
Benzodiazepines
The Good, The Bad
And The Ugly
28th Annual
Fall Psychiatric Symposium

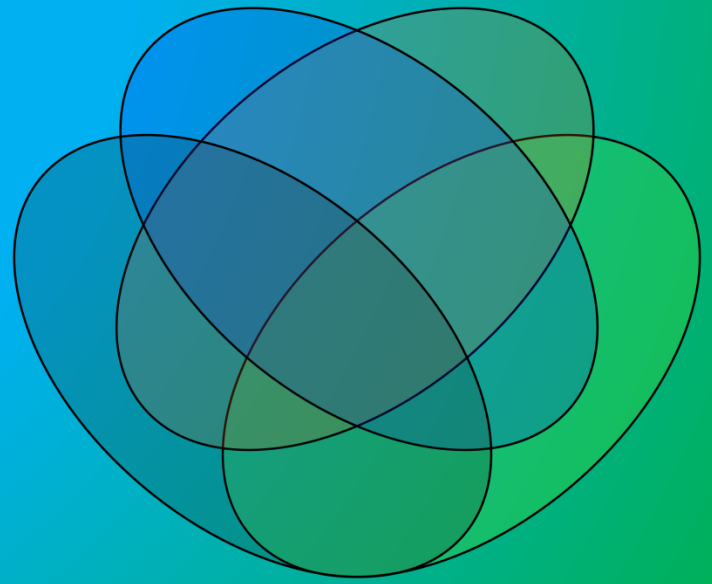
Benzodiazepines:

The Good, The Bad and The Ugly

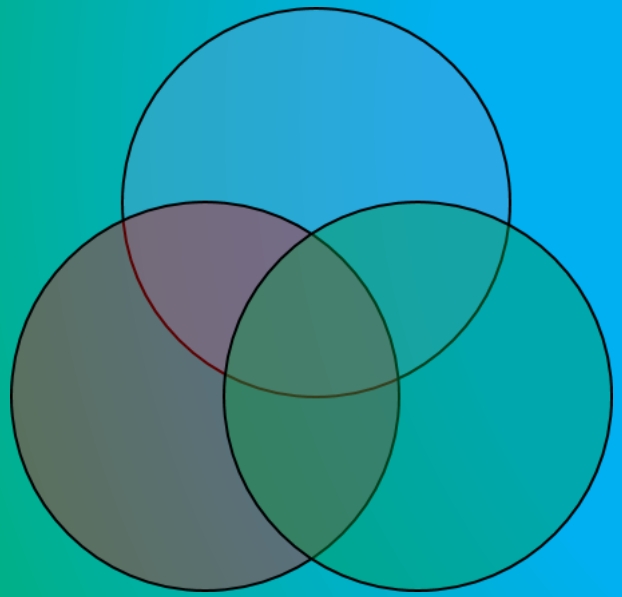
Lane M. Cook, M.D.

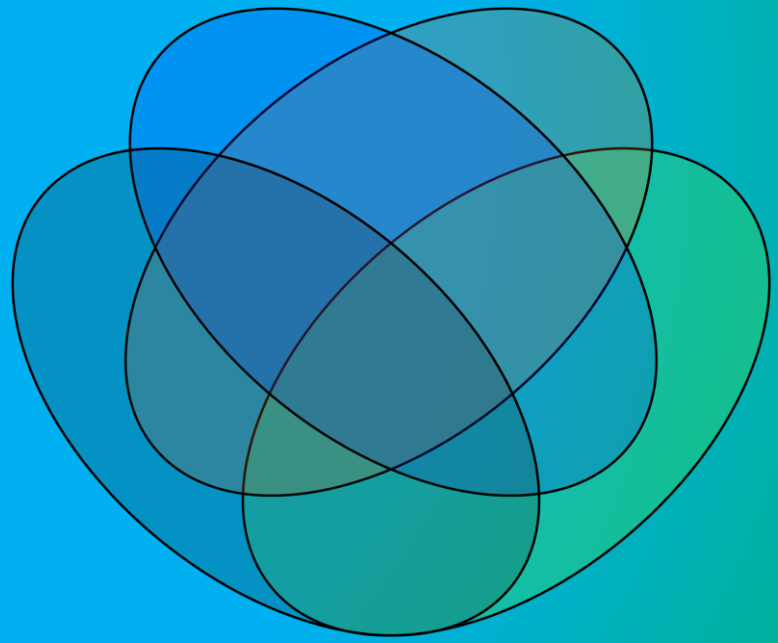
Fall Psychiatric Symposium

November 20, 2025



A Rational Approach to Prescribing





Learning Objectives

Outline the history and chemistry of benzodiazepines

Review the psychopharmacology

Including approved indications, mechanism of action, and differences in half-lives and duration of action

Safety: Are benzodiazepines dangerous?

A review of the literature and separating the treatment from the disease.

Effectiveness: Treatment-resistant anxiety and panic disorders

Review options including benzos for successful outcomes. Review stigma involving benzodiazepines

Review if and when and how to taper benzodiazepines

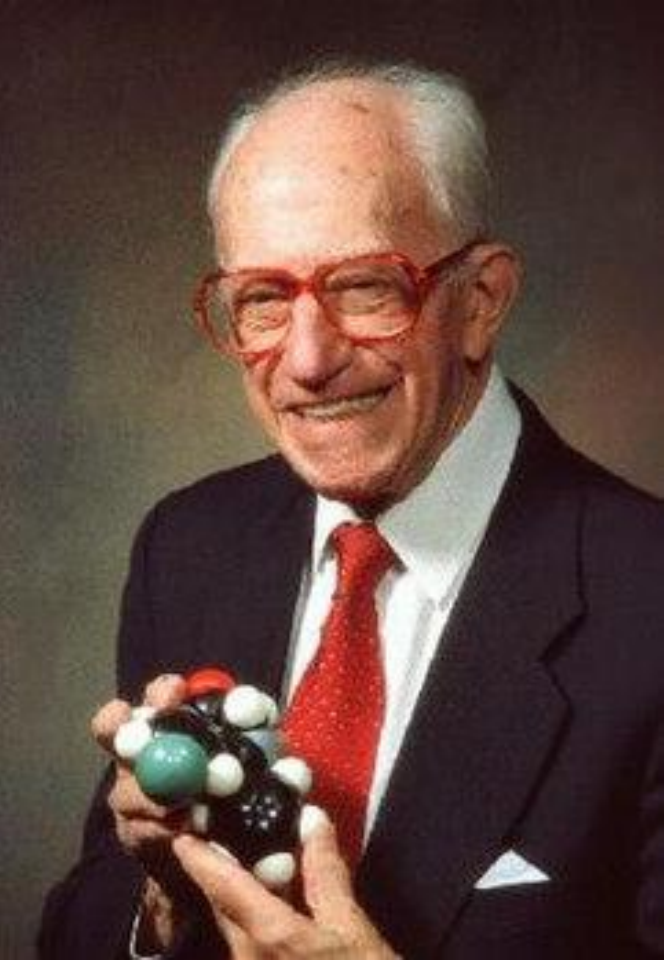
Outlines and recommendations

In Memoriam

Dedicated to
Vladimir Maletic, MD, MS
For his many Fall Psychiatric Symposium talks, his excellent job as a lecturer, psychiatrist, mentor and friend.

Vladimir "Vlad" Maletic, 68, of Greenville, South Carolina and Milwaukee, Wisconsin, unexpectedly passed away on December 11, 2024 while vacationing in Jamaica with his beloved wife and dear friends, Rakesh and Saundra Jain. This was 3 weeks after he presented at the 2024 Symposium.

Clint Eastwood in The Good, The Bad and The Ugly 1966, filmed in Italy and the genre became known as “Spaghetti Westerns”

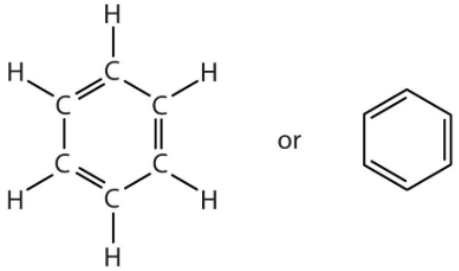


Leo Sternbach, Ph.D.

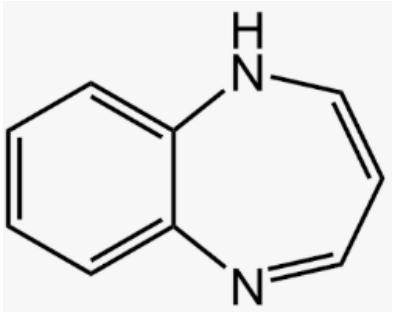
1908-2005

Dr. Sternbach fled Nazi Germany in 1941 and moved to New Jersey. He was employed by pharmaceutical company Hoffmann-LaRoche. He was working on synthesizing alternatives to barbiturates and meprobamate when he was experimenting with azo dyes and came up with chlordiazepoxide/Librium. Later he synthesized diazepam/Valium which between 1969 and 1982 was the most prescribed drug in America, with over 2.3 billion doses sold in its peak year of 1978. In 1977 benzos were the most prescribed drugs in the world. They were appreciated not just for their anxiolytic properties, but also for their usefulness in insomnia, agitation, seizures, muscle spasms, withdrawal and as a surgical premedication. Sternbach also invented flurazepam/Dalmane, flunitrazepam/Rohypnol “Ruffies”, and clonazepam/Klonopin. These compounds turn Swiss Hoffman-LaRoche (now known as Roche) into a pharmaceutical powerhouse.

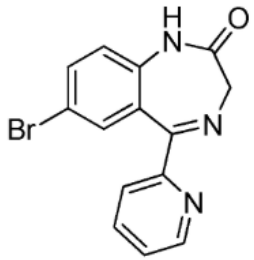
Chemical Structures of BZs



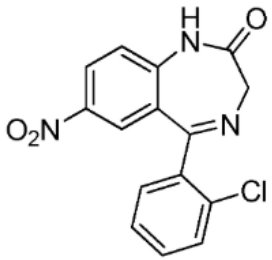
Benzene Ring



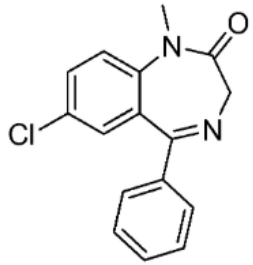
Diazepine



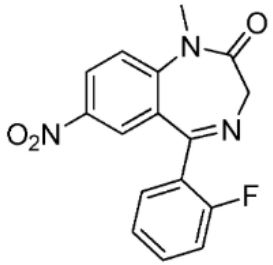
Bromazepam



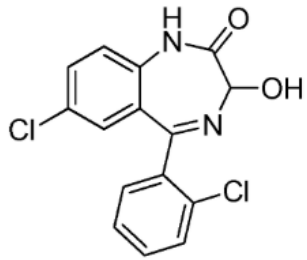
Clonazepam



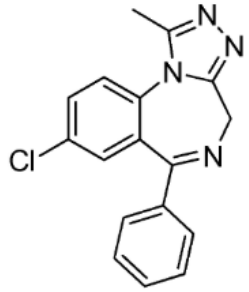
Diazepam



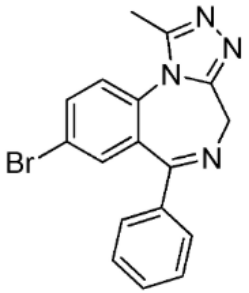
Flunitrazepam



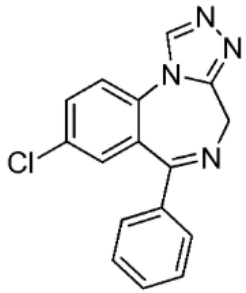
Lorazepam



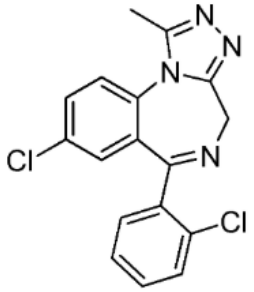
Alprazolam



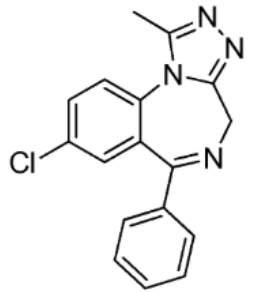
Bromazolam



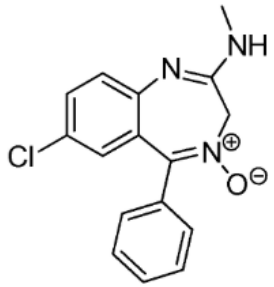
Estazolam



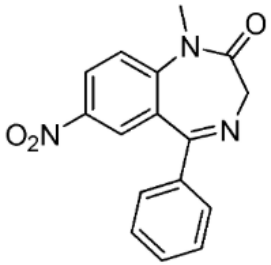
Triazolam



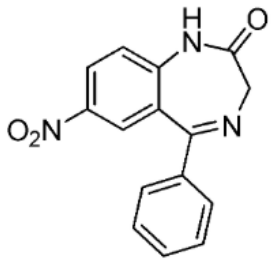
Pyrazolam



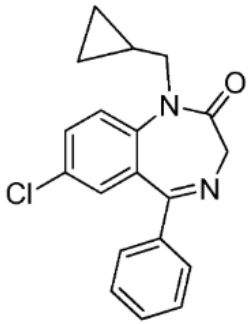
Chlordiazepoxide



Nimetazepam

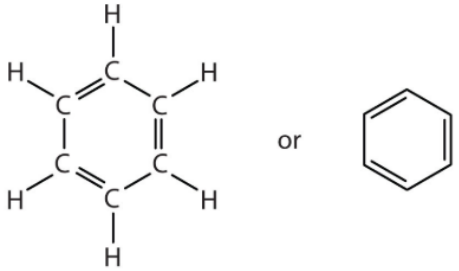


Nitrazepam

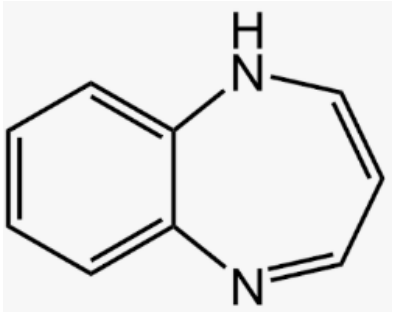


Prazepam

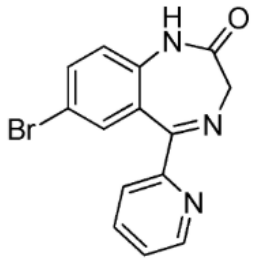
Chemical Structures of BZs



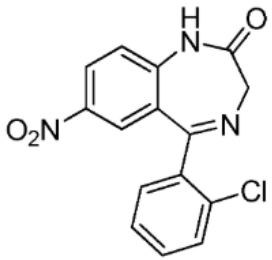
Benzene Ring



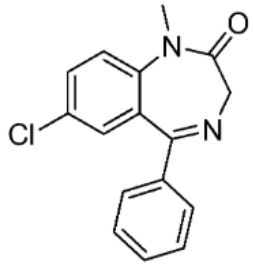
Diazepine



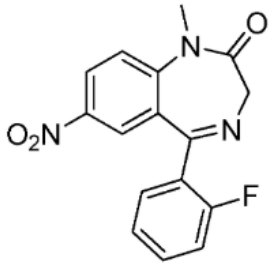
Bromazepam



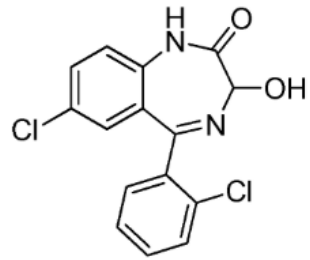
Clonazepam



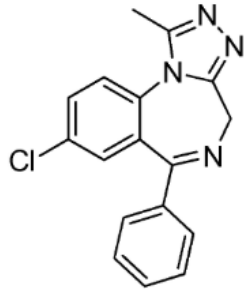
Diazepam



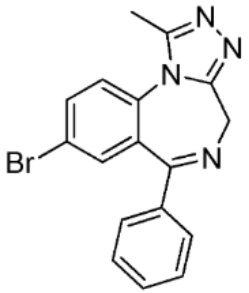
Flunitrazepam



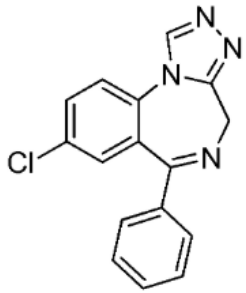
Lorazepam



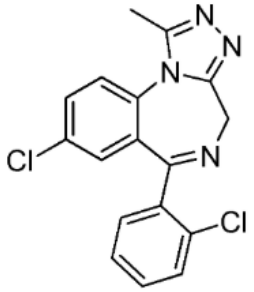
Alprazolam



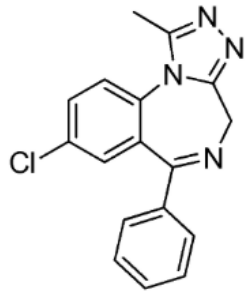
Bromazolam



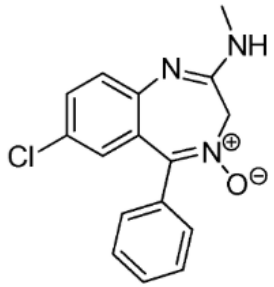
Estazolam



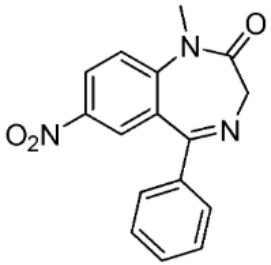
Triazolam



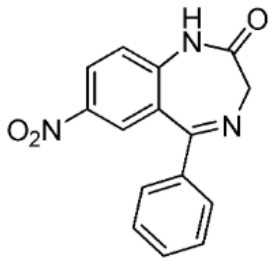
Pyrazolam



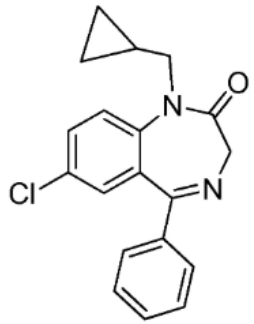
Chlordiazepoxide



Nimetazepam

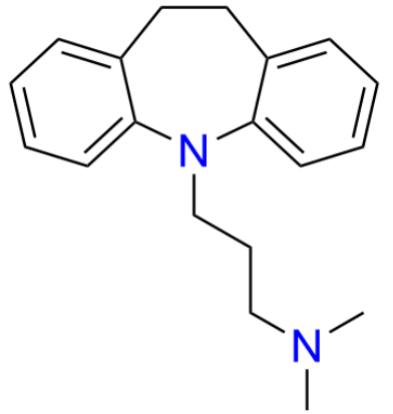


Nitrazepam



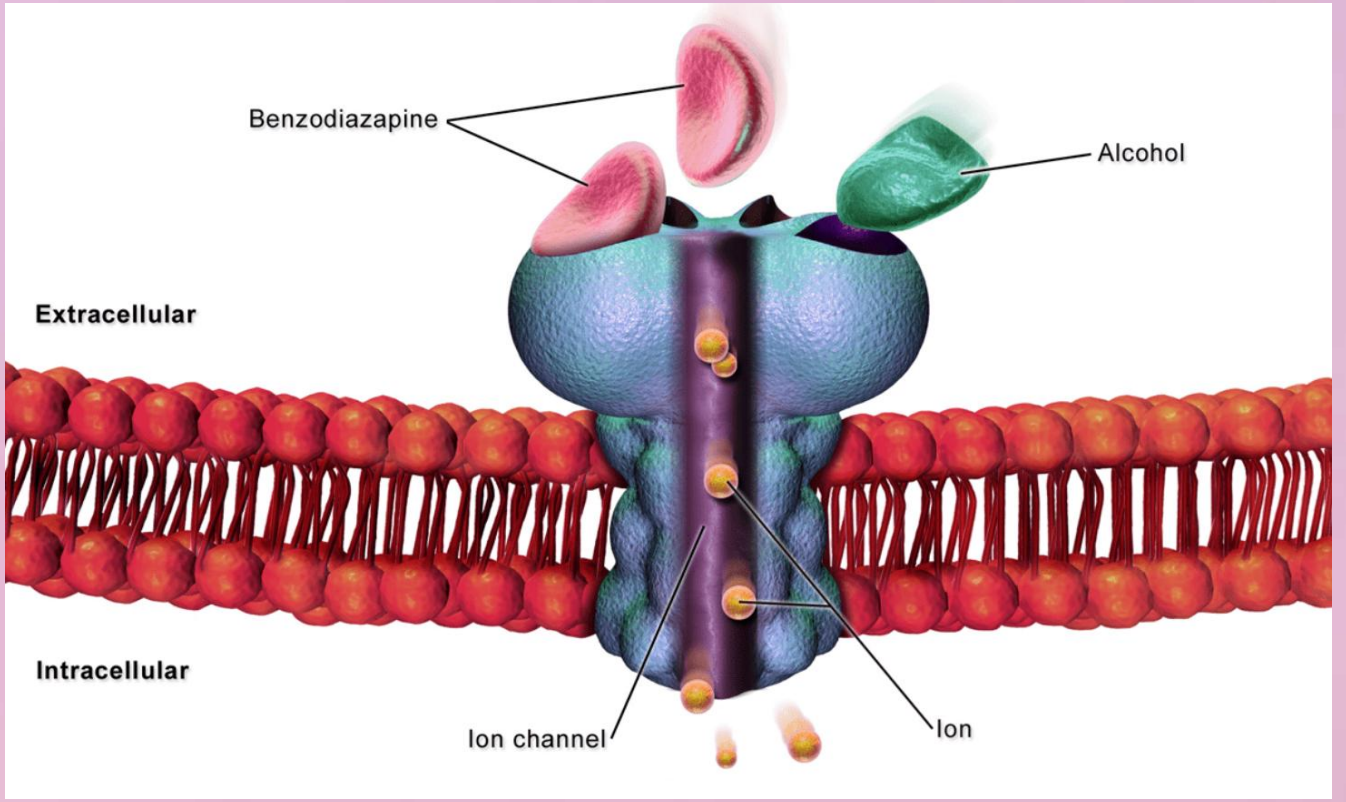
Prazepam

TCA-Imipramine



Stepwise Mechanism of Action of Benzodiazepines

1.Binding to GABA-A receptor complex
Benzodiazepines bind to a **specific site** on the **GABA-A receptor**, located between the **α and γ subunits**.
2.Positive allosteric modulation
They do not activate the receptor directly, but act as **positive allosteric modulators**, enhancing the effect of **endogenous GABA**.
3.Increased chloride ion influx
This binding **increases the frequency** of **chloride channel opening** in response to GABA.
4.Hyperpolarization of the neuron
Chloride influx leads to **membrane hyperpolarization**, making it less likely to fire an action potential.
5.CNS depression
The result is **dose-dependent central nervous system depression**, with effects ranging from **anxiolysis** to **sedation**, **hypnosis**, and **coma**.



GABA is the chief inhibitory neurotransmitter in the mammalian central nervous system. It acts as the “brakes” in the CNS.

Common Feelings and Effects of Benzodiazepines When Taken as Prescribed (e.g., for Anxiety or Panic Disorders):

Calmness and Relaxation: Most people feel a reduction in anxiety, muscle tension, and mental agitation. There's a sense of calm and relief from racing thoughts or panic.

Sedation: Drowsiness is a common effect, which can be helpful for those with insomnia or acute anxiety.

Slowed Thinking and Reaction Time: Some users report feeling mentally slower or less sharp.

Mild Euphoria: Occasionally, people may feel a subtle sense of well-being or contentment.

Common Feelings and Effects of Benzodiazepines When Taken Recreationally or in Higher Doses:

Stronger Sedation: Users may feel very sleepy or even fall asleep for hours.

Euphoria or "Buzz": Some describe a pleasurable, floaty feeling, though it's typically less intense than stimulants or opioids.

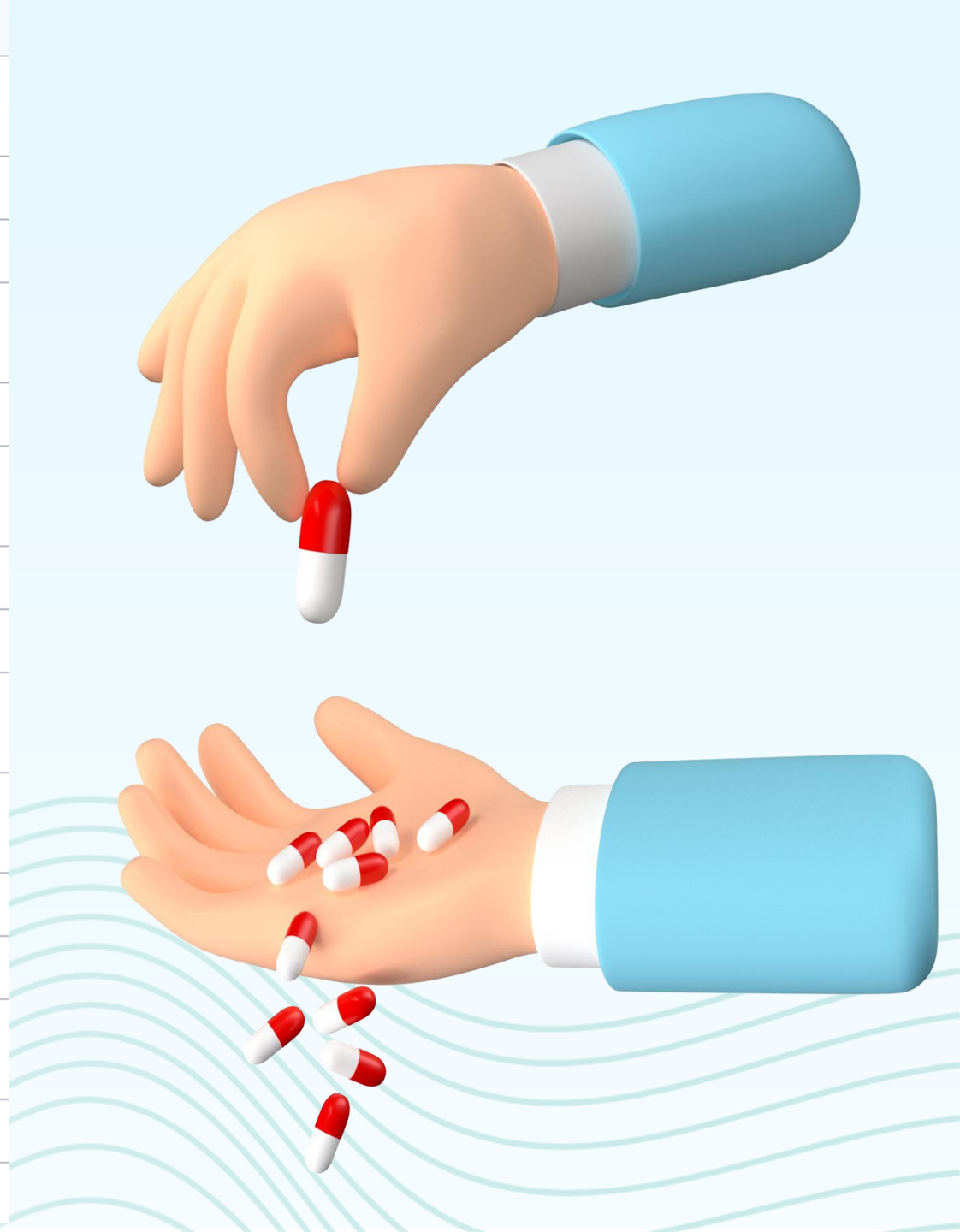
Disinhibition: Reduced social anxiety or inhibition, which can lead to risky behavior.

Memory Impairment: Blackouts or gaps in memory are common, especially with higher doses or when combined with alcohol.

Motor Impairment: Slurred speech, poor coordination, and slowed reflexes may occur.

Essentially the same as alcohol.

Generic Name	Brand Name	Common Uses	Half-life*
alprazolam	Niravam, Xanax, Xanax XR	anxiety, panic disorders	6-26h (short-acting)
chlordiazepoxide	Librium	anxiety, alcohol withdrawal	30-100h (long-acting)
clobazam	Onfi	Lennox-Gastaut syndrome, adjunct (seizures)	71-82h (long-acting)
clonazepam	Klonopin	seizure disorder, panic disorder, neuralgia (nerve pain)	20-50h (long-acting)
clorazepate	Tranxene T-Tab	anxiety, alcohol withdrawal, partial seizures	20-100h (long-acting)
diazepam	Valium	anxiety, sedation, alcohol withdrawal, muscle spasm, seizure disorders	20-100h (long-acting)
estazolam	ProSom	insomnia (short-term use)	10-24h (medium-acting)
flurazepam	Dalmane	insomnia (short-term use)	40-100h (long-acting)
lorazepam	Ativan	anxiety, insomnia (short-term use), seizures, sedation	10-20h (medium-acting)
midazolam	Generic	sedation, preoperative; general anesthesia induction; seizures	2.5h (short-acting)
oxazepam	Generic	anxiety, alcohol withdrawal	5-15h (short-acting)
quazepam	Doral	insomnia (short-term use)	25h (medium-acting)
remimazolam	Byfavo	sedation, preoperative, relaxant before minor procedures	37 - 53 minutes (very short-acting)
temazepam	Restoril	insomnia (short-term use)	10-20h (medium-acting)
triazolam	Halcion	insomnia (short-term use)	2-5h (short-acting)



DEA List of Schedules & Examples

DEA Drug Schedules (I–V)

Schedule I

Medical Use: None accepted in the U.S.
Abuse Potential: Highest
Examples: Heroin, LSD, MDMA, cannabis (federally)

Schedule II

Medical Use: Accepted, but highly restricted
Abuse Potential: High
Examples: Oxycodone, Methamphetamine, Fentanyl, Adderall

Schedule III

Medical Use: Accepted
Abuse Potential: Moderate
Examples: Ketamine, Anabolic steroids, Codeine (≤90 mg/dose)

Schedule IV

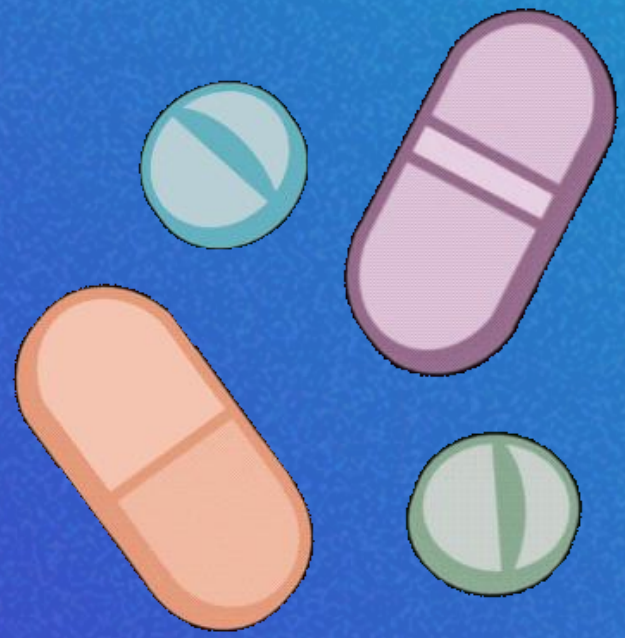
Medical Use: Accepted
Abuse Potential: Low
Examples: Alprazolam (Xanax), Diazepam (Valium), Zolpidem (Ambien)

Schedule V

Medical Use: Accepted
Abuse Potential: Lowest
Examples: Cough syrups with <200 mg codeine, Lomotil, Lyrica

FDA Approved Meds for Panic Disorder

- SSRI's
  - Fluoxetine
  - Sertaline
  - Paroxetine
- SNRI
  - Venlafaxine ER
- BENZODIAZEPINES
  - Alprazolam
  - Clonazepam



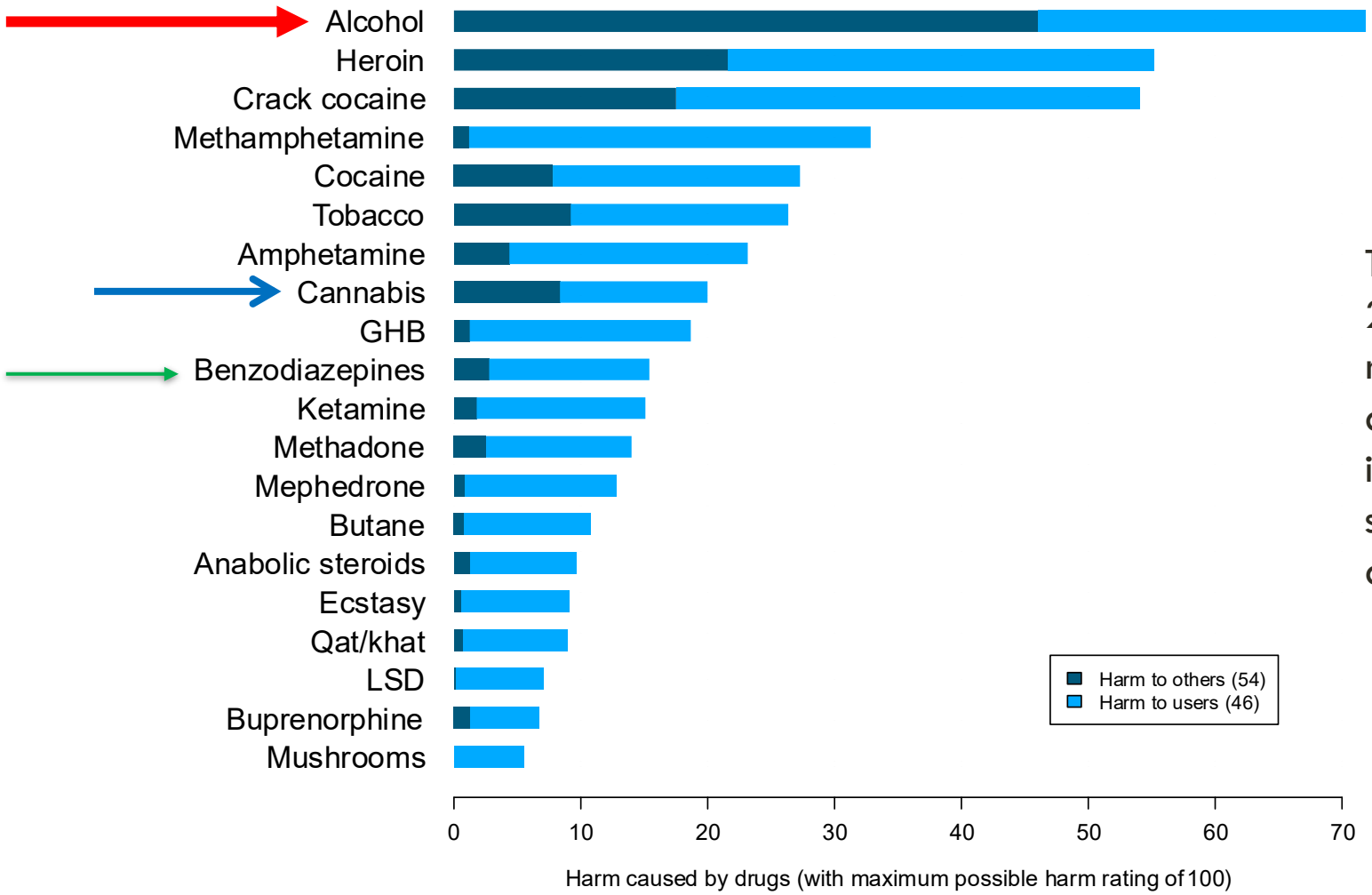


Table from the 2010 ISCD study ranking various drugs (legal and illegal) based on statements by drug-harm experts.

Nutt DJ, King LA, Phillips LD (November 2010). "Drug harms in the UK: a multicriteria decision analysis". *Lancet*. **376** (9752): 1558–1565.

U.S. FOOD & DRUG ADMINISTRATION

FDA Approval, The Package Insert & Approved Indications

01

Step 1 - Approval

- Pharmaceutical company does safety and efficacy studies on animals and people
- For each approved indication, must have 2 randomized, controlled, double-blind studies
- Can seek additional approval (e.g. clonazepam for panic disorder)
- FDA grants 20+ years brand exclusivity for the branded product but can be extended

02

Post Approval

- Any prescriber can use the drug for any reason or indication known as “off-label” prescribing
- Once the patent expires and generics are allowed, companies have no financial incentive to spend $millions to seek another approval
- The wording of the approval cannot be changed so “short-term use” applied to all BZ hypnotics can remain **forever**

Benzos and Z-Drugs (zolpidem, zaleplon, eszopiclone – all have package insert indications for short-term use but can be used off-label long-term

Newer orexin receptor antagonists such as Belsomra, Davigo, and Quviviq all have no duration restrictions and are approved for sleep onset and/or maintenance

Xanax/alprazolam was initially approved in 1981 for both panic disorder and anxiety

Klonopin/clonazepam was initially approved in 1975 for absence seizures and Lennox-Gastaut syndrome and in 1998 for panic disorder

Typical Box Warning of BZ's

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).**

- **The use of benzodiazepines, including Ativan, 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 Ativan and throughout treatment, assess each patient's risk for abuse, misuse, and addiction (see WARNINGS).**

- **The continued use of benzodiazepines, including Ativan 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 Ativan 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 Ativan or reduce the dosage (DOSAGE AND ADMINISTRATION and WARNINGS).**

Typical Medication Guide of BZ's

MEDICATION GUIDE

KLONOPIN (KLON-oh-pin) (clonazepam)
tablets, for oral use, C IV

What is the most important information I should know about KLONOPIN?

- **KLONOPIN is a benzodiazepine medicine. Taking benzodiazepines with opioid medicines, alcohol, or other central nervous system (CNS) depressants (including street drugs) can cause severe drowsiness, breathing problems (respiratory depression), coma, and death.** Get emergency help right away if any of the following happens:
  - shallow or slowed breathing
  - breathing stops (which may lead to the heart stopping)
  - excessive sleepiness (sedation)

  Do not drive or operate heavy machinery until you know how taking KLONOPIN and opioids affects you.
- **Risk of abuse, misuse, and addiction.** There is a risk of abuse, misuse, and addiction with benzodiazepines, including KLONOPIN, which can lead to overdose and serious side effects including coma and death.
  - **Serious side effects including coma and death have happened in people who have abused or misused benzodiazepines, including KLONOPIN.** These serious side effects may also include delirium, paranoia, suicidal thoughts or actions, seizures, and difficulty breathing. **Call your healthcare provider or go to the nearest hospital emergency room right away if you get any of these serious side effects.**
  - **You can develop an addiction even if you take KLONOPIN as prescribed by your healthcare provider.**
  - **Take KLONOPIN exactly as your healthcare provider prescribed.**
  - Do not share your KLONOPIN with other people.
  - Keep KLONOPIN in a safe place and away from children.
- **Physical dependence and withdrawal reactions.** KLONOPIN can cause physical dependence and withdrawal reactions.

The Impact of SSRI's and the DSM-III On Benzodiazepines

In the 1990's SSRI's were invented and first approved for major depression. Most of them were approved prior to the arrival of the DSM-III, when there were just 3 anxiety disorder diagnoses available – anxiety neurosis, phobic neurosis, and OCD. DSM-III established new anxiety disorder diagnoses, e.g., panic disorder, generalized anxiety disorder, social phobia, post-traumatic stress disorder, etc., and SSRIs were FDA-approved for many of those diagnoses.

Balon R, Starcevic V, Silberman E, Cosci F, Dubovsky S, Fava GA, et al. The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed. Braz J Psychiatry. 2020;42:243-244.

The Impact of SSRI's and the DSM-III On Benzodiazepines

In contrast, benzodiazepines were not approved for these indications, since they were mostly off-patent and their manufacturers were not willing to spend money on new clinical trials. Clonazepam was later approved for panic disorder. In the original package insert for Xanax, the range of doses in clinical trials was 1-10mg/day and the average daily dose for panic disorder was 4-5mg per day.

Balon R, Starcevic V, Silberman E, Cosci F, Dubovsky S, Fava GA, et al. The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed. Braz J Psychiatry. 2020;42:243-244.

SSRI's versus Benzodiazepines

The fact that a 2 week supply of a TCA could be fatal in overdose whereas SSRI's are rarely fatal in single overdoses made them superb antidepressants. However high placebo rates in clinical trials with SSRI's showing small differences in outcomes and the original mention of sexual dysfunction in Prozac was originally reported at 1.8% which is far below the actual incidence led to miminizing common side effects.

In addition when SSRI's are discontinued, withdrawal symptoms often emerge but were euphemistically termed "antidepressant discontinuation syndrome" vs "withdrawal" attached to benzos. This gives the impression of dependency in benzos but not SSRI's.

Balon R, Starcevic V, Silberman E, Cosci F, Dubovsky S, Fava GA, et al. The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed. Braz J Psychiatry. 2020;42:243-244.

The American Journal of Psychiatry

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FULL ACCESS | Articles | Publication Date: 20 September 2023

Long-Term Use of Benzodiazepines and Benzodiazepine-Related Drugs: A Register-Based Danish Cohort Study on Determinants and Risk of Dose Escalation

This article has been corrected. VIEW CORRECTION

Thomas Wolff Rosenqvist, M.D., Marie Kim Wium-Andersen, M.D., D.M.Sc., Ida Kim Wium-Andersen, M.D., Ph.D., Martin Balslev Jørgensen, M.D., D.M.Sc., and Merete Osler, M.D., D.M.Sc. AUTHORS INFO & AFFILIATIONS

Publication: American Journal of Psychiatry • Volume 181, Number 3 • https://doi.org/10.1176/appi.ajp.20230075

Rosenqvist, T. W., Wium-Andersen, M. K., Wium-Andersen, I. K., Jørgensen, M. B., & Osler, M. (2024). Long-Term Use of Benzodiazepines and Benzodiazepine-Related Drugs: A Register-Based Danish Cohort Study on Determinants and Risk of Dose Escalation. *American Journal of Psychiatry*, *181*(3), 246–254.

The Data and The Results

Methods:

All adults ages 20–80 years living in Denmark on January 1, 2000 (N=4,297,045) were followed for redeemed prescriptions of BZRAs (benzodiazepine receptor agonists, aka the “Z drugs” of zolpidem, zaleplon and eszopiclone) and in the Danish National Prescription Registry from January 1, 2000, to December 31, 2020. For each drug class, we calculated long-term use for more than 1 or 7 years, and dose escalation measured as increase in dose to a level above the recommended level. Associations were examined using logistic regression.

The Data and The Results

The authors identified 950,767 incident BZRA users. The article pointed out 85% of initial BZRA recipients discontinued the medications within 1 year, and 97% had stopped all BZRA use by 7 years. Additionally, dose escalation was very low. Among the 5% with continuous use over 3 years, less than 7% had dose escalations above recommended levels; this equals 0.35% escalating doses among almost 1 million patients starting BZRAs. Psychiatric comorbidity, especially substance use disorder, was associated with higher risk of long-term use and dose escalation.

Thus, this study does not, under the current regulations, support the belief that BZRA use frequently results in long-term use or dose escalation.

EDITORIALS | JUNE 09 2022

Stigmatization of Benzodiazepines: Pharmacologic and Nonpharmacologic Contributions Free

Subject Area: Psychiatry and Psychology

Edward K. Silberman

Psychother Psychosom (2022) 91 (5): 304–306.
https://doi.org/10.1159/000525208 Article history

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Prescribing benzodiazepines to treat anxiety is widely viewed as problematic in current psychiatry. Residents are warned to avoid them; published guidelines advise using them only as a second-line treatment, rarely as monotherapy, and never chronically; some clinics prohibit them entirely; and practitioners who use them may risk censure from institutions or regulatory agencies [1]. Remarkably, the published literature on benzodiazepine efficacy, toxicity, and abuse potential provides no support for this sweepingly negative view of these medications, and, in fact, largely contradicts it. The comprehensive review by Dubovsky and Marshall [2] is the most recent confirmation of the disconnect between the common wisdom and the evidence base.

https://karger.com/pps/article/91/5/304/826572/Stigmatization-of-Benzodiazepines-Pharmacologic

The American Journal of Psychiatry

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FULL ACCESS | Editorials | Publication Date: 1 March 2024

Setting the Record Straight on Long-Term Use, Dose Escalation, and Potential Misuse of Prescription Benzodiazepines

Stephen B. Soumerai, Sc.D., Mahnum Shahzad, Ph.D., and Carl Salzman, M.D. | AUTHORS INFO & AFFILIATIONS

Publication: American Journal of Psychiatry • Volume 181, Number 3 • https://doi.org/10.1176/appi.ajp.20240030

BENZOS AND DEPENDENCY

Soumerai, S. B., Shahzad, M., & Salzman, C. (2024). Setting the Record Straight on Long-Term Use, Dose Escalation, and Potential Misuse of Prescription Benzodiazepines. American Journal of Psychiatry, 181(3), 186–188.

The authors are all faculty members of Harvard Medical School, Dept. of Population Medicine

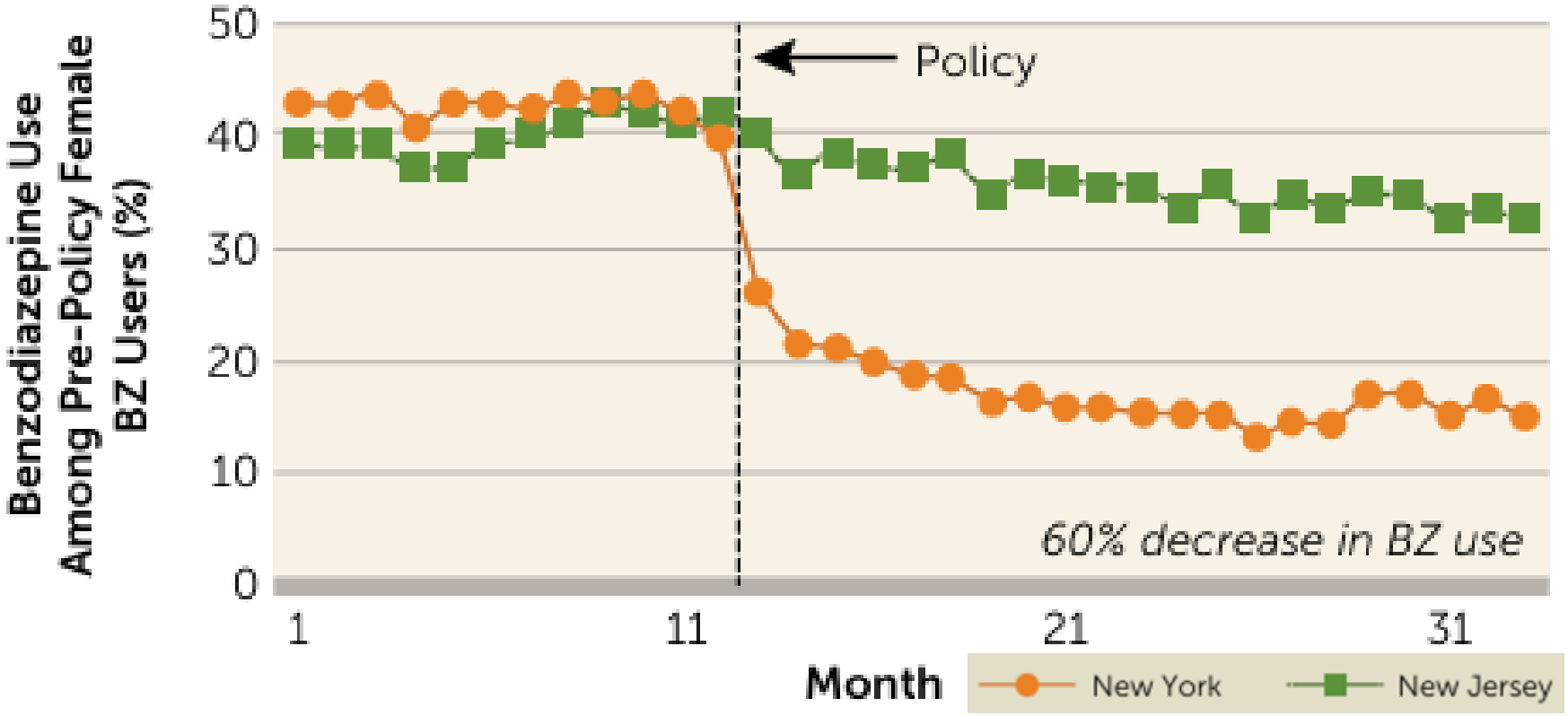
The Data and The Results

The authors cited the prior article as well as others including other studies of escalation. A study of 81,945 BZRA recipients in Norway reported that only 0.9% ended up using higher than prescribed daily doses. And a study of 12,598 patients in Canada recorded that 3.1% of patients who were prescribed benzodiazepines for at least 2 years escalated to doses higher than 40 diazepam milligram equivalents.

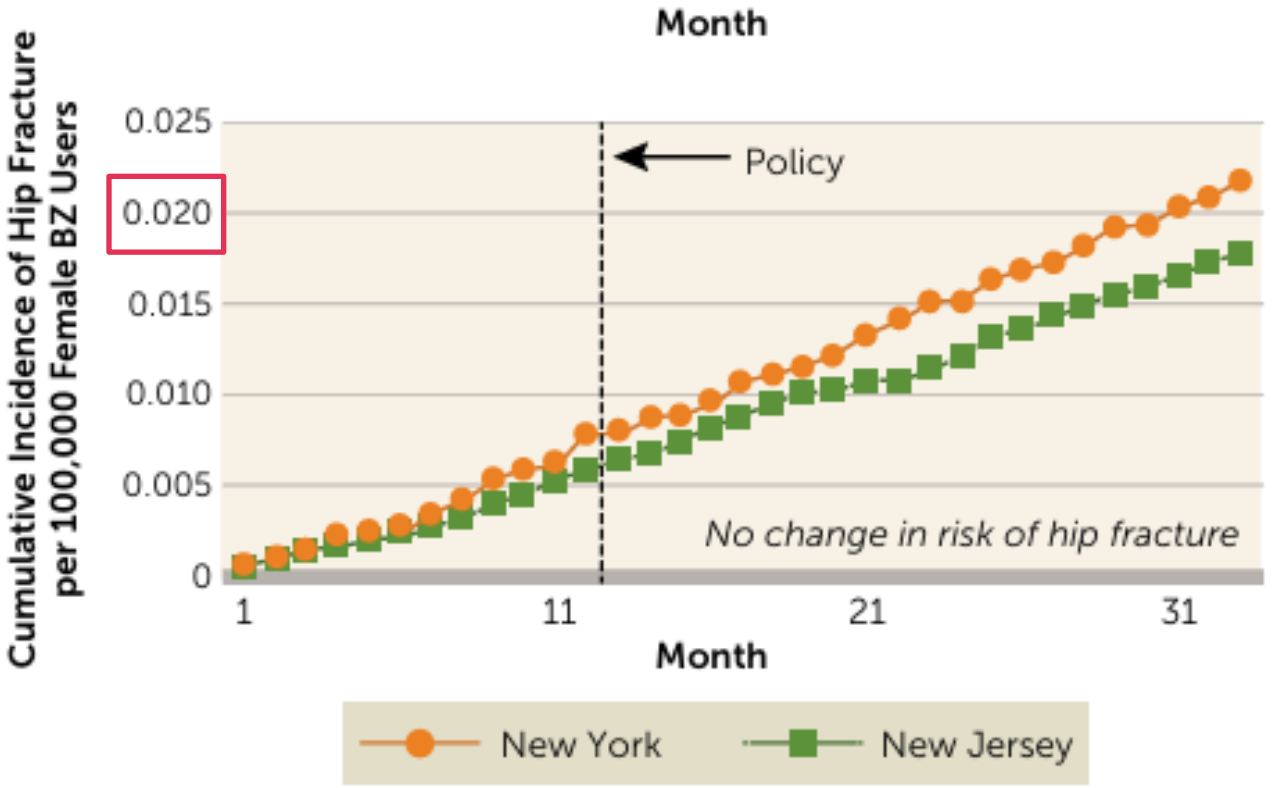
They stated much of the previous research on outcomes of BZRAs (and other psychoactive medications) exaggerated drug harms on the basis of weak cross-sectional pharmacoepidemiologic designs that did not control for confounding by indication. This common bias occurs when physicians preferentially treat sicker or older patients. Conditions such as dementia, drug abuse, and other chronic illnesses often cause the adverse outcome, not the treatment itself. These biases are often hidden because sickness and frailty are poorly measured in common research and insurance databases.

Benzos in the Elderly – Falls Risk?

FIGURE 1. Benzodiazepine use and risk of hip fracture among women enrolled in Medicaid before and after regulatory surveillance restricting benzodiazepine use in New York State[a]



Benzos in the Elderly – Falls Risk?

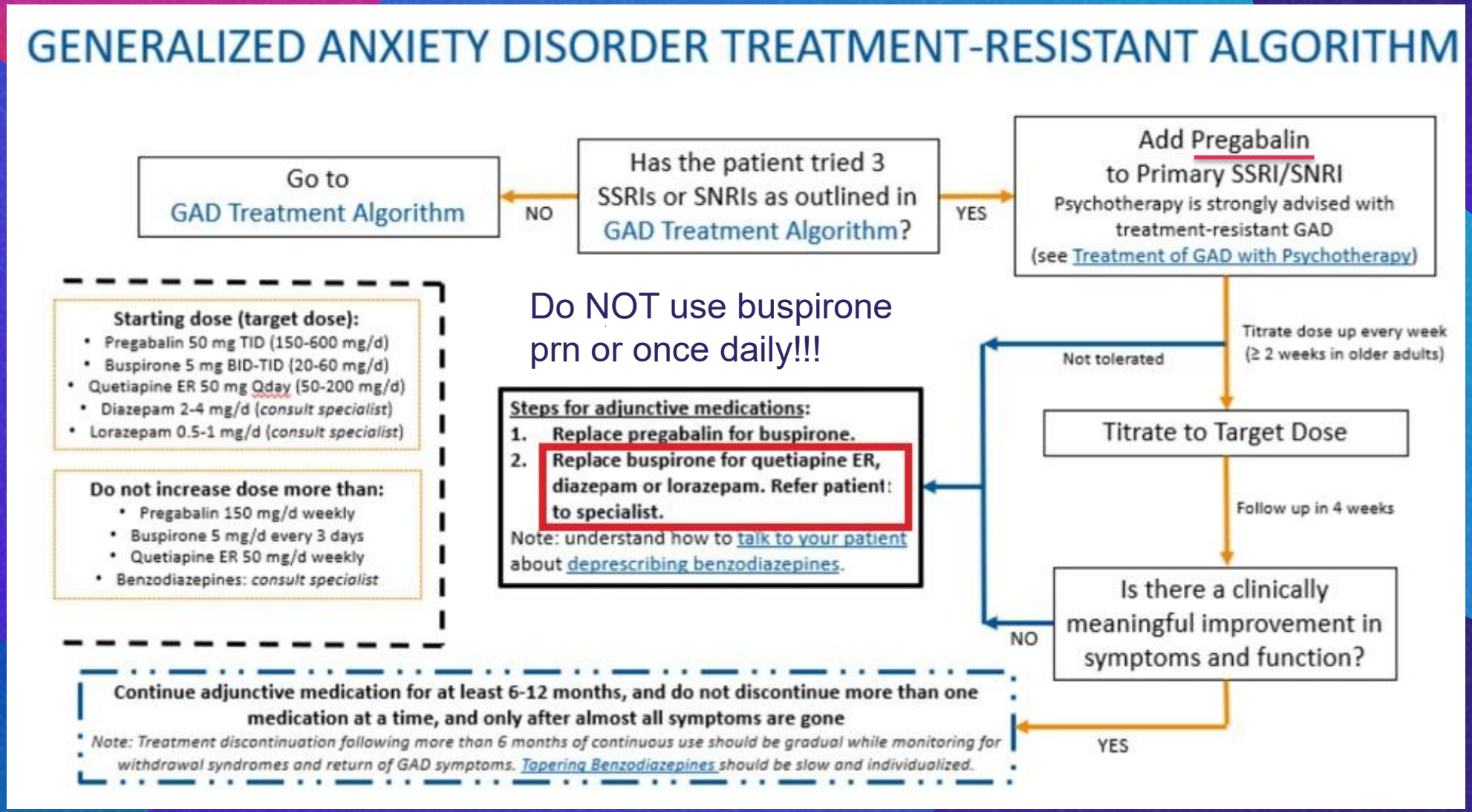


[a] This strong longitudinal study, which controlled for confounding by indication, showed that a sudden, sustained 60% reduction in benzodiazepine (BZ) use did not lower the risk of hip fracture. A BZ user was defined as a person who had received at least one dispensed BZ in the year before the policy was implemented. Figure adapted from Wagner et al. (9); reprinted with permission from *Annals of Internal Medicine*.

The drop in benzo prescriptions was due to NY state's adoption of the triplicate prescription, requiring the original to go to the pharmacy, one to be kept in the patient's chart, and the 3rd copy sent to the state.

Wagner AK, Ross-Degnan D, Gurwitz JH, et al: Effect of New York State regulatory action on benzodiazepine prescribing and hip fracture rates. Ann Intern Med 2007; 146:96–103

Oregon Health Authority Algorithm



https://www.ohsu.edu/sites/default/files/2025-04/Medication%20Treatment%20for%20Adults%20with%20GAD.pdf

Expert Opin Pharmacother. 2018 June ; 19(8): 883–894. doi:10.1080/14656566.2018.1472767.

Comparing the Efficacy of Benzodiazepines and Serotonergic Anti-Depressants for Adults with Generalized Anxiety Disorder: A meta-analytic review

Angelina F. Gomez, **Abigail L. Barthel**, and **Stefan G. Hofmann**
Department of Psychological and Brain Sciences, Boston University

Abstract

Introduction: Generalized anxiety disorder (GAD) is a common form of anxiety disorder. Selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines (BZs) are the most commonly prescribed medications for GAD, but little is known about the relative efficacy of these pharmacological treatments.

Areas Covered: This study provides a meta-analytic review of the efficacy of these medications in the treatment of adults with GAD.A comprehensive literature search yielded 54 articles reporting 56 unique studies with 12,655 participants treated with either pill placebo (6,191 participants), SSRIs (16 trials, 2,712 participants), SNRIs (17 trials, 2,603 participants), or BZs (23 trials, 1,149 participants). The overall combined effect size was modest to moderate (Hedges' $g = 0.37$, $p < 0.0001$). Effect sizes decreased significantly over time. SSRIs (Hedges' $g = 0.33$) and SNRIs (Hedges' $g = 0.36$) demonstrated significantly lower effect sizes than BZs (Hedges' $g = 0.50$).

Expert opinion: These findings were not due to differences in treatment length or publication year. The results of this study suggest that the most common forms of pharmacotherapy for adult GAD are moderately effective, with BZs being the most effective drug.

0.2 = small effect
0.5 = medium effect
0.8 = large effect

SSRI's 0.33
SNRI's 0.36
BZ's 0.50

Pregabalin & Gabapentin Risks for Heart Failure

- A retrospective cohort study included data collected between January 1, 2015, and December 21, 2018, of 246,237 Medicare beneficiaries aged 65 to 89 years with chronic noncancer pain and without a history of heart failure and terminal illnesses.
- 18,622 (7.6%) were new users of pregabalin/Lyrica and 227,615 (92.4%) were new users of gabapentin
- 1.82% of patients in this age group have a risk of heart failure per year with pregabalin and 1.25% with gabapentin. Pregabalin was more likely to be associated with heart failure than gabapentin although only 7.6% of the pregabalin users were new to the drug compared to 92.4% of the gabapentin users were new to the group, indicating a large difference between patients who'd been on pregabalin (chronic use) versus gabapentin.

Park EE, Daniel LL, Dickson AL, et al. Initiation of Pregabalin vs Gabapentin and Development of Heart Failure. JAMA Netw Open. 2025;8(8):e2524451. doi:10.1001/jamanetworkopen.2025.24451
https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2837132

ELSEVIER

Progress in Neuro-Psychopharmacology and Biological Psychiatry

Volume 70, 3 October 2016, Pages 219-226

Treatment-resistant panic disorder: clinical significance, concept and management

Mu-Hong Chen, Shih-Jen Tsai

Mu-Hong Chen, Shih-Jen Tsai,
Treatment-resistant panic disorder: clinical significance, concept and management,
Progress in Neuro-Psychopharmacology and Biological Psychiatry,
Volume 70, 2016, Pages 219-226

Panic Disorder is often Chronic

- Approximately 80% and 65% of patients with panic disorder sought medical treatment during lifetime and in the recent 1 year
- Only 36% of patients make a prompt treatment contact in the first year of onset, with a median duration of 10-year delay in initial treatment contact after onset of panic disorder
- Over 50% of patients with panic disorder still suffered from threshold or subthreshold panic symptoms despite antidepressant and psychotherapy treatment and did not achieve a full remission, while only one-third of the patients can maintain a stable panic-free condition during the follow-up
- A 5-year naturalistic follow-up study conducted by Cowley et al. showed that 30% of the patients were panic-free at 12 months but more than 50% of patients still experienced panic attacks or panic disorder during the follow-up period

Mu-Hong Chen, Shih-Jen Tsai,
Treatment-resistant panic disorder: clinical significance, concept and management,
Progress in Neuro-Psychopharmacology and Biological Psychiatry,
Volume 70, 2016, Pages 219-226

Research

87 studies including a total of 12 800 participants and 12 drug classes were eligible for inclusion.

Drug treatment for panic disorder with or without agoraphobia: systematic review and network meta-analysis of randomised controlled trials

BMJ 2022 ; 376 doi: https://doi.org/10.1136/bmj-2021-066084 (Published 19 January 2022)
Cite this as: *BMJ* 2022;376:e066084

The SUCRA (Surface Under the Cumulative Ranking Curve) score is a metric used in **network meta-analysis (NMA)** to rank treatments based on their likelihood of being among the best options. It ranges from **0% to 100%**, where higher values indicate a greater probability that a treatment is among the top-ranked.

SUCRAs identified benzodiazepines (84.5%, mean rank=2.4), tricyclic antidepressants (68.7%, 3.8), and SSRIs (66.4%, 4.0) as the top three best treatments for remission.

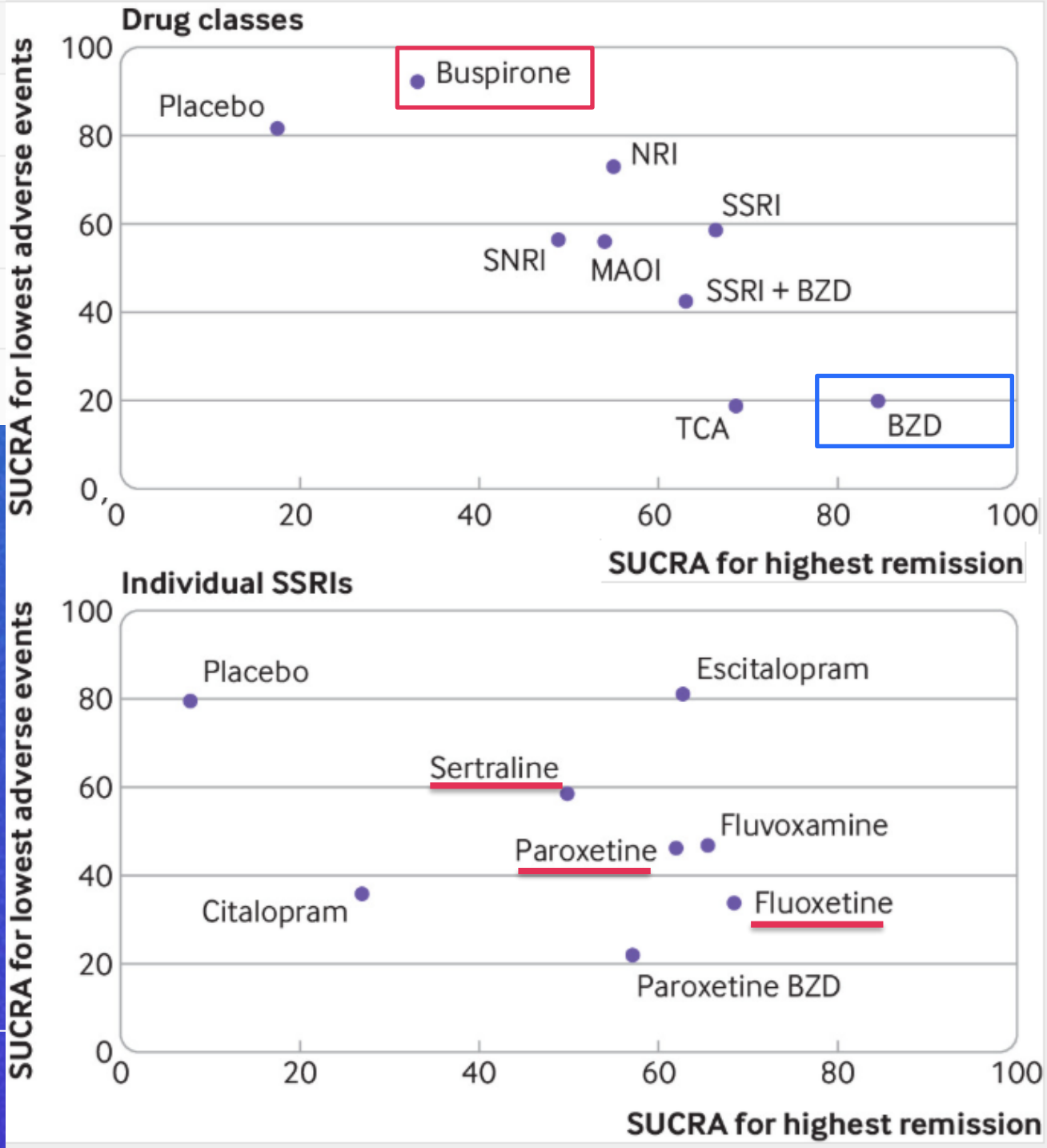
SUCRA Score	Interpretation
>80%	**Strong effect / Top-ranked** treatment
60–80%	**Moderate effect** / Likely among better options
40–60%	**Modest or uncertain effect**
<40%	**Weak effect / Lower-ranked** treatment

Full article at https://www.bmj.com/content/376/bmj-2021-066084

SUCRA Score	Interpretation
>80%	**Strong effect / Top-ranked** treatment
60–80%	**Moderate effect** / Likely among better options
40–60%	**Modest or uncertain effect**
<40%	**Weak effect / Lower-ranked** treatment

Note the ineffectiveness of buspirone and the effectiveness of BZ and in panic disorder

Fluoxetine, paroxetine and sertraline are the only FDA approved antidepressants for panic disorder



Joint Clinical Practice Guideline on Benzodiazepine Tapering: Considerations When Risks Outweigh Benefits

Clinical Guidelines | Open access | Published: 17 June 2025

(2025) Cite this article

Journal of General Internal Medicine

Aims and scope →

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Emily Brunner MD, DFASAM (chair), Chwen-Yuen A. Chen MD, Tracy Klein PhD, ARNP, FAAN, FAANP, Donovan Maust MD, MS, Maryann Mazer-Amirshahi PharmD, MD, MPH, PhD, FACMT, FASAM, Marcia Mecca MD, Deanna Najera MPAS, MS, PA-C, DFAAPA, Chinyere Ogbonna MD, Kiran F. Rajneesh MD, MS, FAAN, Elizabeth Roll MD, Amy E. Sanders MD, MS, MPHIL, FAAN, Brett Snodgrass FNP-C, CPE, ACHPN, FAANP, Amy VandenBerg PharmD, BCPP, Tricia Wright MD, MS, FACOG, DFASAM, Maureen Boyle PhD, Amanda Devoto PhD, Sarah Framnes-DeBoer MS, Bethea Kleykamp PhD, Janette Norrington PhD & Dawn Lindsay PhD

https://link.springer.com/article/10.1007/s11606-025-09499-2

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Recommendations for Considerations for Tapering Benzodiazepines

1. Clinicians should ideally assess the risks and benefits of ongoing BZD prescribing at least every 3 months for each patient taking BZD medications (see Tables 2 and 3; *Clinical Consensus*, Strong Recommendation).

    a At a minimum, clinicians should assess the risks and benefits with each new BZD prescription or BZD prescription renewal (*Clinical Consensus*, Strong Recommendation).

    b Clinicians should review the information in the relevant prescription drug monitoring programs (PDMPs) as part of the risk–benefit assessment (*Clinical Consensus*, Strong Recommendation).

https://link.springer.com/article/10.1007/s11606-025-09499-2

Warnings about BZs+Opioids

****FDA Black Box Warning**

The **FDA issued a black box warning** highlighting the dangers of using opioids and benzodiazepines together, especially regarding **CNS depression, coma, and death.** Co-prescribing should be **avoided whenever possible.** If necessary, it should be done with **extreme caution,** using the **lowest effective doses** and **shortest duration.** [health.ri.gov]

🧠 **CDC Guidelines (2022 Update)**

The **CDC's Clinical Practice Guideline for Prescribing Opioids for Pain** emphasizes:

Avoiding co-prescribing unless absolutely necessary.

Close monitoring of patients who require both medications.

Individualized care that balances risks and benefits.

Non-opioid and non-benzodiazepine alternatives should be considered first. [cdc.gov]

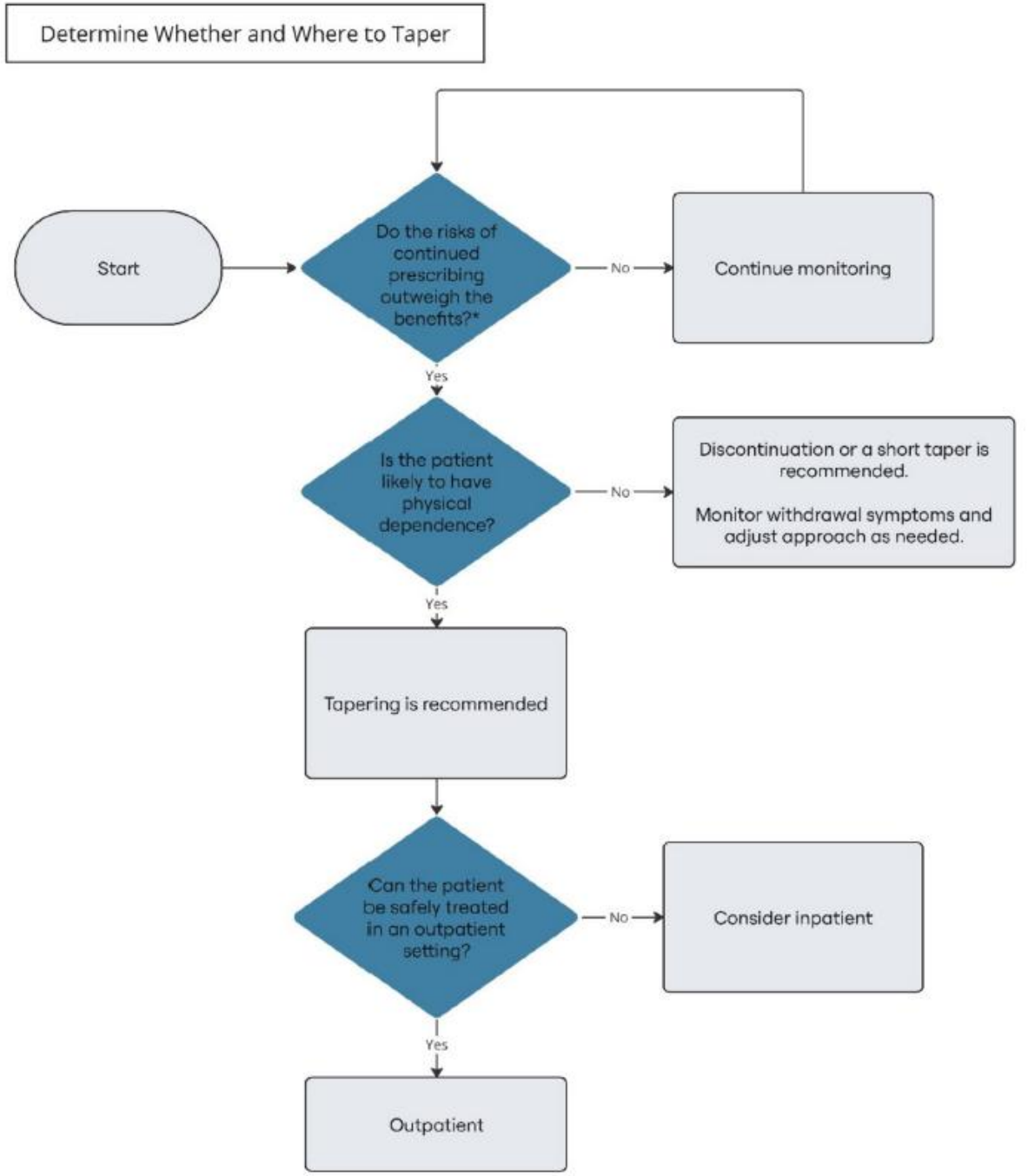
CMS Recommendations for Benzos with opioids

In 2017, 10,010 people died from overdosing with both BZDs and an opioid, which is more than a fifth of the 47,600 total opioid overdose deaths in that year. While exact numbers for opioid-benzodiazepine deaths in 2025 are not yet finalized, **benzodiazepines were involved in approximately 10–15% of opioid-related overdose deaths** in recent years.

There are five central principles for co-prescribing BZDs and opioids:

1. Avoid initial combination by offering alternative approaches
2. If new prescriptions are needed, limit the dose and duration
3. Taper long-standing medications gradually and, whenever possible, discontinue
4. Continue long-term co-prescribing only when necessary and monitor closely
5. Provide rescue medication (for example, naloxone) to high-risk patients and their caregivers

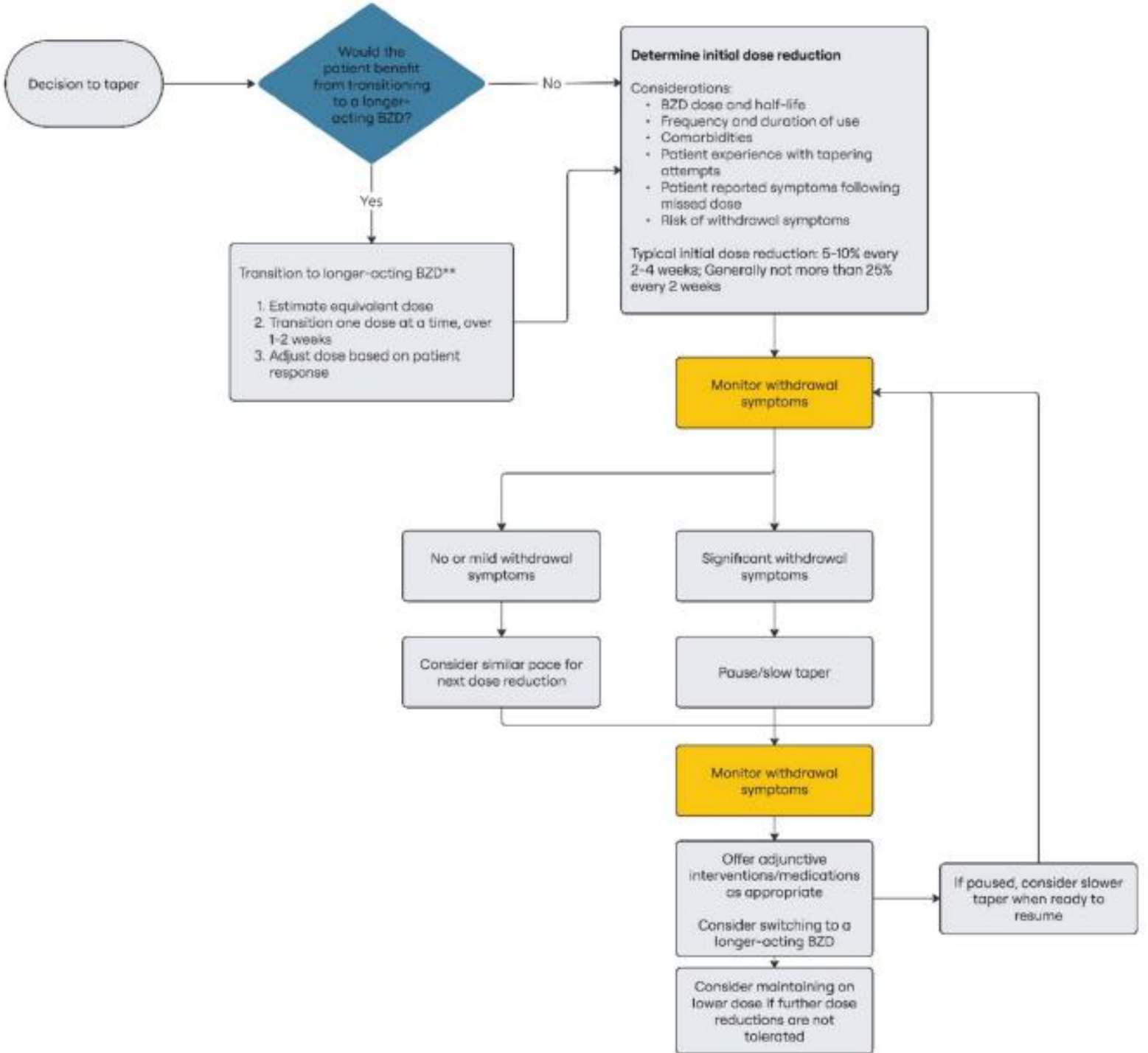
https://link.springer.com/article/10.1007/s11606-025-09499-2



Standard taper

Is 5-10% dose Reduction every 2 weeks

<25% every 2 weeks



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JAMA Netw Open
Published Online: December 20, 2023

Original Investigation | Pharmacy and Clinical Pharmacology

Benzodiazepine Discontinuation and Mortality Among Patients Receiving Long-Term Benzodiazepine Therapy

Donovan T. Maust, MD, MS[1,2,3]; Kierstdea Petzold, MS[2]; Julie Strominger, MS[2]; et al

Did discontinuation increase or decrease mortality?

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JAMA Netw Open
Published Online: December 20, 2023

Original Investigation | Pharmacy and Clinical Pharmacology

Benzodiazepine Discontinuation and Mortality Among Patients Receiving Long-Term Benzodiazepine Therapy

Donovan T. Maust, MD, MS[1,2,3]; Kierstdea Petzold, MS[2]; Julie Strominger, MS[2]; et al

Key Points

Question Given the association of benzodiazepine receipt with patient harms, does prescription discontinuation reduce risk of death and other harms in patients receiving stable long-term benzodiazepine treatment?

Findings In this comparative effectiveness study among 353,576 patients receiving stable long-term treatment with benzodiazepines, discontinuation was associated with small absolute increases in mortality and other potential harms, including nonfatal overdose, suicide attempt, suicidal ideation, and emergency department visits.

Meaning These results suggest benzodiazepine discontinuation among patients prescribed for stable long-term treatment may be associated with unanticipated harms, and that efforts to promote discontinuation should carefully consider the potential risks of discontinuation relative to continuation.

J Clin Psychiatry. 2025 Mar 12;86(2):24m15424. doi: 10.4088/JCP.24m15424.

Suicide Among Veterans Health Administration Patients With Bipolar Disorder: Evidence for Increased Risk Associated With Benzodiazepine Receipt

Link

Kevin G Saulnier [1 2 3], Anna L Philibert [1], Peter P Grau [2 3], Nicholas W Bowersox [1 2 3 4 5]

Affiliations + expand

PMID: 40117569 DOI: 10.4088/JCP.24m15424

Abstract

Objective: To evaluate factors associated with suicide mortality among Veterans Health Administration (VHA) patients with bipolar disorder.

Methods: VHA patients diagnosed with bipolar disorder in calendar year (CY) 2014 who utilized VHA health care services in CY2013 were included in the study cohort. Suicide mortality in the 5 years following the first documented bipolar disorder diagnosis during CY2014 was examined using Cox proportional hazards regression.

Results: 725 of 126,655 VHA patients who had a bipolar disorder diagnosis in CY2014 (0.6%) died by suicide in the following 5 CYs (2014-2019). Suicide was associated with suicide high-risk flags (hazard ratio [HR] = 2.21), prior year emergency department visit (HR = 1.25), having a new bipolar disorder diagnosis (HR= 1.23), and receiving a benzodiazepine prescription of ≥30 days of supply (HR = 1.58). Prescriptions of benzodiazepines of <30 days of supply, other anxiolytics (ie, buspirone), and sedatives were not significantly associated with suicide mortality in the multivariable model.

Conclusions: Among VHA patients diagnosed with bipolar disorder, receipt of a benzodiazepine prescription of ≥30 days was associated with increased suicide risk, even after controlling for clinical and demographic factors. Elucidating mechanisms through which benzodiazepine prescriptions increase suicide risk is an important avenue for future investigations. Additionally, VHA patients with newly diagnosed bipolar disorder may benefit from increased clinical attention, given the elevated suicide risk among this subgroup. Findings highlight targets for suicide prevention initiatives.

Hazard ratio of 1.58 of vet having a Rx of BZ means a 58% increased risk of suicide. Rebuttal next slide.

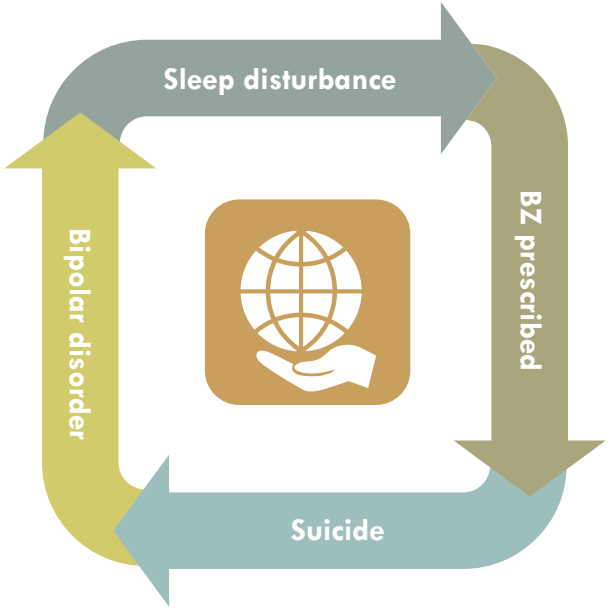
Association vs Causality - In Response

Bipolar disorder

Bipolar disorder confers an increased risk of suicide. Lifetime suicide rate: Estimated at 15–20%, which is 10 to 30 times higher than in the general population. Between 20% to 60% of bipolar patients attempt suicide at least once. BPD patients are twice as likely to die by suicide as MDD patients.

Benzos blamed for suicide

Prolonged BZ prescriptions may serve as a proxy for severe, treatment-resistant sleep disturbances rather than indicating an independent risk factor. If suicide risk is closely tied to the underlying sleep disturbance than to the treatment, efforts to reduce BZ usage may overlook the more urgent need to identify and aggressively treat patients in this population.



Sleep disturbances

Poor sleep can trigger mania, depression and suicidal ideation. Multiple lines of evidence argue that disrupted sleep contributes directly to suicide risk through hopelessness, executive dysfunction, serotonergic dysfunction, hypothathalamic-pituitary axis dysregulation, and nocturnal wakefulness.

Utilizing benzodiazepines for insomnia

Temazepam, triazolam and flurazepam are FDA-approved for sleep and are BZ's. Other BZ's may be prescribed off-label for sleep.

Tubbs AS, Fernandez Fx. Suicide Risk Among Patients with Bipolar Disorder: The Role of Sleep Disruption Versus Benzodiazepine Use *J Clin Psychiatry* 2025;86(3):25lr15890.

Tubbs AS, Fernandez FX, Grandner MA, et al. The mind after midnight: nocturnal wakefulness, behavioral dysregulation, and psychopathology. *Front Netw Physiol*. 2022;1:830338

McCall WV, Black CG. The link between suicide and insomnia: theoretical mechanisms. *Current Psychiatry Rep*. 2013;15(9);389


Wet Streets
Do not
Cause Rain

Anxiety and Suicide

- A systematic literature search of multiple databases was conducted from database inception through August 2011. Forty-two observational studies were included.
- Compared to those without anxiety, patients with anxiety were more likely to have suicidal ideations (OR = 2.89, 95% CI: 2.09, 4.00)
- Odds of attempted suicides (OR = 2.47, 95% CI: 1.96, 3.10)
- Odds of completed suicides (OR = 3.34, 95% CI: 2.13, 5.25)
- Odds of any suicidal behaviors (OR = 2.85, 95% CI: 2.35, 3.46)
- No association with obsessive-compulsive disorder
- An Odds Ratio of 2.47=2.47 times the likelihood of the event

Kanwar, A., Malik, S., Prokop, L.J., Sim, L.A., Feldstein, D., Wang, Z. and Murad, M.H. (2013), THE ASSOCIATION BETWEEN ANXIETY DISORDERS AND SUICIDAL BEHAVIORS: A SYSTEMATIC REVIEW AND META-ANALYSIS. Depress Anxiety, 30: 917-929. https://doi.org/10.1002/da.22074

Panic Disorder and Suicide

- Data was sourced from Taiwan's National Health Insurance Research Database, covering 171,737 individuals diagnosed with PD and 686,948 matched controls from 2003 to 2017.
- PD was identified as an independent risk factor for suicide, with a hazard ratio (HR) of 1.85, indicating an increased likelihood of suicide among individuals with PD compared to those without.
- Among various psychiatric comorbidities, major depressive disorder (MDD) significantly heightened suicide risk, with an HR of 6.08 for those with both PD and MDD.
- Other comorbidities associated with increased suicide risk included
  - autism spectrum disorder (HR = 4.52)
  - schizophrenia (HR = 3.34)
  - bipolar disorder (HR = 3.20)
  - alcohol use disorder (HR = 2.99)
  - substance use disorder (HR = 2.82)
  - obsessive-compulsive disorder (HR = 2.10). Not seen with GAD?
- The study found that the presence of MDD in patients with PD was particularly concerning, as it substantially elevated the risk of suicide.

Persons with both major depressive disorder and panic disorder were 6.08 times more likely to have high risk

Tsai, S.-J., Cheng, C.-M., Chang, W.-H., Bai, Y.-M., Su, T.-P., Chen, T.-J., & Chen, M.-H. (2025). Panic disorder and suicide. Psychological Medicine, 55, e38,

Affirming Psychiatry : Episode 21
Commentary | **Article** | August 5, 2025

Will the Benzodiazepine Wars Ever End?

Author(s): Daniel Morehead, MD

Listen 0:00 / 16:25

Benzodiazepines spark ongoing debate, balancing effective anxiety relief with addiction risks, as cultural attitudes shape their use and perception.

AFFIRMING PSYCHIATRY

First released in the early 1960s, benzodiazepines quickly became the most widely prescribed medications in the world.[1] By the 1970s, they had become the most controversial as well. Newspaper headlines such as, "A New Kind of Drug Abuse Epidemic," appeared, followed by the international best-selling tale of benzodiazepine addiction, *I'm Dancing as Fast as I Can*.[2]

Affirming Psychiatry : Episode 15

Blog | Article | April 23, 2024

Benzodiazepines: Fellow Psychiatrists, We Still Have Work to Do

Author(s): Daniel Morehead, MD

While benzodiazepine prescribing certainly carries risks, those risks have been demonstrably exaggerated in the minds of government officials, critics, and the public at large.

luchschenF/AdobeStock

AFFIRMING PSYCHIATRY

Benzodiazepines are Bad

The Wall Street Journal has published an editorial entitled, "The Danger of Relying on Anti-Anxiety Drugs," by Jenny Taitz,

News | Article | June 6, 2024
Psychiatric Times
Vol 41, Issue 6 | Volume

Everyone Is Wrong About Benzodiazepines

Author(s): Daniel Morehead, MD

The Wall Street Journal recently published an essay entitled, "The Danger of Relying on Anti-Anxiety Drugs," by Jenny Taitz, PsyD. She says essentially, benzodiazepines numb individuals, fostering avoidance and inhibiting the constructive action that would lead to symptom resolution and growth. For Taitz, benzodiazepines throw a blanket over symptoms rather than rooting them out. Secondly, Taitz notes, those who start taking benzodiazepines go down a slippery slope leading to overuse, physical dependency, and chronic symptoms.

So, although benzodiazepine prescribing certainly carries risks, those risks have been demonstrably exaggerated in the minds of government officials, critics, and the public at large. Most patients use benzodiazepines safely and for limited amounts of time.

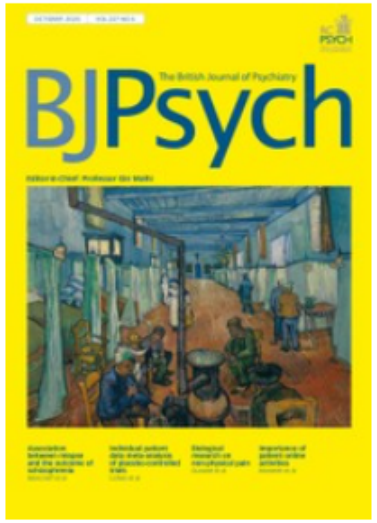
And, of course, overuse and dependence are real dangers.

However, knowledge of such dangers is commonplace among psychiatrists, who are ethically bound to educate their patients about such risks and work to minimize them.

Yes, Taitz cites the early mass marketing of Valium as "mother's little helper," but this literally occurred 60 years ago, and appreciation of the risks of benzodiazepines has been prominent since the early1980s.

When doses of medication are too low, severe anxiety can so paralyze patients that they are unable to take the actions that would lead to diminished symptoms, such as initiating new outside activities with social phobia or addressing intimidating subjects in psychotherapy.

https://www.cambridge.org/core/journals/the-british-journal-of-psychiatry/article/benzodiazepines-its-time-to-return-to-the-evidence/B4DBF992E78EBCC53DC15930829B79E6



The British Journal of Psychiatry

Article contents

Benzodiazepines: it's time to return to the evidence

Published online by Cambridge University Press: **12 October 2020**

Edward Silberman, Richard Balon, Vladan Starcevic, Richard Shader, Fiammetta Cosci, Giovanni A. Fava, Antonio E. Nardi, Carl Salzman and Nicoletta Sonino

Show author details

"*Benzodiazepines are dangerous in overdose.* Benzodiazepines alone are among the safest of psychotropic medications, with lethal dose LD_{50} estimates for most in the range of thousands of mg/kg. Even alprazolam, which may be more toxic, has an estimated LD_{50} range of 300–2000 mg/kg. Taken in conjunction with alcohol or opioids, they markedly raise the lethality of these already dangerous substances."

Silberman E, Balon R, Starcevic V, et al. Benzodiazepines: it's time to return to the evidence. *The British Journal of Psychiatry*. 2021;218(3):125-127. doi:10.1192/bjp.2020.164

Special Report: Refractory Anxiety Disorders

Part 1: First-Line Treatments

Sarah K. Rivelli, MD, FACP, FAPA. System Director, Consult Liaison, Department of Psychiatry and Behavioral Medicine, Carilion Clinic. Chris Aiken, MD. Editor-in-Chief, The Carlat Psychiatry Report; *Assistant Professor, NYU Langone Department of Psychiatry; practicing psychiatrist, Winston-Salem, NC.*

The authors have no financial relationships with companies related to this material.

There's a reason treatment-resistant anxiety is common in practice. Our first-line medications are not very effective for anxiety disorders. Selective serotonin reuptake inhibitors (SSRIs) have only a small to moderate effect size in panic disorder (0.3–0.5). Cognitive behavioral therapy (CBT) performs a little better, but access to quality psychotherapy is a limitation.

Highlights From This Issue

Refractory anxiety disorders. Treatment-resistant anxiety disorders may require you to go off the beaten path. MAOIs, pindolol, pregabalin, lavender extract (Silexan), and quetiapine are candidates, and the choice is best guided by the type of anxiety disorder. More in our two-part special report (on the cover and on page 5).

Q&A on page 1. Most cognitive domains decline with age, but one does not: wisdom.

From the Carlat Report

MAO inhibitors !
Really?
Over benzos?
Would you do it?

Buspirone effect size is 0.2
Hydroxyzine E.S. is 0.4-0.5
SSRIs 0.5
Benzos 0.5-0.6

Gomez, A.F., (2018). Comparing the efficacy of benzodiazepines and serotonergic anti-depressants for adults with generalized anxiety disorder: A meta-analytic review. Expert Opinion on Pharmacotherapy, 19(8), 883–894.

The Good

Betty

70 yo married woman who says her anxiety has been present 3 months. Describes feeling of panic almost constantly-tremory/jittery, "I burn“ In addition she complains of a lack of interest, poor appetite, fatigue. Wakes up around 4am, sleeping in recliner due to neck pain. She developed agoraphobia, feelings of impending doom, always on edge, avoiding activities and social things that she enjoys, catastrophizing thoughts. In addition she has long-standing restless sleep, vivid dreams, kicking/speaking/struggling in her sleep. Straps herself in to sleep due to having had falls from the bed.

Has been on 50mg Zoloft since the 1990s with excellent response. Her PCP had increased her dose to 75mg but didn't like how it made her feel (jittery, anxious, possible akathisia) so she went back down to 50mg. Three months ago she had the onset of neck/shoulder pain, intense pain to the point that could not sleep. Anxiety started at that time, she saw the word "severe" on report of C5/6 disease which led to catastrophic thoughts. She describe the pain in her neck and shoulder, shooting pain and stabbing pain. Has lost a lot of her day to day activities due to pain. Diagnosed with degenerative disk disease C5-C6. She has lost 60 pounds in the last year due to low appetite. Also has arthritis in her shoulder. PCP added lorazepam 0.5mg bid with little benefit.

Intervention: Diagnosed panic disorder with agoraphobia, major depressive disorder, severe, REM sleep behavior disorder (G47.52), stopped lorazepam, continued 50mg sertraline, added clonazepam 1mg 1 twice to three times daily.

Followup in 2 weeks: No further panic attacks and no further REM behavior disorder. She got a special pillow that helps her neck more. She is back in the bed, still "strapping myself in" due to fear of falling out of bed. She is just taking 1mg twice daily of clonazepam, 9:30am and 10:30pm and sleeping better. "I am sleeping the best I have in years." She confessed to reading a lot on the internet about meds, medical conditions. Told her to take care and consider the source. She admits to having some catastrophic thinking. No further nightmares and even had some nice ones.

Jean-François Gagnon, PhD, Ronald B. Postuma, MD, and Jacques Montplaisir, MD, PhD, FRCPc, Update on the pharmacology of REM sleep behavior disorder, *Neurology*, September 12, 2006 issue 7 (5) 742-747 **https://doi.org/10.1212/01.wnl.0000233926.47469.73**

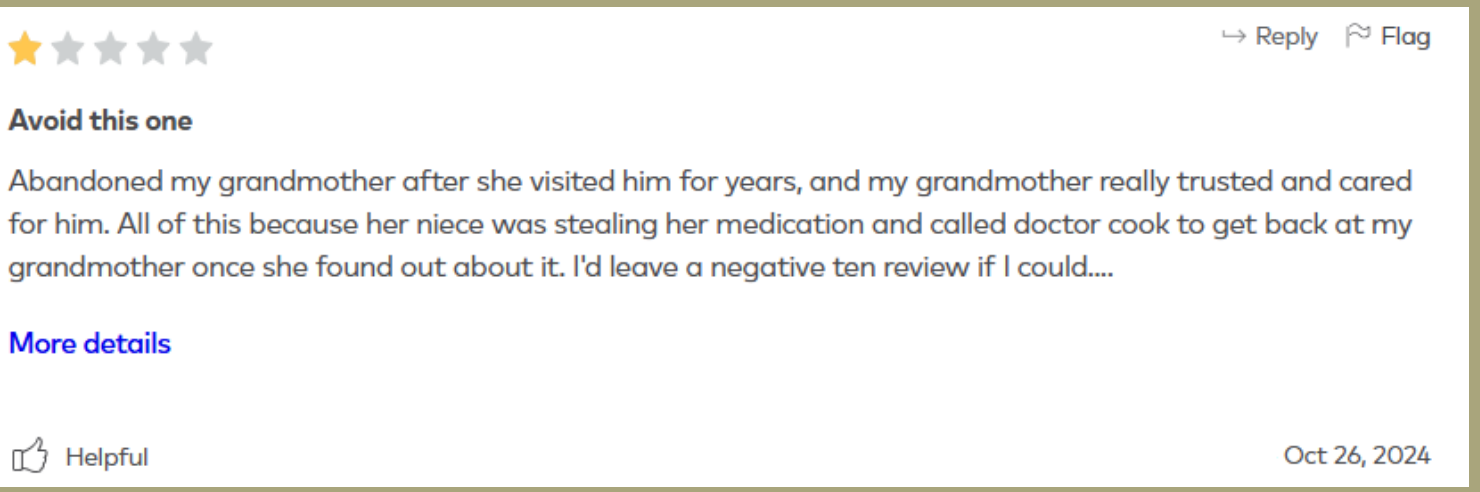
Carlos H. Schenck, Scott R. Bundlie, Milton G. Ettinger, Mark W. Mahowald, Chronic Behavioral Disorders of Human REM Sleep: A New Category of Parasomnia, *Sleep*, Volume 9, Issue 2, June 1986, Pages 293–308, https://doi.org/10.1093/sleep/9.2.293

The Bad

50yo woman treated with Xanax 0.5mg ½-1 tab three times daily and fluoxetine 20mg daily for several years for panic disorder, successful at this dose for several years. After 14 years began having heart palpitations leading to catastrophic thinking that she was having a heart attack, panic worse, Xanax increased to 1mg three times daily. Remained on that dose for several years. Husband diagnosed with cancer, panic increased, began having "clock-watching" waiting on next dose of Xanax and increased to 1mg four times daily. Husband later entered hospice and died of metastatic cancer. Grandson (20yo) moved in with her.

Two years later in 2013 her niece moved in with them. Niece contacted me and said that her aunt was sharing her Xanax with the grandson and they were getting high. Next visit confronted her and she became angry and stormed out of the office and never returned.

THE UGLY



I had terminated her care in 2013 due to the niece's revelation and other red flags including learning of the grandson's near-death overdose on Xanax and alcohol. Claiming the niece was stealing her medication was a poor disclaimer as she would have never had turned in her aunt and had her supply cut off. Then the grandson apparently held the grudge quite awhile.

THANK YOU

Questions?

THANK YOU

Questions?