: _____
 Other names: _____
 DOB: _____ Sex: M F UR
 Number: _____

TIME/DATE																	
AGITATION																	
TREMOR																	
SWEATING																	
CLIENT'S SCORE (from pg 1)																	
TOTAL SCORE																	
BLOOD PRESSURE																	
PULSE																	
TEMPERATURE per axilla																	
RESPIRATIONS																	
ALERT, ORIENTATED, OBEYS COMMANDS? If NO, complete GCS* and review.	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N	Y / N
PUPIL SIZE/REACTION (In mm)	L																
	R																

TOTAL SCORE FOR ITEMS 1 - 20
 1-20 = mild withdrawal 21-40 = moderate withdrawal 41-60 = severe withdrawal 61 - 80 = very severe withdrawal

*Glasgow Coma Scale

When
alcohol
distorts
reality...

Librium[®] an important aid
in the
treatment of
alcoholism

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