Risks & Benefits of Benzodiazepines

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Advisory / Consultant Role: Sage Therapeutics; Seelos; Syneos; Noema Pharmaceuticals; Nview Health aka Proem Health;

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None of the above disclosures, to the best of my knowledge, relate to the content of this presentation on Benzodiazepines.

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Benzodiazepine Use & Misuse Data

- 12.6% of US Adults (30.6 million) (up from 4-6% in 2013 & 2014 survey)
  - 10.4% as prescribed & 2.2% misuse
- 17.2% of overall use is misuse

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and misuse among adults in the United States. Psychiatric Services (2018 December 17;Epub ahead of print) Based on 2016 & 2016 National Survey on Drug Use & Health data.

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Benzodiazepine Use & Misuse Data

- Highest prescribed use - 12.9% (age 50-64)
- Highest use "more frequently than prescribed" in ages ≥50
- Highest misuse - 5.2% (age 18-25) (lowest in >65 at 0.6%)

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and misuse among adults in the United States. Psychiatric Services (2018 December 17;Epub ahead of print) Based on 2016 & 2016 National Survey on Drug Use & Health data.

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Benzodiazepine Use & Misuse Data

- Misuse reasons (to relax, relieve tension & insomnia)
- M > F
- Most common source of nonprescribed BNZ
  - a friend or relative
- Strong link with misuse & abuse of opiates & amphetamines

Maust DT, Lin LA, Blow FC. Benzodiazepine Use and misuse among adults in the United States. Psychiatric Services (2018 December 17;Epub ahead of print) Based on 2016 & 2016 National Survey on Drug Use & Health data.

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Abuse

- Self administration of
- Large dose
- Outside therapeutic context

DSM III-R & IV American Psychiatric Association Washington DC 1987 & 1994

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Dependence

- Substance Dependence
  - Impairment + 3/7
- "Physiological Dependence"
  - Tolerance or withdrawal

DSM III-R & IV American Psychiatric Association Washington DC 1987 & 1994

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Abuse Data

- Basel - 300,000. 1985
- 35 MDs. 80% participated
- Reported abuse 0.06%
- All Actual Abuse 0.04%
- Exclusive BZ abuse 0.01%

Ladewig D, Grossenbacher H. Pharmacopsychiatry (1988:21;104-108)

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Hospitalization

- Random sample (n = 32,679) of all Swedish psychiatric hospitalizations over 15 years (1967-1983)
- 38 admissions for substance dependence on sedative hypnotics
- 21 / 38 polysubstance abuse
- 17 / 38 sedative - hypnotic abuse only

Allgulander C Amer J Public Health (1989:79;1006-1010)

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Admissions for Drug Use Medical Problems

- Stockholm County
- All (medical + psychiatric) hospitalizations
- N = 1.6 million
- 0.04% of "prescribed medication" users (including BZ) ever admitted for medical problems relating to their drug use

Allgulander C. Human Psychopharmacology (1996:11;S49-S54)

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Physician BZ Abuse & Dependence

Sample	N	% of Total	% of Users
All MDs	5426 / 9600		
Users	628	11.9	
Abuse	4	0.07	0.6
Dependence	3	0.06	0.5

Hughes P et al. JAMA 1996

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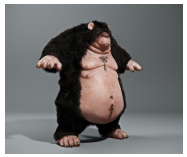
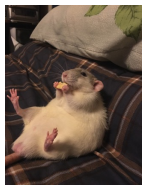
LD_{50}



- Alprazolam = 331 - 2171 mg/kg
  - C-P collapse recorded at 195 mg/kg alprazolam
  - 0.2 mg/kg = 10 mg/day
  - 195 mg/kg = 975 times the maximum recommended human dose of 10 mg/day
  - = 9750 mg/day
- 10,000 mg/day
  - = 10,000 x 1 mg tabs / day
  - = 20,000 x 0.5 mg tabs / day
  - = 222 bottles of 90 tabs / day (one month supply of 0.5 mg t.i.d.)
  - Is there enough room in the abdominal cavity to accommodate this?



Source: http://penemonchelli.tumblr.com/post/14045384694/leland-are-you-kidding-me
https://forums.cgsociety.org/t/extremely-fat-rat-concept-david-a-f-3d/1613648

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LD_{50}

- Dose required to kill 50% of the tested population
- Sucrose = 29,700 mg/kg
- Fructose = 4,000 mg/kg
- Common salt = 3,000 mg/kg
- Alprazolam = 331 - 2,171 mg/kg
  - Cannabidiol = 980 mg/kg
  - Ethanol = 7,060 mg/kg (= 251 drinks @ 14 gm in a standard drink)
  - Ibuprofen = 636 mg/kg
  - Aspirin = 200 mg/kg
  - Caffeine = 192 mg/kg
  - Fentanyl = 300 µg/kg

Source: https://www.niaaa.nih.gov/alcohol-health/overview-alcohol-consumption/what-standard-drink

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2021 Updated FDA Boxed Warning

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

See full prescribing information for complete boxed warning.

- **Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death. Reserve concomitant prescribing for use in 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. (5.1, 7.1)**
- **The use of benzodiazepines, including XANAX, exposes users to risks of abuse, misuse, and addiction, which can lead to overdose or death. Before prescribing XANAX and throughout treatment, assess each patient's risk for abuse, misuse, and addiction. (5.2)**
- **Abrupt discontinuation or rapid dosage reduction of XANAX 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 XANAX or reduce the dosage. (2.2, 5.3)**

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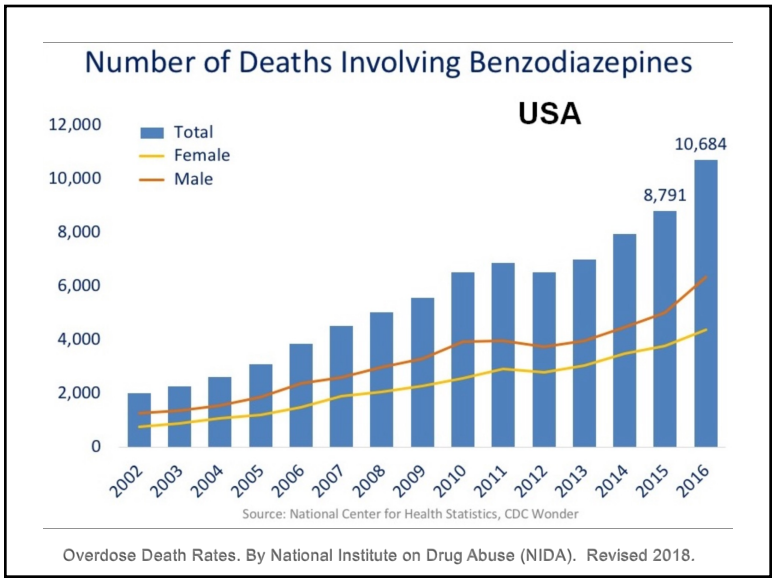

Overdose Death Rates. By National Institute on Drug Abuse (NIDA). Revised 2018.

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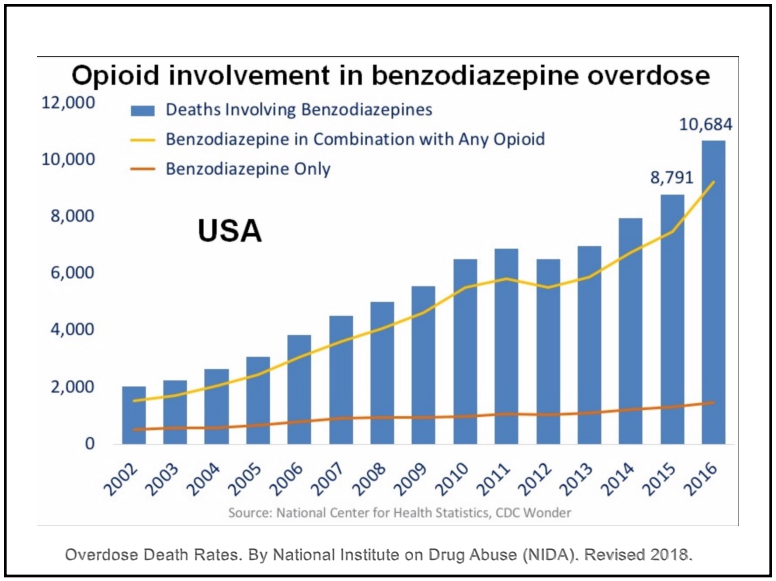

Overdose Death Rates. By National Institute on Drug Abuse (NIDA). Revised 2018.

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Controlled Substances Act(s)

- Schedule IV
- Flunitrazepam (Rohypnol) is Schedule III
- Require specially coded prescription pads in some states
- Prescription requires consultation with PDMP

  (Prescription Drug Monitoring Program)

Puri BK, Tyrer P (28 August 1998). "Clinical psychopharmacology". Sciences Basic to Psychiatry (2nd ed.). Churchill Livingstone. pp. 155–156. ISBN 978-0-443-05514-0. Retrieved 11 July 2009.

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Use in Clinical Practice

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Detection Window in Urine Drug Screening

Parent Drug	Approximate Dose Equivalents (mg)	Detection Window in UDS (Days)
Diazepam	5	10-30
Alprazolam	0.5	5
Clonazepam	0.25	5
Lorazepam	1	5
Chlordiazepoxide	25	5-30
Oxazepam	15	5
Temazepam	15	1-4
Midazolam	5	0.5-2
Triazolam	0.25	7-15 hours
Flurazepam	15	4-16
Estazolam	1-2	1-4
Quazepam	10	2-4

Benzodiazepine Metabolism and Pharmacokinetics
Complied by Mena Raouf, Pharm.D. Candidate, 2016, reviewed and edited by Dr. Jeffrey Fudin
from http://paindr.com/wp-content/uploads/2015/10/Revised-BZD_-9-30.pdf

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Half Life vs. Speed of Onset

Parent Drug	Half-Life (range, hours)	Speed of Onset
Diazepam	5	Fast
Alprazolam	12-15	Intermediate
Clonazepam	19-60	Slow
Lorazepam	10-20	Intermediate
Chlordiazepoxide	10-30	Intermediate
Oxazepam	5-10	Slow
Flunitrazepam	18-26	Fast
Midazolam	1.5-2.5	Fast
Prazepam	50-200	Slow

O'Brien CP (2005). "Benzodiazepine Use, Abuse, and Dependence"
The Journal of Clinical Psychiatry: 66. Retrieved 5 September 2013.

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Half-life vs.

Duration of Therapeutic Action

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Alprazolam

Duration of Action = 4 – 6 hours

Half Life = 12 hours

Half life not a good predictor of duration of action

Sheehan DV et al. 1982;2(1):40-46.

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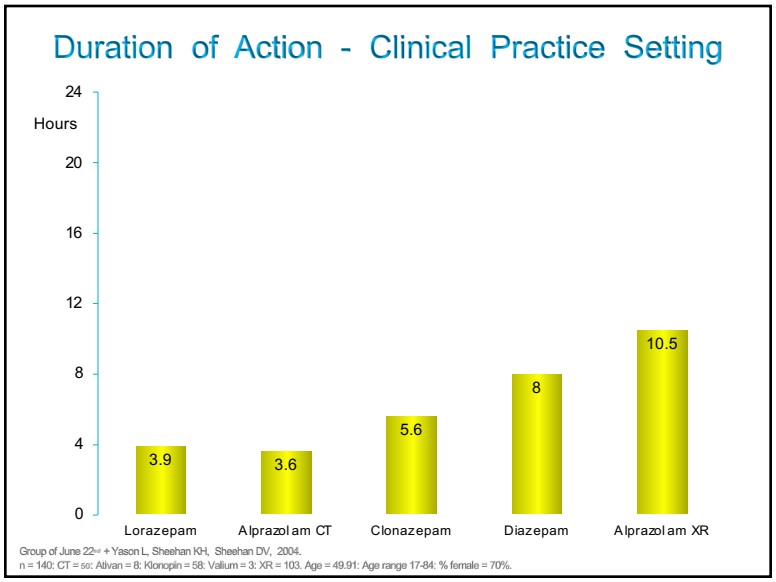
Duration of Action - Clinical Practice Setting
24
Hours
20
16
12
8
4
0
3.9
3.6
5.6
8
10.5
Lorazepam
Alprazolam CT
Clonazepam
Diazepam
Alprazolam XR
Group of June 22nd + Yason L, Sheehan KH, Sheehan DV, 2004.
n = 140: CT = 50: Ativan = 8: Klonopin = 58: Valium = 3: XR = 103. Age = 49.91: Age range 17-84: % female = 70%.

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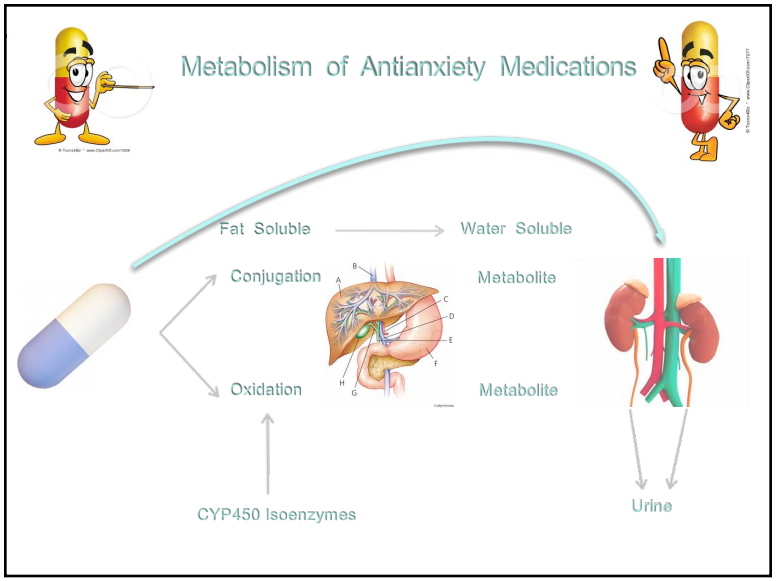
Metabolism of Antianxiety Medications
Fat Soluble
Water Soluble
Conjugation
Metabolite
Oxidation
Metabolite
CYP450 Isoenzymes
Urine

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Conjugated Benzodiazepines

- ✓ Lorazepam
- ✓ Oxazepam
- ✓ Tamazepam

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Why are some anxiolytics and some hypnotics?

- BZ Hypnotics in low dose are anxiolytic
- BZ Anxiolytics in high dose are hypnotics

Puri BK, Tyrer P (28 August 1998). "Clinical psychopharmacology". Sciences Basic to Psychiatry (2nd ed.). Churchill Livingstone. pp. 155–156. ISBN 978-0-443-05514-0. Retrieved 11 July 2009.

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Overdose of Benzodiazepines

- Responsible for 3.8% of deaths from a single drug in UK
- Taken alone they rarely cause serious problems in OD
- Toxicity increased in combination with opioids, antidepressants, alcohol
- Respiratory depression and cardiorespiratory arrest
- Flumazenil is antidote

Charlson F, Degenhardt L, McLaren J, Hall W, Lynskey M (2009). "A systematic review of research examining benzodiazepine-related mortality". *Pharmacoepidemiology and Drug Safety*. **18** (2): 93–103. doi:10.1002/pds.1694. PMID 19125401

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Flumazenil

- Not routinely recommended
- High risk of re-sedation (61%) and seizures
- ~1% serious adverse events
- Only suitable in 10% of cases of BNZ overdose
- Contraindicated in
  - long term BNZ use
  - in ODs with meds that
    - lower the seizure threshold
    - could cause an arrhythmia
    - are associated with abnormal vital signs

1. Seger DL (2004). "Flumazenil--treatment or toxin". *Journal of Toxicology: Clinical Toxicology*. **42** (2): 209–16. doi:10.1081/CLT-120030946. PMID 15214628.
2. "Treatment of benzodiazepine overdose with flumazenil. The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group". Clinical Therapeutics. 14 (6): 978–95. 1992. PMID 1286503. 3. Spivey WH (1992). "Flumazenil and seizures: analysis of 43 cases". Clinical Therapeutics. 14 (2): 292–305. PMID 1611650

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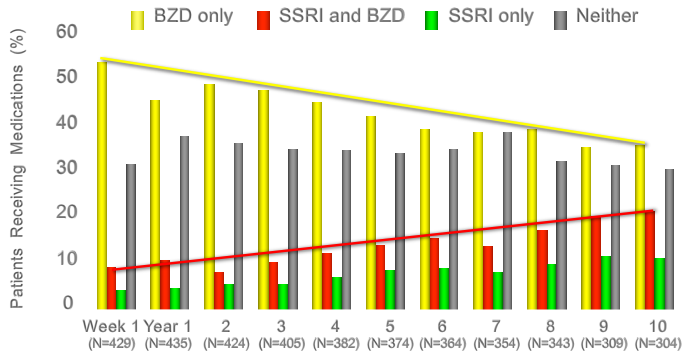
Medications Used for Panic Disorder

HARP Study (1989 - 2001)



Bruce SE, Vasile RG, Goisman RM, et al. Am J Psychiatry. 2003(Aug);160(8):1432-1438

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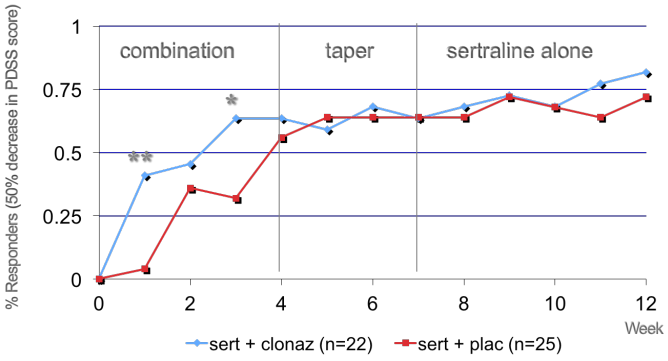
Panic Disorder

Sertraline + Clonazepam vs. Sertraline + placebo



Goddard AW et al, *Arch Gen Psychiatry*, 2001;58:681-686

* p<0.05 ** p<0.003

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Panic Disorder

Sertraline + Clonazepam vs. Sertraline + placebo

- Dropouts :
- 38% (sert + plac) vs.
- 25% (sert + clonaz)

Goddard AW et al, *Arch Gen Psychiatry*, 2001;58:681-686

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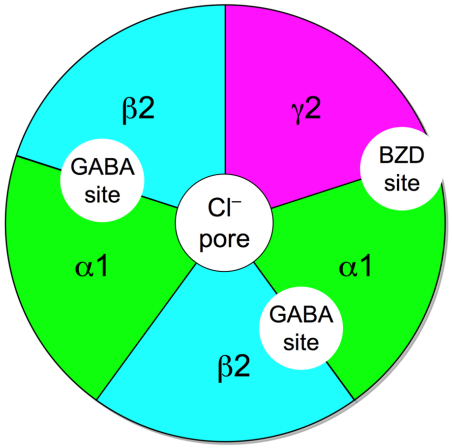
Mechanism of Action



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Pregnancy – 1st & 2nd Trimester

- Risk of teratogenicity controversial
- Many recent better controlled studies “do not support an association between fetal exposure to benzodiazepines and major malformations”.

Dolovich et al 1998. Sheehan DV 2017 & 2022.

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Pregnancy – 3rd Trimester

- Reports of teratogenicity conflicting
- Many recent better controlled studies “do not support an association between fetal exposure to benzodiazepines and major malformations”.

Dolovich et al 1998. Sheehan DV 2017 & 2022.

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Pregnancy – Labor

- Neonatal withdrawal
  - irritability, hyperactivity
  - dose and duration dependent
- CNS depression
  - hypotonia, lethargy, "floppy infant syndrome", sucking difficulties, decreased fetal movements, respiratory depression, thermogenesis, loss of cardiac beat to beat variability.
- Apgar scores in doses >30 mg during labor

Dolovich et al 1998. Sheehan DV 2017 & 2022.

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Breast Feeding on Benzodiazepines

- Excreted in breast milk
- Infant has limited capacity to metabolize
- "3 decades of studies support low incidence of toxicity & adverse events"
- Advise caution & weight monitoring

Birnbaum et al 1999. Llewellyn and Stowe 1998.

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Controversial Associations

- Infections
- Dementia
- Cancer
- Pancreatitis

Ladewig D, Grossenbacher H. Pharmacopsychiatry (1988:21;104-108)

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Pneumonia Risk with Benzodiazepines in Alzheimer's

- 30% more likely with benzos in Alzheimer's
- 1.22 odds ratio
- Risk only observed during first 30 days
- 5,232 on benzos vs. 3,269 on ALZ-related meds
- Not designed for a direct comparison

Taipale H, Tolppanen A, Koponen M, et al. Risk of Pneumonia Associated With Incident Benzodiazepine Use Among Community-Dwelling Adults With Alzheimer's Disease. CMAJ April 10, 2017;189(14): E519-E529 http://www.cmaj.ca/content/189/14/E519 A national registry study.

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Motor Impairment – Hip Fractures

- ↑ in elderly
- similar with short & long acting benzos
- no change in age-adjusted hip fractures after 50% drop in benzos, following NY Triplicate prescription law

Wang et al 2001

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Motor Impairment – Accidents

- ↑ in elderly
- ↑ when >30 mg/day diazepam equivalents
- ↑ in 1st 2 weeks of use

Neutel 1995; Skegg et al 1979; Hemmelgarn et al 1997; Wagner et al 2007; Wang et al 2001.

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Cognitive Impairment

- Reports of long-term cognitive impairment persisting after discontinuation
- CT scan studies conflicting, but weight of recent evidence supports no difference
- Most studies support reversal of any cognitive impairments after taper

Golombok et al 1988; Lucki et al 1986; Rickels et al 1999; Sheehan DV 2016

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Cognitive Impairment & Alzheimer's Disease

- 1 inferential report suggested use of benzos >3 months may be associated with Alzheimer's Disease
- Results "could be interpreted to suggest that benzodiazepine use does not cause increased Alzheimer's disease, but Alzheimer's Disease causes an increased need for benzodiazepine treatment in some patients".

Billioti de Gage 2014; Salzman C & Shader R 2015; Pariente et al 2016; Gray et al 2016

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Cognitive Impairment & Alzheimer's Disease

- 3,434 adults aged 65 and older for 7 years
- "no link between dementia or cognitive decline and:
  - highest level of BNZ use
  - BNZ use longer than 4 months"
- A small increased risk with moderate (1-4 months) and low (up to 1 month) BNZ use
- Findings do "not support the theory that cumulative benzodiazepine use at the levels observed in our population is causally related to an increased risk for dementia or cognitive decline"

Gray SL, Dublin S, Yu O, et al: Benzodiazepine use and risk of incident dementia or cognitive decline: prospective population based study. BMJ 352:i90, 2016 26837813

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Document Patient Education

- Never abruptly stop or rapidly taper benzodiazepines
- Avoid alcohol and sedating meds
- Avoid opiates / opioids
- Caution when driving & operating dangerous equipment

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Summary

- Abuse, dependence, overuse, mortality, morbidity, illegal use, impairment with BZs are all very low
- Current policies are adequate
- No new edicts, restrictions or prohibitions
- Trust the intelligence & judgment of colleagues

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Summary

- The content of this presentation is reviewed in greater detail in:
- Sheehan DV. Benzodiazepines. Chapter XX, pg. XXX- XXX in: American Psychiatric Publishing Textbook of Psychopharmacology. 6th edition. Schatzberg A. F. and Nemeroff C.B. ISBN XXX. In press.

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Questions?

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Back Up Slides

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Other Benzodiazepine Formulations

- Sustained / Extended Release
  - Xanax XR (Alprazolam XR)
  - Valrelease (Diazepam XR)
  - Loreev XR (Lorazepam XR)
- Fast acting (acute Rx of seizures >5 minutes)
  - Diastat (diazepam per rectum)
  - Valtoco (diazepam nasal spray)
- IV (acute Rx for seizures or in ER)
  - IV Lorazepam

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Prescribing Benzodiazepines in SUD

- Complicated
- Nuanced
- Needs to be personalized

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When to Consider a Benzodiazepine in SUD

- Do they have co-morbid:
  - Anxiety
  - Insomnia
  - MDD with Anxious Distress?
- Especially during the recovery process
- All 3 can trigger a relapse into SUD

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Clinician Factors in SUD Rx with BNZs

- Knowledge
- Skill set
- Knowledge
- Experience
- Training
- Attitude – some very punitive
- You shouldn't punish everyone

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Clinician Factors in SUD Rx with BNZs

- Monitor
- Verify (e.g., drug screen)
- Use trusted sources
- PDMP
  - Narx score

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Patient Factors in SUD Rx with BNZs

- How much control do they have over SUD?
- Do they abuse this privilege?
- Do they divert the meds you prescribe?
- Past history in similar states?
- Family history of SUD?

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Patient Factors in SUD Rx with BNZs

- If they use benzos, how do they use them?
  - Do they minimize or overuse their dose?
    - ✓Some underuse or try to underuse
    - ✓Others try to overuse

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Patient Factors in SUD Rx with BNZs

- How are they in a sobriety state?
  - Liars
  - Antisocial Personality Disorder
  - Trustworthy
  - Motivated
  - Tenacious / persistent

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Relationship Factors in SUD Rx with BNZs

- Shared decision making
  - A true partner with you in recovery?
  - A matter of trust

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Issues to Address in SUD Recovery Rx with BNZs

- In sobriety or not
- Substances (single, multiple, and which)
- Co-morbidities (A/D/B)
- Stressors
- Lifestyle chaos
- Support

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BNZ Use During COVID-19

- COVID-19 declared a national emergency on March 13, 2020
- Linked to an increase in:
  - mental health problems
  - drug overdoses
- Linked to abuse of:
  - alcohol
  - controlled substances
  - illicit substances

1. Holland, K. M., Jones, C., Vivolo-Kantor, A. M., Idaikkadar, N., Zwald, M., Hoots, B., ... & Houry, D. (2021). Trends in US emergency department visits for mental health, overdose, and violence outcomes before and during the COVID-19 pandemic. JAMA psychiatry, 78(4), 372-379.
2. de Dios, C., Fernandes, B. S., Whalen, K., Bandewar, S., Suchting, R., Weaver, M. F., & Selvaraj, S. (2021). Prescription fill patterns for benzodiazepine and opioid drugs during the COVID-19 pandemic in the United States. Drug and alcohol dependence, 229, 109176.

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BNZ Prescription Patterns pre vs. post March 13, 2020
(COVID-19)

- Compared to all controlled substances:
  - 2.0% ↑ in proportion of BNZ scripts
  - 1.7% ↓ in proportion of opioid scripts
- Only opioid script rate returned to pre-declaration levels after 5/18/20[1]
- BNZ scripts returned to forecasted prescription pattern in April – May 2020[2]

1. Milani, S. A., Raji, M. A., Chen, L., & Kuo, Y. F. (2021). Trends in the Use of Benzodiazepines, Z-Hypnotics, and Serotonergic Drugs Among US Women and Men Before and During the COVID-19 Pandemic. JAMA network open, 4(10), e2131012-e2131012.
2. Jones, C. M., Guy Jr, G. P., & Board, A. (2021). Comparing actual and forecasted numbers of unique patients dispensed select medications for opioid use disorder, opioid overdose reversal, and mental health, during the COVID-19 pandemic, United States, January 2019 to May 2020. Drug and alcohol dependence, 219, 108486.

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BNZ Prescription Rate Pre vs. During COVID-19

- Records of 15 – 17 million adults studied from 2018 - March 2021
- BNZ prescription rate:
  - for women:
    - ↓ 0.03% monthly from 2018 to Jan 2020
    - ↑ 0.06% monthly from January 2020 to April 2020
    - ↓ 0.04% monthly from April 2020 to March 2020
  - for men:
    - No statistically significant change in slope of rates over same periods
  - for ≥ 65 years:
    - similar to women

1. Milani, S. A., Raji, M. A., Chen, L., & Kuo, Y. F. (2021). Trends in the Use of Benzodiazepines, Z-Hypnotics, and Serotonergic Drugs Among US Women and Men Before and During the COVID-19 Pandemic. JAMA network open, 4(10), e2131012-e2131012.

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Questions?

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