That’s a Disturbing message......

• 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
Rise of Benzodiazepines
The Hidden Epidemic

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Assistant Professor Dept of Psychiatry OHSU
Disclosures

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

• Review Historical Perspective
  – Dark marketing strategies directed at women
• Review Problems associated with benzodiazepine use
• Review Current Standards for detoxification/deprescribing
• Review some new research challenging these standards
• I will be going fast....
• Purpose is to provide an overview...
• Slides are very comprehensive....
  – Can use as reference in future
"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
Relative to benzodiazepines......

We May Have Been Mislead by some of these “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
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
• As we know from the Architect in the Matrix,
  – Pain has a Purpose

• It’s a Call To Action
Anybody Picking up on a trend Here

• “Welcome to the dissociation generation, baby! In this dawning new age, doctors prescribe party drugs, politicians push weed legalization as historic budget deficits loom, and everyone is tripping balls in the name of self-care.”
  — There will be consequences to this!

• Oregon Measure 110
• Cannabis Legalization
• Benzodiazepine epidemic

Life is Hard! --- People are escaping in different ways
Benzodiazepines act at the GABA Receptor

Positive allosteric modulators
It Gets Much More Complicated
Two Different receptors –Multiple Ligands at multiple Subunits

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

picrotoxins
barbiturate site
benzodiazepine site
extracellular site

Neurosteroid site
GABA site
muscimol ethanol

allosteric binding site
BR2
BR1
GABA

Cl⁻
The Tortoise & the Hare

• **GABA**
  - 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**
  - G-Protein coupled Receptor (GPRC)
  - Slowly maintains the inhibitory tone
    - Bettler et all 2004
    - Bowery et all 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)
The Balance between the Two is Key

- **GABA = Inhibitory**
  - GABAa, GABAb
- **Glutamate = Excitatory**
  - AMPA, KA, NMDA

- Proper Function of the CNS depends on physiological homeostasis
  - Maintained by two opposite forces acting independently
Why is \textbf{GABA} So Important

- “GABA and Glutamate are present in practically all functions in the CNS”

- Together they are involved in \textbf{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

• 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
  - **Insomnia**
    - **30%** of people report 1 or more symptoms of insomnia

- **Anxiolysis**
- **Muscle Relaxant**
- **Sedation Hypnotic**
- **Sleep, Anesthesia**
- **Anticonvulsant**
- **Alcohol withdrawal**
This Is The Story Of What Happened....
It all Started with Chloral Hydrate

- It was discovered in 1832 in Germany
  - Indirect GABA agent (Flumazenil reverses)

- A safe drug Used to treat insomnia
We Quickly learned it wasn’t safe

- Nietzsche abused it for insomnia late in life
  - May have led to his “nervous Breakdown”
- Rapidly develops tolerance
- Widely misused
  - “Mickey Fin” when mixed with alcohol
- Very narrow therapeutic window
  - Respiratory depression, cardiac dysfunction
  - Liver, heart and Kidney failure with repeated use
Barbiturates Arrived on the Scene

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

- Pharma’s Early attempts to convince us we need a pill to cope
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; it has a familiar sedative effect. But Mebaral has the advantage of “... extremely low incidence of toxicity ...” and does not produce sedative daze. Often physicians prefer the sedative effects of Mebaral to those of phenobarbital.

WHEN SHE OVERREACTS TO ANY SITUATION

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

MEBARAL
Brand of mephobarbital

SEDATION WITHOUT SEDATIVE DAZE


Winthrop LABORATORIES
New York 18

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“Facts”
But They Weren't Safe
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. Caution when using alcohol and amounts prescribed, especially for patients prone to overuse. 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 withdrawal symptoms. 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 persists, reduces dosage. Dizziness, vertigo, and headache have also occurred. Other reactions include drowsiness, dizziness, and nausea. Withdrawal symptoms may be reported in psychotic patients. Minor allergic reactions (rash, pruritus, arthralgia, and maculopapular) are rare. Nausea, ataxia, blurred vision, diuresis, drowsiness, tremor, and ataxia are rare and generally reversible by dosage reduction. Although rare, insomnia and hypertensive dysrhythmias including tachycardia 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 effects 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.
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

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
Pharma found another niche for xanax

275/500 patients inherited from a psychoanalytic center were on BZD’s
By Now, You get the Idea

"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 2017—
  - 70,000 People surveyed in person

• **2:1 Female : Male**

• **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.

Two Disturbing trends
JAMA Psychiatry - Olfson 2015

![Graph showing age-related trends in benzodiazepine use for men and women. The graph indicates a steady increase in use with age for both genders, with women showing a slightly higher percentage of use compared to men.]
Prevalence

• Chronic daily use also increases with age
  – 14.7% young adults who use
  – 31.4% elderly

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


Whose Prescribing them?
IQVIA National Prescription Audit 2020

Prescriber Specialty
Estimates of outpatient retail prescriptions dispensed for benzodiazepines by top five prescriber specialties in 2020

- IM/FM/GP*: 37.73%
- PA/NP*: 22.3%
- Psychiatry: 16.4%
- Osteopathic Medicine: 9.7%
- Neurology: 2.6%
- All Other prescribers: 11.4%

Primary Care Workforce 300k
Only 28K psychiatrists

IM: Internal Medicine, FP: Family Medicine, GP: General Practitioner, PA: Physician Assistant, NP: Nurse Practitioner
Which ones are prescribed Most?

Prescriptions Dispensed for Individual Benzodiazepines

Estimated benzodiazepine prescriptions dispensed from US outpatient pharmacies annually, 2015-2020

*Other Benzos include clobazam, chlordiazepoxide, clorazepate, estazolam, flurazepam, midazolam, oxazepam, triazolam, and quazepam

Symphony Health – Private consulting company that gathers and manages health care Data
What are they being prescribed for?

Diagnoses Associated with Benzodiazepine Prescribing

Top groups of diagnoses (ICD-10) associated with the mentions of top 5 benzodiazepines* as reported by

F419 Anxiety disorder, unspecified - 33.8%
F411 Generalized anxiety disorder - 20.8%
F410 Panic disorder [episodic paroxysmal anxiety] - 7.5%
G4700 Insomnia, unspecified - 6.1%
F319 Bipolar disorder, unspecified - 2.3%
All Other diagnoses - 29.5%

*Top 5 Benzodiazepines: Alprazolam, Clonazepam, Lorazepam, Diazepam, Temazepam
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


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...........

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 GABAa 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
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"
Benzodiazepine Boxed Warning

WARNING: RISKS FROM CONCOMITANT USE WITH OPIOIDS; ABUSE, MISUSE, AND ADDICTION; and DEPENDENCE AND WITHDRAWAL REACTIONS

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing of these drugs for patients for whom alternative treatment options are inadequate. Limit dosages and durations to the minimum required. Follow patients for signs and symptoms of respiratory depression and sedation [see Warnings and Precautions (5.1), Drug Interactions (7.1)].

- The use of benzodiazepines, including [DRUG], exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Abuse and misuse of benzodiazepines commonly involve concomitant use of other medications, alcohol, and/or illicit substances, which is associated with an increased frequency of serious adverse outcomes. Before prescribing [DRUG] and throughout treatment, assess each patient’s risk for abuse, misuse, and addiction [see Warnings and Precautions (5.2)].

- The continued use of benzodiazepines, including [DRUG], may lead to clinically significant physical dependence. The risks of dependence and withdrawal increase with longer treatment duration and higher daily dose. Abrupt discontinuation or rapid dosage reduction of [DRUG] after continued use may precipitate acute withdrawal reactions, which can be life-threatening. To reduce the risk of withdrawal reactions, use a gradual taper to discontinue [DRUG] or reduce the dosage [see Dosage and Administration (2.2), Warnings and Precautions (5.3)].
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
"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

Thomas J. Moore, AB. JAMA Internal Medicine February 2017 Volume 177, Number 2
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
    • De la Cuevas Psychopharmacology 2003
Not all Benzo’s are Equal

• Can Buy in the Tenderloin (Illicit market)
  – 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
This Article also Reviewed the Past

“A Review of Alprazolam Use, Misuse, Withdrawal”
Nassima Ait Daoud J Add Med 1/18

- Works Better Than Placebo for depression????????
  - Cochrane Review 2012
  - For Depression
    - (HAM-D Scale)
    - “Neurotic Depression”
      - Depressive Sx’s in personality D/O’s

It's Best we be careful here
The Data may be misleading
Alprazolam

- SAMHSA 2013, Grohol 2016
  - Xanax is related to more ED visits than any other Benzo from analysis of PDMP data
    - 1 in 311 Xanax
    - 1 in 321 Klonopin
    - 1 in 540 Ativan
    - 1 in 517 Valium
  - ED visits related to misuse/prescription written

- Ferrer et al 2001
  - Alprazolam created greater dopamine release in striatum than Lorazepam
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 all 1991—animal study
- More Likely to Cause BZD induced hyperanxiety
  - Fyer at al 1987
  - Pecknold et al 1988
Ever More Scary

- **Withdrawal Sx’s** can’t be treated effectively by other Benzos
  - Lorazepam
  - Chlordiazepoxide
  - Diazepam
  - **All ineffective at treating Xanax withdrawal**
    - Schweizer et al 1993
    - Sachdev et al 2014
    - Risse et al 1990
    - Albeck 1987
  - **Limited Data that:**
    - Clonazepam will work (Paterson 1990)
    - Carbamezapine and Clonidine (Klein et al 1986)
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 & 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)


2020 JAMA

• Retrospective Cohort analysis 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.
2022 article

- Data were sourced from two nationwide opioid surveillance programs of treatment-seeking individuals with opioid use disorder (OUD)
- 12,792 new entrants 2019-2020
  - 9.3% non-medical use of gabapentin
    - 63% of those were on opiates
      - 35.3% methadone
      - 49% buprenorphine

- In other words- most people who abuse gabapentin are on an opioid

- Nonmedical use of gabapentin and opioid agonist medications in treatment-seeking individuals with opioid use disorder, Matthew S. Ellis, Drug and Alcohol Dependence, 2022
This Data simply documents what we all know and are seeing....
Gabapentin

- Overall...I think its gotten a bad rap
  - I use it all the time
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
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**
  - **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
  - **High-dose zolpidem dependence - Psychostimulant effects? A case report and literature review**
  - **Review of Safety and Efficacy of Sleep Medicines in Older Adults**
    - Schroek, 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
  - 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 Tillenburg, Jorg Dirmaier, Silke Kuhn, Martin Harter and Uwe Verthein Peerj. 6 (May 22, 2018): pe4614.
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

“I have become comfortably numb”
-Pink Floyd
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


The risk of Alzheimer’s disease associated with benzodiazepines and related drugs: a nested case–control study
V. Tapainen, Acta Psychiatrica Scandanavia, 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 Osler ¹, Martin Balslev Jørgensen ¹· 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”
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
  – **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
The Benzodiazepine Suboxone Issue

• **It’s complicated**
  - FDA placed a “Black Box” warning in 2016 on the buprenorphine package insert
    • BPN should be avoided in combination with benzodiazepines and other CNS suppressants
  - FDA Drug Safety Communication 2017
    • Buprenorphine should not be withheld from patients who are already taking benzodiazepines as prescribed because the risks of overdose from opiates outweigh the risks of concomitant benzodiazepine and buprenorphine use
  - 2020 Warning persists
    • No longer Boxed

Mixed signals from the government makes it hard to interpret

No Green light to start Benzos if already on suboxone
We’re Getting Better But it’s 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.

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
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]).
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


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
What do patients say – how Benzo’s have affected them?
2022 Survey of 1207 Patients

Table 4. The use or withdrawal from benzodiazepines was associated with a number of adverse life events.

<table>
<thead>
<tr>
<th>Life consequence</th>
<th>n = 1207</th>
</tr>
</thead>
<tbody>
<tr>
<td>Significantly affected marriage, other relationships</td>
<td>56.8%</td>
</tr>
<tr>
<td>Suicidal thoughts or attempted suicide</td>
<td>54.4%</td>
</tr>
<tr>
<td>Lost a job, fired, became unable to work</td>
<td>46.8%</td>
</tr>
<tr>
<td>Experienced significant increase in medical costs</td>
<td>40.9%</td>
</tr>
<tr>
<td>Loss of wages or lower wages in reduced job capacity</td>
<td>32.6%</td>
</tr>
<tr>
<td>Lost savings or retirement funds</td>
<td>26.7%</td>
</tr>
<tr>
<td>Violent thoughts or actual violence against others</td>
<td>23.5%</td>
</tr>
<tr>
<td>Lost a home</td>
<td>12.6%</td>
</tr>
<tr>
<td>Lost a business (if business owner)</td>
<td>8.4%</td>
</tr>
<tr>
<td>Lost child custody</td>
<td>2.6%</td>
</tr>
<tr>
<td>None of these apply</td>
<td>18.6%</td>
</tr>
</tbody>
</table>

- Experiences with benzodiazepine use, tapering, and discontinuation: an Internet survey Alistair J. Reid Finlayson, Ther Adv Psychopharmacol 2022, Vol. 12: 1–10
76.2% stated they had not been informed that benzodiazepines were indicated for short-term use only and that discontinuation might be difficult.

31.5% reported food allergies and/or seasonal allergies that occurred only after benzodiazepine use.
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

*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.
Grapefruit Juice

• What Happens?
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 Medikamentabhangigkeit 2015

• Specific Recs are pretty non specific
  – Taper over 4-12 weeks
  – 10-50% reductions at a time
“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

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

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

Not even about tapering from benzodiazepines!!!
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
Maybe Benzo’s aren’t the gold standard even for alcohol withdrawal

2017 Cochrane review on BZD’s for Alcohol W/D

- Included 64 studies (n=4309), evaluated benzodiazepine (BZDP) against placebos, BZDPs against other medications (including other anticonvulsants), and one BZDP against a different BZDP.
- “The data revealed that studies were small, had large heterogeneity, had variable assessment outcomes, and most did not reach statistical significance. Ultimately, the only statistically significant finding was that BZDPs were more effective than placebo for preventing withdrawal seizures; however, they were not shown to be superior to anticonvulsants or other agents.”

Cochrane Database of Systematic Reviews
Alternative Discontinuation

- Rapid taper of Benzo over 3 days
  - 1/3—1/3—0
    - Usually Inpatient
- Cross Titrating
  - Depakote 500mg tid or
  - Carbamezepine 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?

• Phenobarbital with Alpha 2 agonists
Inpatient Barbiturate Taper For BZD detox.

- 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

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

\( ^{a} \) Patients who were discharged against medical advice were not included.

**Main outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizures</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Delirium</td>
<td>3 (1.0%)</td>
</tr>
<tr>
<td>Falls</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Sedation</td>
<td>84 (27.1%)</td>
</tr>
<tr>
<td>Left against medical advice</td>
<td>53 (17.1%)</td>
</tr>
<tr>
<td>ED visits within 30 days</td>
<td>22 (7.1%)</td>
</tr>
<tr>
<td>Readmission with 30 days</td>
<td>19 (6.1%)</td>
</tr>
</tbody>
</table>

Kawasaki J. Sub. Ab Tr 2012
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
I use a Modified Maldonado

- **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 - 2 years)

• 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!
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

• 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

<table>
<thead>
<tr>
<th>Non Specific Sx’s</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insomnia</td>
<td>71%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>56%</td>
</tr>
<tr>
<td>Mood Swings</td>
<td>49%</td>
</tr>
<tr>
<td>Myalgia/Twitching</td>
<td>49%</td>
</tr>
<tr>
<td>Headache, Tremor</td>
<td>38%</td>
</tr>
<tr>
<td>N/V, Anorexia</td>
<td>36%</td>
</tr>
<tr>
<td>Sweating, Blurred Vision</td>
<td>22%</td>
</tr>
</tbody>
</table>

## Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosis</td>
<td>7%</td>
</tr>
<tr>
<td>Seizures</td>
<td>4%</td>
</tr>
</tbody>
</table>

## Hypersensitivity

<table>
<thead>
<tr>
<th>Hypersensitivity</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noise</td>
<td>38%</td>
</tr>
<tr>
<td>Light</td>
<td>24%</td>
</tr>
<tr>
<td>Smell/Touch</td>
<td>15%/7%</td>
</tr>
</tbody>
</table>

## Hyposensitivity

<table>
<thead>
<tr>
<th>Hyposensitivity</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smells/Taste</td>
<td>15%/4%</td>
</tr>
</tbody>
</table>

## Qualitative Changes

<table>
<thead>
<tr>
<th>Qualitative Changes</th>
<th>Frequency %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement</td>
<td>24%</td>
</tr>
<tr>
<td>Vision, Taste</td>
<td>13%</td>
</tr>
<tr>
<td>Derealization</td>
<td>24%</td>
</tr>
</tbody>
</table>

Janhsen, Deutsches Arzteblatt Intnl 2015
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: 1-3 Days

Peaks: Week 2

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.
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
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

- 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

• Medications
  – Strongest Evidence is for anti-epileptic meds
    • Carbamezepine, Oxcarbazapine, Topiramate
    • Trileptal/gabapentin
  – Some limited evidence
    • Baclofen
    • Acamprosate
    • Atomoxetine

• How long?
  • Not much guidance from literature
  • I often do 6 months

Anticonvulsants for the Treatment of Alcohol Withdrawal Syndrome and Alcohol Use Disorders
Christopher J. Hammond CNS Drugs. 2015 April; 29(4): 293–311.
Antiepileptics for Alcohol PAWS

• Article reviewing the use of Antiepileptics in the treatment of alcohol withdrawal
  – “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

Anticonvulsants for the Treatment of Alcohol Withdrawal Syndrome and Alcohol Use Disorders
Christopher J. Hammond CNS Drugs. 2015 April; 29(4): 293–311.
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?
PAWS causes Relapses

THIS TOO,

SHALL PASS!!!
PAWS Treatment-- Future

• **Flumazenil**
  – Selective GABA$_A$ Antagonist
  – Speeds up the process
Something I’ve noticed

- Not too many cases of primary Benzo abuse
- Very commonly abused in combination with other substances
  - Often to enhance or self manage the side effects of other substances
- Very commonly creates residual problems when other substance abuse is successfully treated
We don’t have good data on prevalence of benzo use d/o (NSDUH data suggest it might be 500,000)
Drugs of abuse reported by People entering publically funded tx programs (TEDS)- - more report abusing benzos than opiates
Less report it being their primary drug of abuse
Complex Persistent Opioid Dependence

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

• “Complex Persistent Benzodiazepine Dependence”
  – Pts on long term therapy during taper experience withdrawal that results in:
    • Worsening anxiety/insomnia
    • Declining function
    • Clinical instability
    • Aberrant behaviors
CPBD

• Case #1
  – 78 yo woman on valium for 30 years - stopped working – re-emergence of anxiety, mood lability, falls
    • Taperd off
    • Tried everything for 2 years as outpatient to treat her inability to function
  – Free floating anxiety – debilitating
    • Unlimited reservoir of neurotic anxiety projected onto everything
  – Perseverative
    • Called her daughter 10x/day “I’m not OK”
  – Eventually restarted

• Case #2
  – 70 yo man Xanax for 25 yrs – inpt psych for SA in setting of escalating doses
    • Inpt detox on phenobarb
    • Became catatonic
    • Even had medical student try to throw baseball to him (Huge Phillies Fan)
    • Gave in weeks later- one dose klonopin – within 30 minutes – walking around eating snacks
Why Do these extreme Situations Happen?

• Arrested development?
  – Eriksonian stages of development-throughout our lives
    • Doesn’t stop at 18 yo
  – Benzos preclude people from developing resiliency and coping mechanisms and from aging with the equipment you need to handle the slings and arrows of life

• This can help explain the CPBD symptoms
  – Be patient
  – Know what they are going through is complex
    • May need to make compromises with your expectations
    • Back to Basics –DBT skills
    • May need to restart benzo’s
      – After extensive informed consent with family involvement
  • Only real answer is never starting them
Future

- Opiate induced hyperalgesia
- Benzo induced hyperanxiety
  - Fyer et al 1987
  - Pecknold et al 1988
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

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.
Designer Benzos

- Immunoassays generally have good cross-reactivity for non-FDA approved benzodiazepines
  - Some exceptions are:
    - Fortazolam
    - Ketazolam
- Many of these will not show up on GCMS
- 1 Swedish study showed that 40% of positive benzodiazepines results actually contained a nonapproved benzodiazepine
Benzos

- Alprazolam, clonazepam, lorezapam
  - Most ELISA are designed to detect oxazepam, nordiazepam
    - Will often miss Alprazolam, clonazepam, lorezapam
      - Clonazepam and lorezapam are very unlikely to cross react
      - Alprazolam more likely to cross react
    - Most other Benzos metabolize to these
  - Also cut off concentrations are too high for more potent benzos
    - Alprazolam, clonazepam, lorezapam

- Sertraline
  - 30% will turn benxo screen positive

Table 2. DRI Benzodiazepine Assay Cross-Reactivity Levels

<table>
<thead>
<tr>
<th>Compound</th>
<th>Concentration, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alprazolam</td>
<td>105</td>
</tr>
<tr>
<td>Bromazepam</td>
<td>225</td>
</tr>
<tr>
<td>7-Aminoclonazepam</td>
<td>2500</td>
</tr>
<tr>
<td>Chlordiazepoxide</td>
<td>1100</td>
</tr>
<tr>
<td>Clobazam</td>
<td>145</td>
</tr>
<tr>
<td>Clonazepam</td>
<td>500</td>
</tr>
<tr>
<td>Clorazepine</td>
<td>120</td>
</tr>
<tr>
<td>Delorazepam</td>
<td>110</td>
</tr>
<tr>
<td>Desmethyldiazepam</td>
<td>100</td>
</tr>
<tr>
<td>Diazepam</td>
<td>95</td>
</tr>
<tr>
<td>Fiumitrazepam</td>
<td>175</td>
</tr>
<tr>
<td>Flurazepam</td>
<td>140</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>1000</td>
</tr>
<tr>
<td>Lormetazepam</td>
<td>225</td>
</tr>
<tr>
<td>Medazepam</td>
<td>225</td>
</tr>
<tr>
<td>Nitrazepam</td>
<td>175</td>
</tr>
<tr>
<td>Norfludiazepam</td>
<td>115</td>
</tr>
<tr>
<td>Prazepam</td>
<td>110</td>
</tr>
<tr>
<td>Temazepam</td>
<td>125</td>
</tr>
<tr>
<td>Triazolam</td>
<td>125</td>
</tr>
</tbody>
</table>

The higher the number - the less likely it is to cross react and turn test positive
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 the 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


– 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
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

= 

Walker & Ettinberg 2001
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

Maldonado
Targeting the Tigers

• Carbamezapine

• 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 Na1 channels
  – Inhibition of cortical GLUTAMATE release
Gabapentin
- Voltage-gated Ca\textsubscript{1} channel blockade
- Decreases cortical GLU release
- NMDA antagonism
- Activation of spinal alpha-2 adrenergic receptors
- Attenuation of Na\textsubscript{1}-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 Carbamezapine, oxcarbamezapine
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.”
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?
<table>
<thead>
<tr>
<th>Medication</th>
<th>Brand Names</th>
<th>Drug Class (Use)</th>
<th>Causes False + Reaction</th>
<th>Reference:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Promethazine</td>
<td>Phenergan</td>
<td>Typical Antipsychotic; Phenothiazine</td>
<td>Amphetamine or Methadone</td>
<td>Arch Pathol Lab Med 2006;130:1834–8.</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>Oleptro</td>
<td>Antidepressant; Serotonin Reuptake Inhibitor (SSRI)</td>
<td>Amphetamine or Methadephtamine</td>
<td>Br J Psychiatry 1996;169:669–70.</td>
</tr>
</tbody>
</table>
Benzodiazepines Commonly Used for Treatment Of Alcohol Withdrawal

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

Why So Much Variability
What Does a half life Really Mean?

First Order Kinetics

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

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

- **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

Is Problematic to interpret

Higher Cut-Off levels miss them

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
**BENZODIAZEPINE WITHDRAWAL SCALE (CIWA-B)**

**CLINICIAN SHEET**

**Clinician observations**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 None, normal activity</td>
<td>0 No tremor</td>
<td>0 No sweating visible</td>
</tr>
<tr>
<td>1</td>
<td>1 Not visible, can be felt in fingers</td>
<td>1 Barely perceptible sweating, palms moist</td>
</tr>
<tr>
<td>2 Restless</td>
<td>2 Visible but mild</td>
<td>2 Palms and forehead moist, reports armpit sweating</td>
</tr>
<tr>
<td>3</td>
<td>3 Moderate with arms extended</td>
<td>3 Beads of sweat on forehead</td>
</tr>
<tr>
<td>4 Pieces back and forth, unable to sit still</td>
<td>4 Severe, with arms not extended</td>
<td>4 Severe drenching sweats</td>
</tr>
</tbody>
</table>

**TIME/DATE**

<table>
<thead>
<tr>
<th>AGITATION</th>
<th>TREMOR</th>
<th>SWEATING</th>
<th>CLIENT'S SCORE (from pg 1)</th>
<th>TOTAL SCORE</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>BLOOD PRESSURE</th>
<th>PULSE</th>
<th>TEMPERATURE (per axilla)</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ALERT, ORIENTATED, HEARS COMMANDS?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>RESPIRATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
</tbody>
</table>

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</tr>
</thead>
<tbody>
<tr>
<td>Y</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PUPIL SIZE/REACTION (in mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L</td>
</tr>
<tr>
<td>R</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TOTAL SCORE FOR ITEMS 1 - 20</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-20 = mild withdrawal</td>
</tr>
<tr>
<td>21-40 = moderate withdrawal</td>
</tr>
<tr>
<td>41-60 = severe withdrawal</td>
</tr>
<tr>
<td>61 - 80 = very severe withdrawal</td>
</tr>
</tbody>
</table>

*Glasgow Coma Scale*
# Benzodiazepine Withdrawal Scale (CIWA-S) 1

**CLIENT SHEET**

For each of the following items, insert the number that best describes how you feel.

<table>
<thead>
<tr>
<th></th>
<th>0 Not at all</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4 Very much so</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Do you feel irritable?</td>
</tr>
<tr>
<td>2</td>
<td>Do you feel fatigued?</td>
</tr>
<tr>
<td>3</td>
<td>Do you feel tense?</td>
</tr>
<tr>
<td>4</td>
<td>Do you have difficulties concentrating?</td>
</tr>
<tr>
<td>5</td>
<td>Do you have any loss of appetite?</td>
</tr>
<tr>
<td>6</td>
<td>Have you any numbness or burning in your face, hands or feet?</td>
</tr>
<tr>
<td>7</td>
<td>Do you feel your heart racing? (palpitations)</td>
</tr>
<tr>
<td>8</td>
<td>Does your head feel full or achy?</td>
</tr>
<tr>
<td>9</td>
<td>Do you feel muscle aches or stiffness?</td>
</tr>
<tr>
<td>10</td>
<td>Do you feel anxious, nervous or jittery?</td>
</tr>
<tr>
<td>11</td>
<td>Do you feel upset?</td>
</tr>
<tr>
<td>12</td>
<td>How restless was your sleep last night? (0 = very much so; 4 = not at all)</td>
</tr>
<tr>
<td>13</td>
<td>Do you feel weak?</td>
</tr>
<tr>
<td>14</td>
<td>Do you think you had enough sleep last night? (0 = very much so; 4 = not at all)</td>
</tr>
<tr>
<td>15</td>
<td>Do you have any visual disturbances? (sensitivity to light, blurred vision)</td>
</tr>
<tr>
<td>16</td>
<td>Are you fearful?</td>
</tr>
<tr>
<td>17</td>
<td>Have you been worrying about possible misfortunes lately?</td>
</tr>
</tbody>
</table>

**SUB-TOTAL**
When alcohol distorts reality...

Librium, an important aid in the treatment of alcoholism.
Relative to benzodiazepines......
We May Have Been Mislead by some of these “Facts”

- “I Love Rumors! Facts can be misleading, where rumors, whether true or false can be revealing.”
  – Hans Landa
- Dark Comedy by Tarantino