

JAMH Session 27 July 2023
GV Health ECHO Hub

Benzodiazepines

Which One, When and Why

Ravi Bhat

Balon R, Starcevic V, Silberman E, Cosci F, Dubovsky S, Fava GA, Nardi AE, Rickels K, Salzman C, Shader RI, Sonino N. *The rise and fall and rise of benzodiazepines: a return of the stigmatized and repressed*. Braz J Psychiatry. 2020;42(3):243-244. doi: 10.1590/1516-4446-2019-0773. Epub 2020 Mar 9. PMID: 32159714; PMCID: PMC7236156.

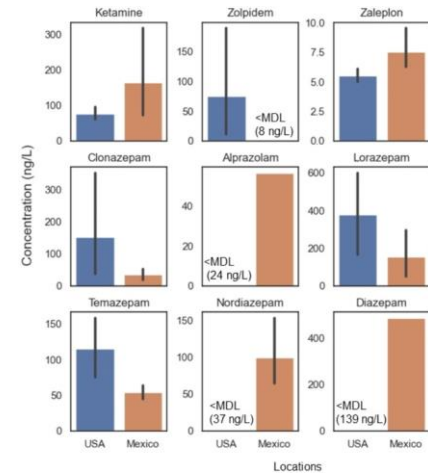
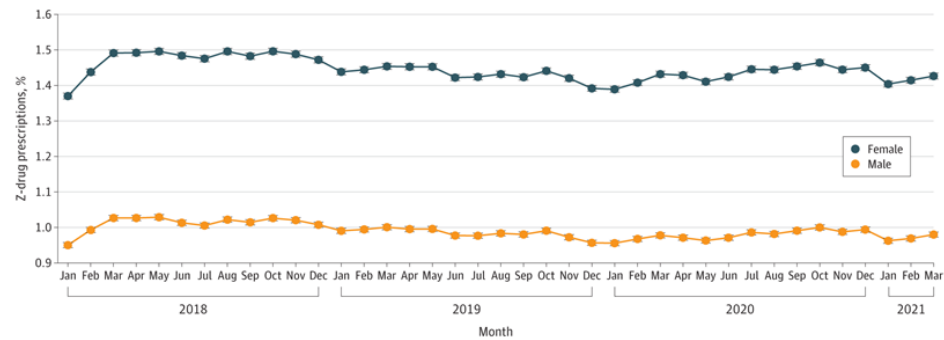
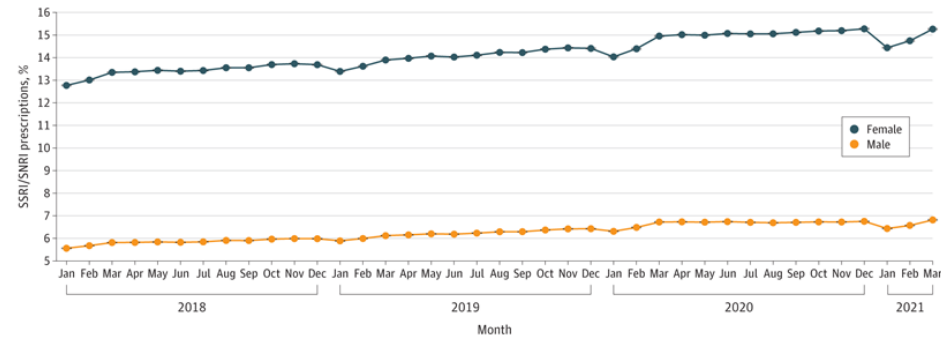
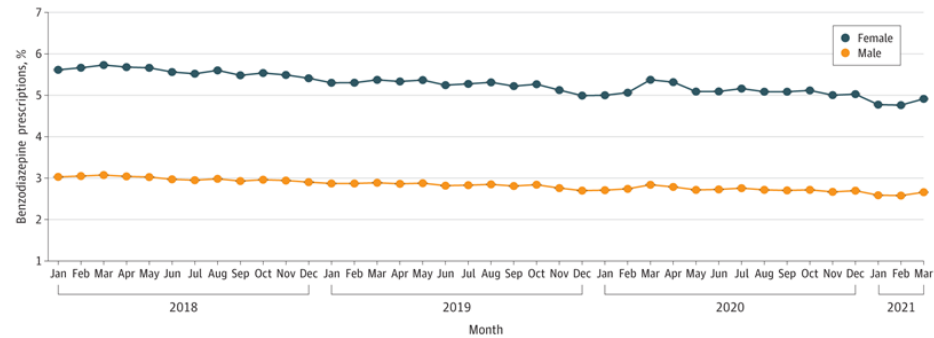
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Dubovsky SL, Marshall D. *Benzodiazepines Remain Important Therapeutic Options in Psychiatric Practice*. Psychother Psychosom. 2022;91(5):307-334. doi: 10.1159/000524400. Epub 2022 May 3. PMID: 35504267.

The anxiety within us



Milani SA, Raji MA, Chen L, Kuo YF. Trends in the Use of Benzodiazepines, Z-Hypnotics, and Serotonergic Drugs Among US Women and Men Before and During the COVID-19 Pandemic. JAMA Netw Open. 2021 Oct 1;4(10):e2131012. doi: 10.1001/jamanetworkopen.2021.31012. PMID: 34694388; PMCID: PMC8546497.

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Regulatory restrictions

What should health care professionals do?

When deciding whether the benefits of prescribing a benzodiazepine outweigh the risks, health care professionals should consider the patient's condition and the other medicines being taken, and [assess the risk of abuse, misuse, and addiction](#). Particular caution should be taken when [prescribing benzodiazepines with opioids](#) and other medicines that depress the central nervous system (CNS), which has resulted in serious side effects, including severe respiratory depression and death. Advise patients to seek immediate medical attention if they experience symptoms, such as difficulty breathing.

Limit the dosage and duration of each medicine to the minimum needed to achieve the desired clinical effect when prescribing benzodiazepines, alone or in combination with other medicines. Throughout therapy, monitor the patient for signs and symptoms of abuse, misuse, or addiction. If a substance use disorder is suspected, evaluate the patient and institute, or refer them for, early substance abuse treatment, as appropriate.

To reduce the risk of acute withdrawal reactions, use a gradual taper to reduce the dosage or to discontinue benzodiazepines. No standard benzodiazepine tapering schedule is suitable for all patients; therefore, create a patient-specific plan to gradually reduce the dosage, and ensure ongoing monitoring and support as needed to avoid serious withdrawal symptoms or worsening of the patient's medical condition.

<https://www.fda.gov/drugs/drug-safety-and-availability/fda-requiring-boxed-warning-updated-improve-safe-use-benzodiazepine-drug-class#:~:text=FDA%20is%20requiring%20the%20Boxed,and%20life%2Dthreatening%20side%20effects>.

<https://www.health.vic.gov.au/drugs-and-poisons/alprazolam-permits-and-prescription-guidelines>

Schaffer AL, Buckley NA, Cairns R, Pearson S. Comparison of Prescribing Patterns Before and After Implementation of a National Policy to Reduce Inappropriate Alprazolam Prescribing in Australia. JAMA Netw Open. 2019 Sep 4;2(9):e1911590. doi: 10.1001/jamanetworkopen.2019.11590. PMID: 31532519; PMCID: PMC6751760.

Sutherland R, Peacock A, Nielsen S, Bruno R. Alprazolam use among a sample of Australians who inject drugs: Trends up to six years post regulatory changes. Int J Drug Policy. 2020 Apr 11;79:102721. doi: 10.1016/j.drugpo.2020.102721. Epub ahead of print. PMID: 32289592.

Alprazolam – indications for use

The approved indications for alprazolam, as listed on the Australian Register of Therapeutic Goods, are:

- anxiety – short-term symptomatic treatment of anxiety, including treatment of anxious patients with some symptoms of depression
- panic disorder – treatment of panic disorder, with or without some phobic avoidance, and for blocking or attenuation of panic attacks and phobias in patients who have agoraphobia with panic attacks.

Requirements for permits to prescribe alprazolam

Applications for permits to prescribe alprazolam will generally require evidence of recent support from a specialist in a field relevant to the patient's medical condition.

Alprazolam is indicated for the short-term treatment of anxiety or panic disorder, so support from a psychiatrist will generally be required. Where there are addiction-related issues, support from an addiction medicine specialist will generally be required. Without such evidence, permit applications may be refused.

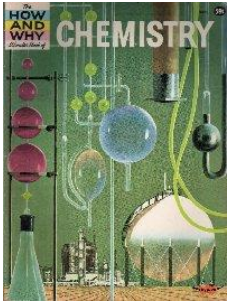
Medication	Onset of action	Duration of action ^b	Diazepam 10 mg equivalence	Usual daily dose, mg	Active metabolite(s)
Alprazolam*	Rapid	Short	0.5	0.25–4	No
Bromazepam	Rapid	Short	6	10–18	No
Chlordiazepoxide*	Intermediate	Long	25–50	15–100	Yes
Clobazam*	Intermediate	Long	10	5–40	Yes
Clonazepam*	Intermediate	Intermediate	1–2	0.5–4	No
Clorazepate (prodrug for oxazepam)*	Slow	Intermediate	15–20	15–60	Yes
Clothiazepam	Rapid	Short	5–10	5–15	No
Cloxazolam	Slow	Long	1–2	2–9	Yes
Diazepam*	Rapid	Long	10	2–40 oral 5–20 intranasal 5–20 buccal 5–20 vaginal suppository 12.5–20 rectal suppository	Yes
Ketazolam	Slow	Long	15–30	15–60	Yes
Lorazepam*	Intermediate	Intermediate	1	0.5–5	No
Loflazepate	Rapid	Long	1–2	1–3	Yes
Midazolam*	Rapid	Short	5	0.25–20 IM, IV 5–20 intranasal	No
Nordiazepam	Rapid	Long	20	10–15	No
Oxazepam*	Slow	Intermediate	20	30–120	No
Prazepam	Slow	Long	10–20	20–60	Yes
Remimazolam	Rapid	Intermediate	1	1.25–5 mg IV ^c	No
Tetrazepam	Rapid	Intermediate	25	50–150	No
<i>Hypnotics</i>					
Brotizolam	Rapid	Short	0.25–0.5	0.25–0.5	No
Estazolam*	Intermediate	Short	1	1–2	No
Flunitrazepam	Rapid	Short	0.5–1	0.5–1	No
Flurazepam	Fast	Long	15–30	15–30	Yes
Loprazolam	Intermediate	Intermediate	1–2	1–2	No
Lormetazepam	Rapid	Short	1–2	1–2	No
Nitrazepam	Rapid	Intermediate	5–10	5–10	No
Quazepam*	Intermediate	Long	15	7.5–15	Yes
Temazepam*	Intermediate	Intermediate	20	7.5–30	No
Triazolam*	Rapid	Short	0.25–0.5	0.125–0.5	No
<i>Z-Drugs</i>					
Zaleplon*	Rapid	Short	15–20	5–20	No
Zopiclone	Rapid	Intermediate	3.75	3.75–7.5	No
Eszopiclone*	Rapid	Intermediate	1–2	1–3	No
Zolpidem*	Intermediate	Intermediate	5–10	1.75–10 (IR) 6.25–12.5 (ER)	No

IM, intramuscular; IV, intravenous; IR, immediate release; ER, extended release. * Available in the USA. ^b Including metabolites. ^c For procedural sedation.

Table 1: Benzodiazepines available in Australia

Generic Name	Trade Name
Alprazolam (S8)	Alprax, Kalma, Xanax, Ralozam, Aprazolam –DP, Genrx Alprazolam, Zamhexal
Bromazepam	Lexotan
Clobazam	Frisium
Clonazepam	Rivotril, Paxam
Diazepam	Valium, Ducen, Antenex, Genrx Diazepam, Diazepam –DP, Valpam, Ranzepam
Flunitrazepam (S8)	Hynodorm, Rohypnol
Lorazepam	Ativan
Nitrazepam	Alodorm, Mogadon
Oxazepam	Alepam, Murelax, Serepax
Temazepam	Euphynos, Nocturne, Normison, Temaze, Temtabs
Triazolam	Halcion

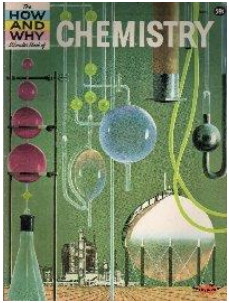
Non-benzodiazepine hypnotics	
Zolpidem	Dormizol, Somidem, Stildern, Stilnox, Zolpibell
Zopiclone	Imovane, Imrest



Benzodiazepine	Lipophilicity	Protein binding	Volume of distribution	Active metabolites
Diazepam	benchmark	98%	0.8 to 1.0 L/kg	Desmethyldiazepam, oxazepam & temazepam
Alprazolam	↓	68%	0.8-1.3L/kg	None
Clonazepam	↓↓	85%	3 L/kg	None
Lorazepam	↓	85%	1.3 L/kg	None
Oxazepam	↓↓	97%	Not known	None
Temazepam	↑	96%	1.3-1.5 L/kg	None
Midazolam	↑	97%	1.0 to 3.1 L/kg	
Bromazepam	↓↓	70%	1.56 L/kg	None

Information in this table: Bhat, R 2023

Stimpfl JN, Mills JA, Strawn JR. Pharmacologic predictors of benzodiazepine response trajectory in anxiety disorders: a Bayesian hierarchical modeling meta-analysis. CNS Spectr. 2023 Feb;28(1):53-60. doi: 10.1017/S1092852921000870. Epub 2021 Oct 1. PMID: 34593077; PMCID: PMC8971141.



- Consider the relative benefit to risk ratio and consider the patient's history of substance use, age, fall, and fracture risk.
- In anxiety disorders lower benzodiazepine doses produce the fastest improvement compared to doses >3 mg of lorazepam equivalent dose per day.
- ↑ lipophilic benzodiazepines produce:
 - Faster *onset* of response
 - ↓ amnesic effects.
- ↓ lipophilic benzodiazepines produce:
 - Greater response
 - More rapid improvement.

When

- *Anxiety Disorders* – acute situational anxiety; Generalised Anxiety Disorder and; Panic Disorder.
- *Insomnia* – acute insomnia associated with hospitalization, acute illness or time-limited stress.
- *Depressive Disorders* – Anxious Depression; ?other depressive disorders.
- *Bipolar Disorder* – acute manic episode.
- *Catatonia* – first line treatment prior to electroconvulsive therapy (ECT)
- *Gastrointestinal (GI) Disorders* – ?medically unexplained GI disorders
- *Cardiovascular Disorders* – acute states (MI etc.)
- *Alcohol Withdrawal* – of course.
- *Agitation* – management of acute agitation (ED etc.)

Which

- *Anxiety Disorders* –

- Acute situational anxiety: any intermediate to long-acting benzodiazepine that is ↑lipophilic.
- GAD: benzodiazepine effective but poorly tolerated per a recent network meta-analysis. ↓ anxiety very early.
- Panic Disorder: trial psychotherapies first, antidepressants next and then consider – studied drugs include alprazolam, clonazepam and a smattering of others BZs.

- *Insomnia* –

- ↑lipophilic → faster onset → initial insomnia; ↓lipophilic → middle/terminal insomnia.
- Short elimination half-lives, ↓ daytime hangover but not effective for middle/terminal insomnia.
- Tolerance develops for hypnotic effect after 1-2 months and subjective sleep quality ↓ after 24 weeks.
- z-drugs similar effects. Zolpidem unlike zopiclone is a selective benzodiazepine-1 agonist, so has hypnotic but not muscle relaxant effects and because of lack of effect on benzodiazepine-3 receptors likely results in a lower incidence of withdrawal and rebound symptoms in lower doses and in the short-term.

- *Depressive Disorders*

- Initial treatment?

Which

- *Bipolar Disorder* –
 - Clonazepam and lorazepam. Avoid alprazolam.
- *Catatonia* –
 - Lorazepam (IM or sublingual) 1-2 mg in adults and 0.5-1.0 mg in children and older adults. If $\geq 50\%$ improvement then dose increased to 6 mg/day in divided doses.
- *Gastrointestinal (GI) Disorders* –
 - Unclear role. Any suitable benzodiazepine.
- *Cardiovascular Disorders* –
 - Especially acute situational anxiety, so treatment similar.
- *Alcohol Withdrawal* –
 - Mostly diazepam but lorazepam too (see Turning Point guidelines).
- *Agitation* –
 - Diazepam (oral), midazolam (parenteral), lorazepam (parenteral) (see Safer Care Victoria guidance on management of acute behavioural disturbance in emergency settings)

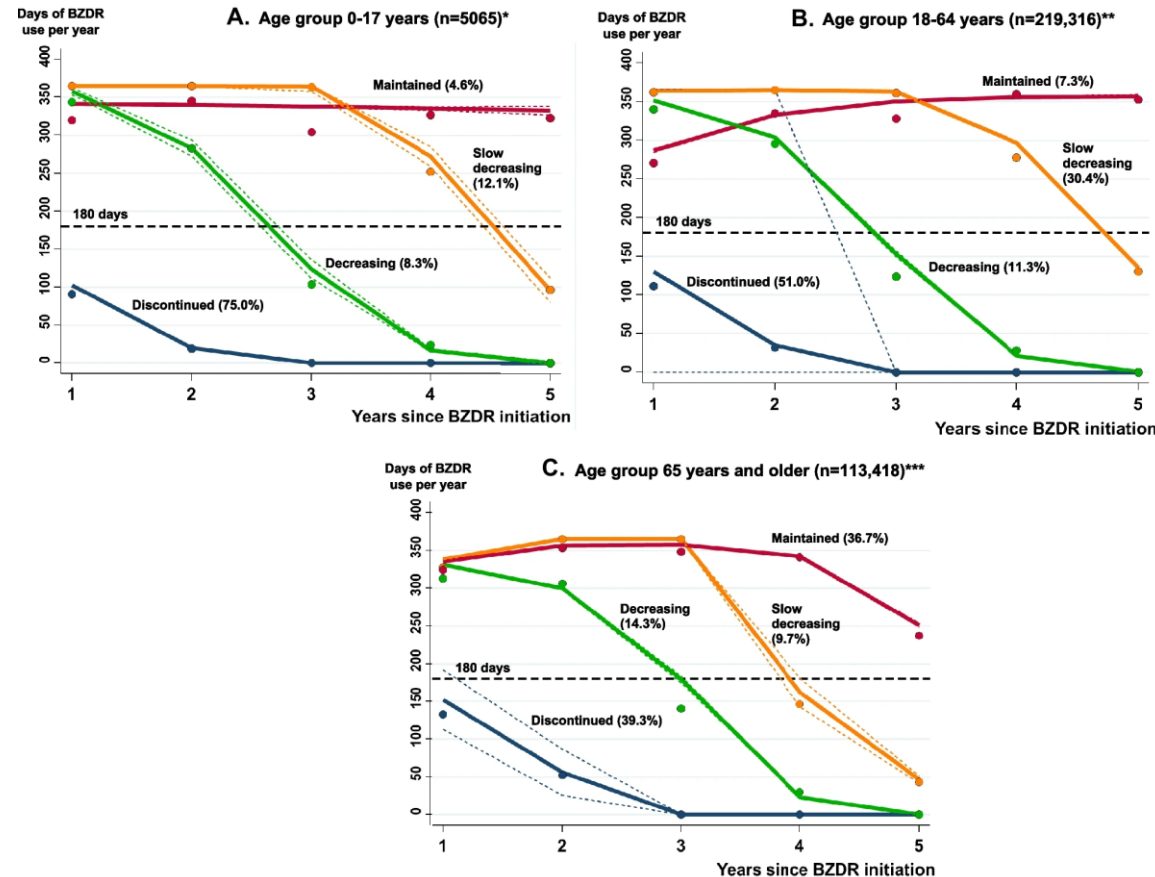
Table 10: Examples of benzodiazepine dosing regimen

Level of Dependence/ Setting of Withdrawal	Example of Diazepam Dosing
Mild dependence in outpatient withdrawal setting	Day 1: 5-10mg QID Day 2: 5-10mg QID Day 3: 5-10mg TDS Day 4: 10mg BD Day 5: 5mg BD
Moderate severity dependence in inpatient setting	5-20mg 2-4 hourly as needed if CIWA-Ar score > 10 for 3-4 days
High level of dependency and/ or risk of complex withdrawal in inpatient setting	Loading doses of 10-20mg every 2-4 hours until light sedation achieved followed by CIWA-Ar triggered or fixed dose therapy for 3-4 days

<https://www.dacas.org.au/clinical-resources/gp-factsheets/management-alcohol-withdrawal> and see <https://www.dacas.org.au/clinical-resources/clinical-guidelines> for Turning Point guidelines.

<https://www.safercare.vic.gov.au/clinical-guidance/emergency/acute-behavioural-disturbance>

Transition to long-term use



Isomura K, Wang X, Chang Z, Hellner C, Hasselström J, Ekheden I, Jayaram-Lindström N, Lichtenstein P, D'Onofrio BM, Mataix-Cols D, Sidorchuk A. Factors associated with long-term benzodiazepine and Z-drug use across the lifespan and 5-year temporal trajectories among incident users: a Swedish nationwide register-based study. *Eur J Clin Pharmacol.* 2023 Aug;79(8):1091-1105. doi: 10.1007/s00228-023-03515-2. Epub 2023 Jun 9. PMID: 37294340; PMCID: PMC10361867.

predictors of long-term BZDR use

- Multiple BZDRs at the treatment initiation.
- Any initial BZDs and Z-drugs (compared to being started as anxiolytics)
- Co-dispensing - concurrent dispensing of BZDR and other psychotropic, antiepileptic and analgesic drugs. Severity?
- Multiple-prescriber BZDR prescriptions. i.e., simultaneous dispensation of several BZDR prescriptions issued by different prescribers. Severity? Doctor-shopping? Pays to check SafeScript.
- Patient factors: somatic multimorbidity, SUD and disability pension in adults. Otherwise none!

Isomura K, Wang X, Chang Z, Hellner C, Hasselström J, Ekheden I, Jayaram-Lindström N, Lichtenstein P, D'Onofrio BM, Mataix-Cols D, Sidorchuk A. Factors associated with long-term benzodiazepine and Z-drug use across the lifespan and 5-year temporal trajectories among incident users: a Swedish nationwide register-based study. *Eur J Clin Pharmacol*. 2023 Aug;79(8):1091-1105. doi: 10.1007/s00228-023-03515-2. Epub 2023 Jun 9. PMID: 37294340; PMCID: PMC10361867.

(Not so) novel benzodiazepines

- Clonazepam (1971)
- Bromazepam (1976)
- Etizolam (1972)
- Flubromazepam (1960)
- Flualprazolam (1976)
- 40 overdose deaths involving novel benzodiazepines in Australia between 2015-2021 . In Victoria, there's been a sharp increase in deaths from novel benzodiazepines - from one in 2018; to 10 in 2019; and, 28 in 2020.

<https://adf.org.au/insights/novel-benzos/>

<https://www.health.vic.gov.au/drug-alerts/high-potency-benzodiazepine-tablets>

Edinoff AN, Nix CA, Odisho AS, Babin CP, Derouen AG, Lutfallah SC, Cornett EM, Murnane KS, Kaye AM, Kaye AD. Novel Designer Benzodiazepines: Comprehensive Review of Evolving Clinical and Adverse Effects. *Neurol Int.* 2022 Aug 22;14(3):648-663. doi: 10.3390/neurolint14030053. PMID: 35997362; PMCID: PMC9397074.