GV Health

BENZODIAZEPINE EQUIVALENCE CONVERSION AND IMPACT ON PATIENT CARE

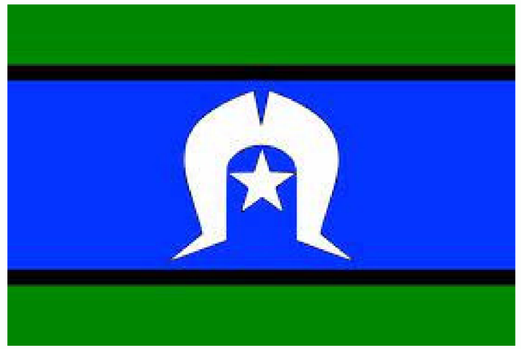
JAMH ECHO AUGUST 2023

Dr. Andrew Lam
GVADS Psychiatry Registrar

Acknowledgment of Country

I would like to acknowledge the Yorta Yorta people, Traditional Custodians of the land on which we virtually meet today, and pay my respects to their Elders past and present.

I extend that respect to Aboriginal and Torres Strait Islander peoples here and online today.



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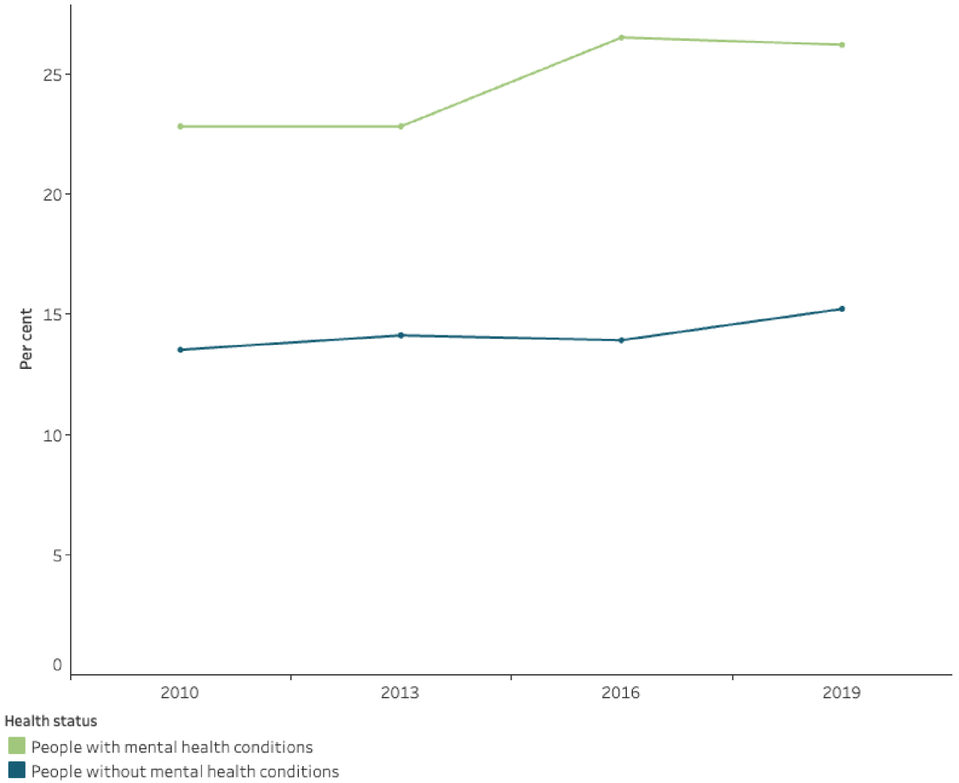
How are we managing distress?

Mental health related illicit use of Tranquilisers - AIHW 2021

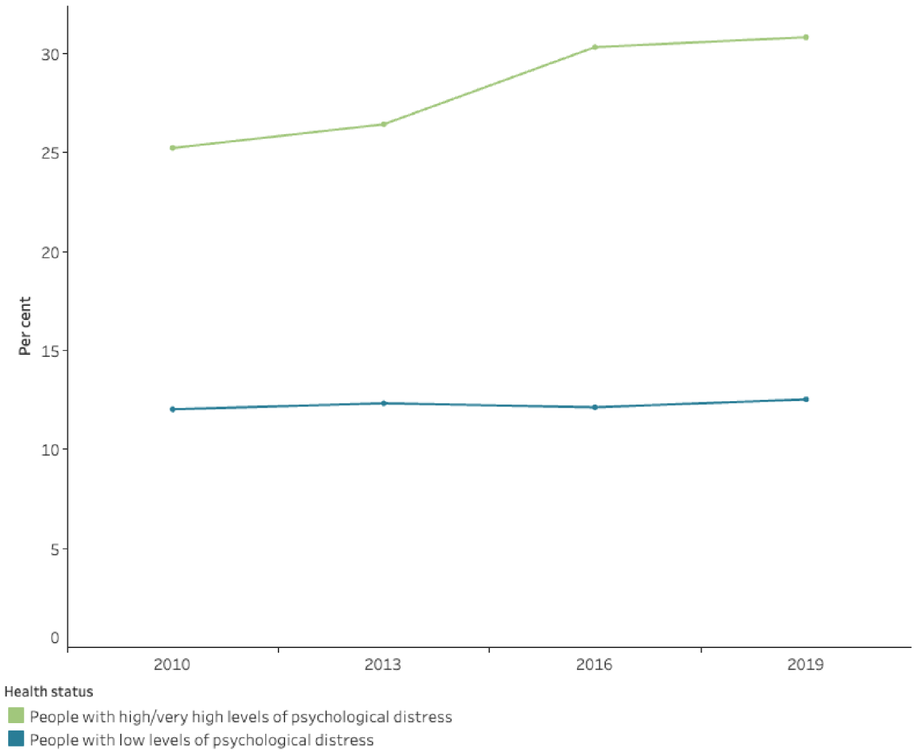
Mental health related conditions

Figure MENTALHEALTH3: Recent[a] illicit drug use, by self-reported mental health condition[b] or psychological distress[c] and drug type, people aged 18 and over, 2010 to 2019 (percent)



Psychological distress

Figure MENTALHEALTH3: Recent[a] illicit drug use, by self-reported mental health condition[b] or psychological distress[c] and drug type, people aged 18 and over, 2010 to 2019 (percent)



Australian Institute of Health and Welfare (AIHW) . Alcohol, tobacco & other drugs in Australia. AIHW 2021.

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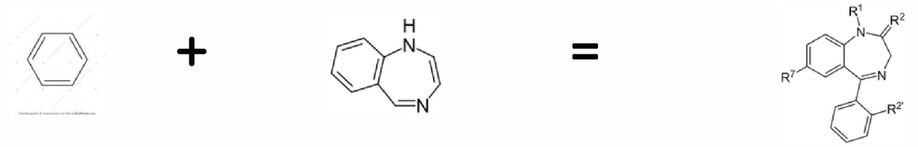
What are Benzodiazepines (BZD)?

(Benzene + Diazepine ring = Benzodiazepine)



Benzodiazepines are a group of "hypnotic"/ "sedative"/"tranquiliser" medications

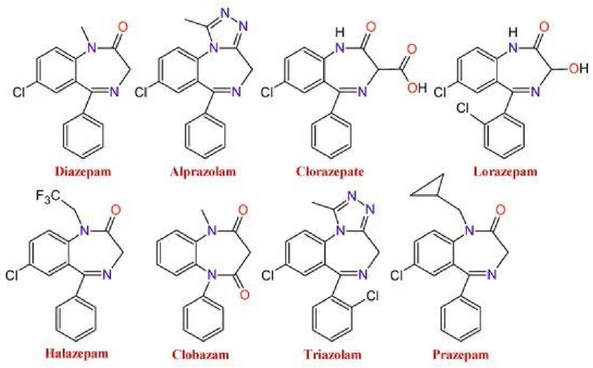
5 primary effects

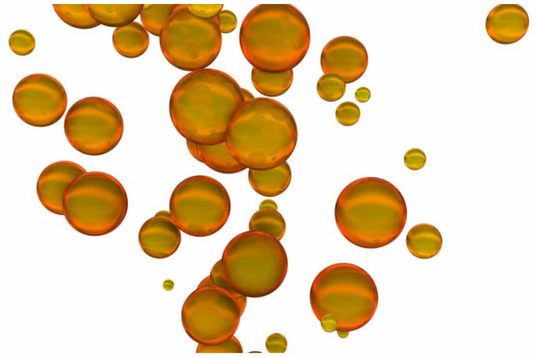
- **Hypnotic** (sedation)
- **Anxiolytic** (reduce anxiety)
- **Anti-convulsant** (reduce probability of seizures)
- **Muscle relaxant** (reduce muscle tension)
- **Amnesic** (disrupt long/short term memory)

Common Benzodiazepines available in Australia:

- Diazepam (Valium)
- Alprazolam (Xanax)
- Oxazepam (Serepax)
- Lorazepam (Ativan)
- Temazepam (Temaze)
- Midazolam (Hypnovel
- Nitrazepam (Mogadon)
- Flunitrazepam (Hypnodorm)
- Bromazepam (Lexotan)
- Clobazam (Frisium)

+ many more!





"lipophillic"*

AMH Rossi, S. (2006). Australian medicines handbook
tahl, S. M. (2021). Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge university press.

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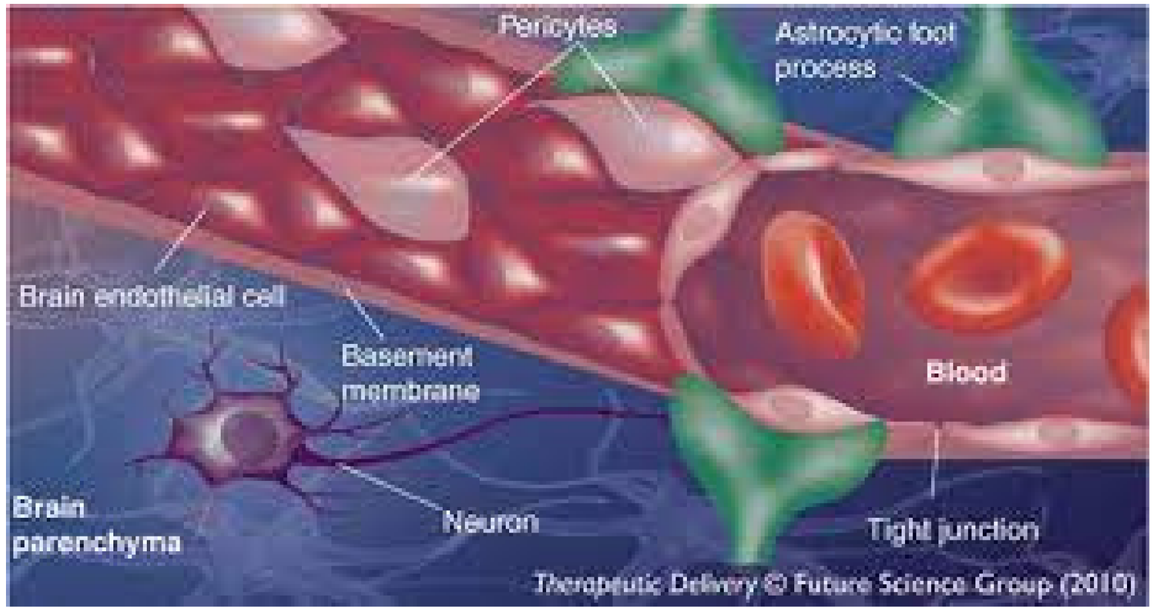
How do they work?

Pharmacology:
What determines its effects:

- ability to enter CNS
  - cross Blood Brain Barrier (BBB) - passive diffusion (i.e. lipophilicity)
- location of the receptor
- affinity to receptor type
  - GABA - A subunit (BZ)

- More Lipophilic
  - faster onset and less amnesic effects
  - i.e. Diazepam/Midazolam
- Less Lipophilic
  - greater response, more rapid improvement



Stahl, S. M. (2021). Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge university press

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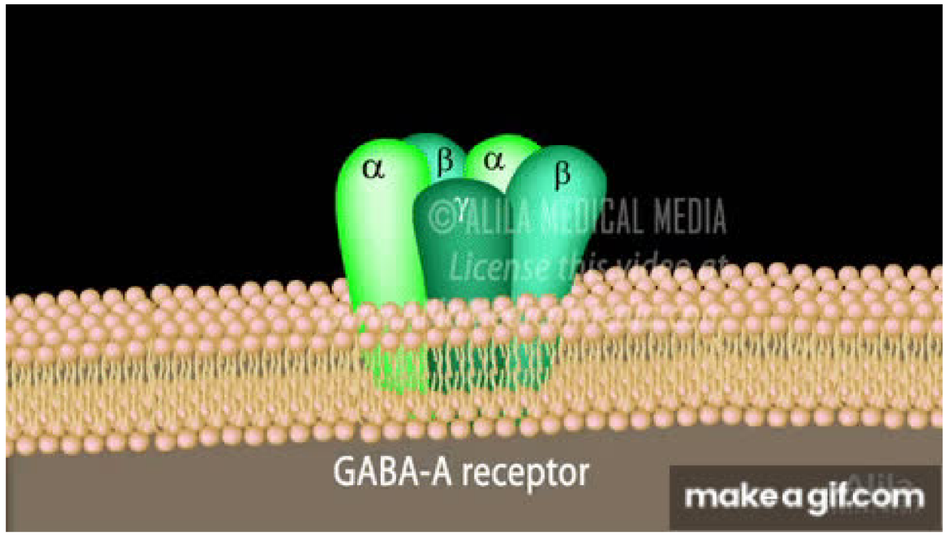
How do they work?

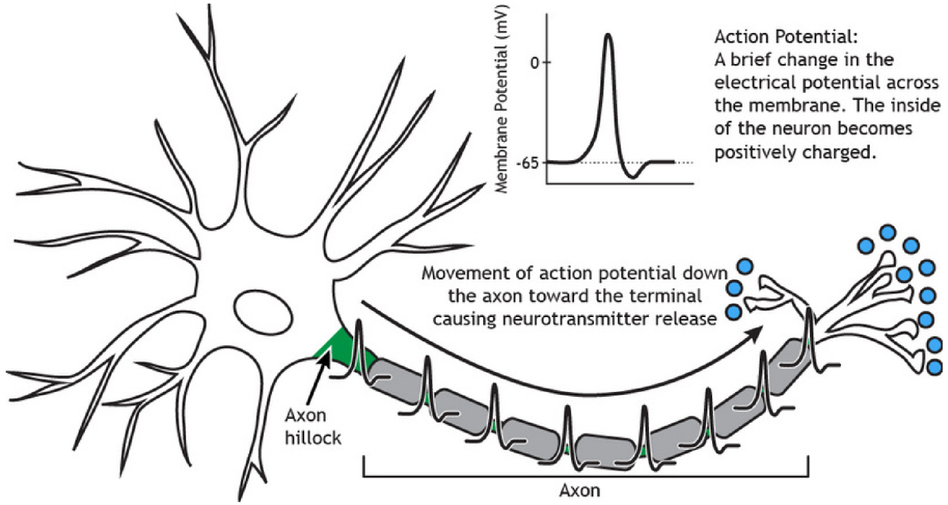
Pharmacology:

Mechanism of action:

- GABA receptor - postive allosteric modulator
  - reduces probability of action potentials propagating (a.k.a neuron's firing)

GABA- A receptor
  - BZ subunits
- BZ - a1 (60%)
  - cortex, thalamus, cerebellum
    - (sedative/anterograde amnesia)
- BZ - a2
  - limbic system
    - (anxiolytic)
  - motor neurons, dorsal horn of spinal cord
    - (muscle relaxant)





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Psychdb - Introduction to Benzodiazepines: ttps://www.psychdb.com/meds/benzos/home#metabolism
AMH Rossi, S. (2006). Australian medicines handbook

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Benefits vs Risks

Indications:

- Psychiatric
  - Anxiety Disorders (PD/GAD)
  - BPAD - acute mania
  - MDD - agitated depression/antidepressant initiation
  - Catatonia
  - Acute Agitation
- Seizure Disorders
- Insomnia
- Spastic muscular disorders
- Substance Use disorders
  - Withdrawal management
    - Alcohol
    - Opioid
    - THC withdrawal
- + Others

Risks

- Sedation
- Falls/fractures
- Respiratory depression
- Cognitive impairment/confusion/ memory impairment
- Combined effects w other depressant substances (i.e. alcohol/opioids)
- Withdrawal
- Traffic accidents
- Pregnancy - Neonatal abstinence syndrome
- Physical/psychological dependence/misuse
- Death

Stahl, S. M. (2021). Stahl's essential psychopharmacology: neuroscientific basis and practical applications. Cambridge university press.
Psychdb - Introduction to Benzodiazepines: ttps://www.psychdb.com/meds/benzos/home#metabolism
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Not all made equal

- **Dose**
- **Formulation**
  - PO(liq/tab)/IV/SL/IM/IN/PR
- **Pharmacokinetics (PK)**
  - Absorption/distribution/ metabolism/excretion
- **Pharmacodynamics (PD)**
  - Drugs effect on the body
- **Regulations**
  - Schedule (S4/S8)
  - Permit requirements

Table 22: Conversion table for benzodiazepine or Z-drug to diazepam transfer *

Drug	Trade Name	Approximate Equivalent to 5mg Diazepam (mg)	Half-life (hours)
Benzodiazepines			
Alprazolam	Xanax, Kalma, Alprax, Ralozam	0.5-1	6-25
Oxazepam	Serepax, Murelax, Alepam	15-30	4-15
Clonazepam	Rivotril, Paxam	0.25-0.5	22-54
Nitrazepam	Mogadon, Aldorm	5	16-48
Lorazepam	Ativan	0.5-1	12-16
Temazepam	Normison, Temaze, Temtabs	10-20	5-15
Z-drugs			
Zolpidem	Dormizol, Somidem, Stildem, Stilnox, Zolpibell	10	1.4-4.5
Zopiclone	Imovane, Imrest	7.5	5

* The above conversions are approximates only and clinical judgement is required

Source: NSW Department of Health, (2008a)

Name	Duration of Action #	Approx dose equiv to 5mg diazepam	Trade names	Tablet strengths	Schedule
Alprazolam	Short	**0.5** - 1mg	Alprax, Kalma, Xanax, Ralozam	0.25mg, 0.5mg, 1mg, 2mg	Schedule 8 Controlled Drug: Drugs of Dependence Unit (DDU)
Bromazepam	Intermediate	**3** - 6mg	Lexotan	3mg, 6mg	S4
Clobazam	Long	**10** - 15mg	Frisium	10mg	S4
Clonazepam	Long	**0.25** - 0.5mg	Rivotril, Paxam	0.5mg, 2mg	S4
Diazepam	Long	**5**mg	Antenex, Ducene, Ranzepam, Valium, Valpam	2mg, 5mg	S4
Flunitrazepam	Long	**1** - 2mg	Hypnodorm	1mg	Schedule 8 Controlled Drug: Drugs of Dependence Unit (DDU)
Lorazepam	Intermediate	0.5 - **1**mg	Ativan	1mg, 2.5mg	S4
Nitrazepam	Long	5mg	Alodorm, Mogadon	5mg	S4
Oxazepam	Short	30mg	Alepam, Murelax, Serepax	15mg, 30mg	S4
Temazepam	Short	**10** - 20mg	Normison, Temaze, Temtabs	10mg	S4
Triazolam	Very short	**0.25**mg	Halcion	0.125mg	S4
Zolpidem	Very short	10mg	Dormizol, Somidem, Stildem, Stilnox, Zolpibell	10mg (6.25mg & 12.5mg Modified Release)	S4
Zopiclone	Very short	7.5mg	Imovane, Imrest	7.5mg	S4

Approximate duration of action:

Very short	< 6hours
Short	6-12 hours
Intermediate	12-24 hours
Long	> 24 hours

DACAS - Alcohol and Drug Withdrawal Guidelines -2018
SA Health - Benzodiazepine Equivalents 2014

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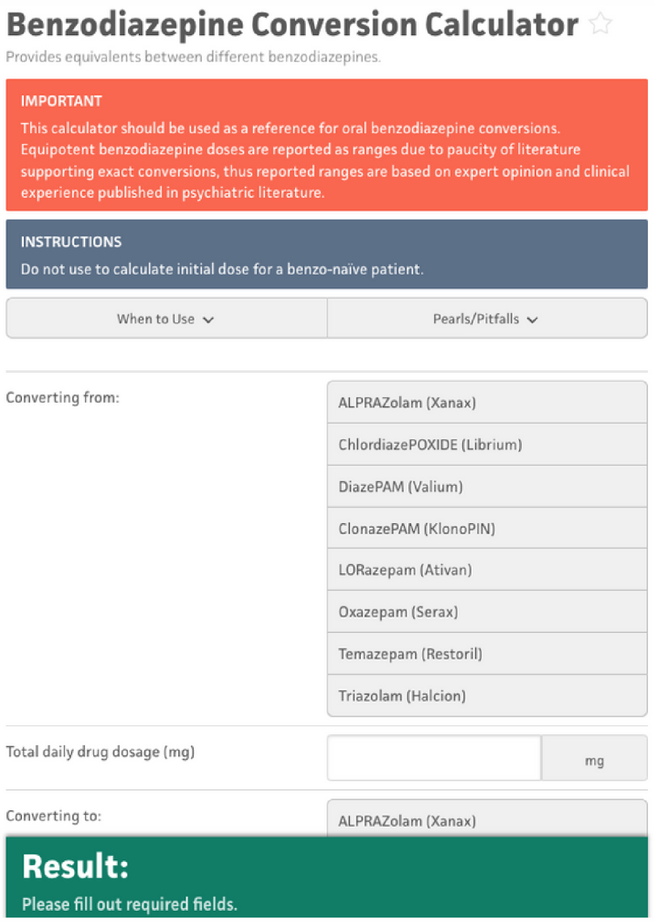
Dose Equivalence and Calculation



Benzodiazepine	Approximate equivalent dose (mg)
Diazepam	5mg
Alprazolam	0.5mg
Bromazepam	3mg
Clobazam	10mg
Clonazepam	0.25mg
Flunitrazepam	0.5mg
Lorazepam	1mg
Nitrazepam	5mg
Ozazepam	15mg
Temazepam	10mg

Not just Maths!

Consider other factors

- the patient
  - Pharmacokinetics/Pharmacodynamics
    - half life, metabolites, age, interactions, hepatic, renal function, accumulation, metabolism/excretion
- the dosage form

MDCalc - Benzodiazepine Conversion Calculator

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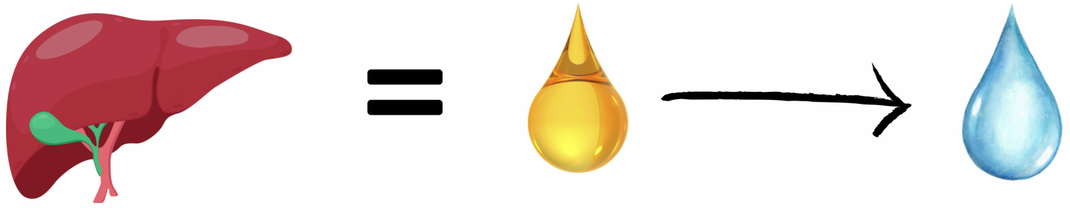
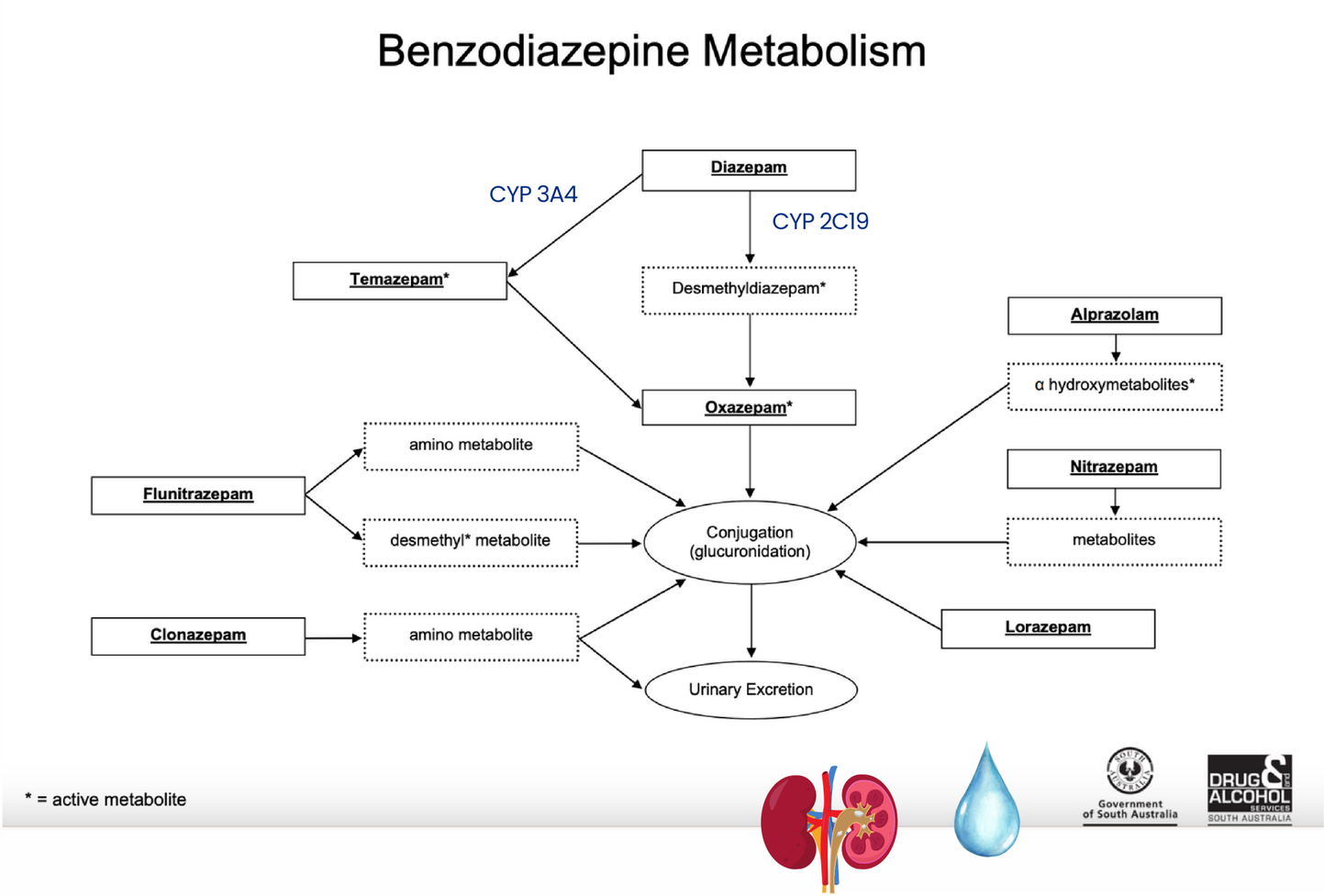
Metabolism & Excretion



- Most metabolised by the liver
  - CYP 450 enzyme (Phase I)
  - Glucuronidation (Phase II)
    - Lorazepam/Oxazepam/Temazepam

Considerations

- Diazepam
  - metabolites
    - Desmethyldiazepam
    - Oxazepam
    - Temazepam
    - Urine Drug Screen - ? +ve
  - Accumulative effects = prolong duration of action certain patient populations (i.e. elderly/liver dysfunction)
- Liver Dysfunction
  - Phase II - glucuronidation is generally preserved - choice of Oxazepam



DACAS - Alcohol and Drug Withdrawal Guidelines -2018

SA Health - Benzodiazepine Equivalents 2014

BZD Withdrawal Syndrome

Onset:
- 1 - 3 days
  - depending on BZD half life

Severity
- worse with short half-life BZD

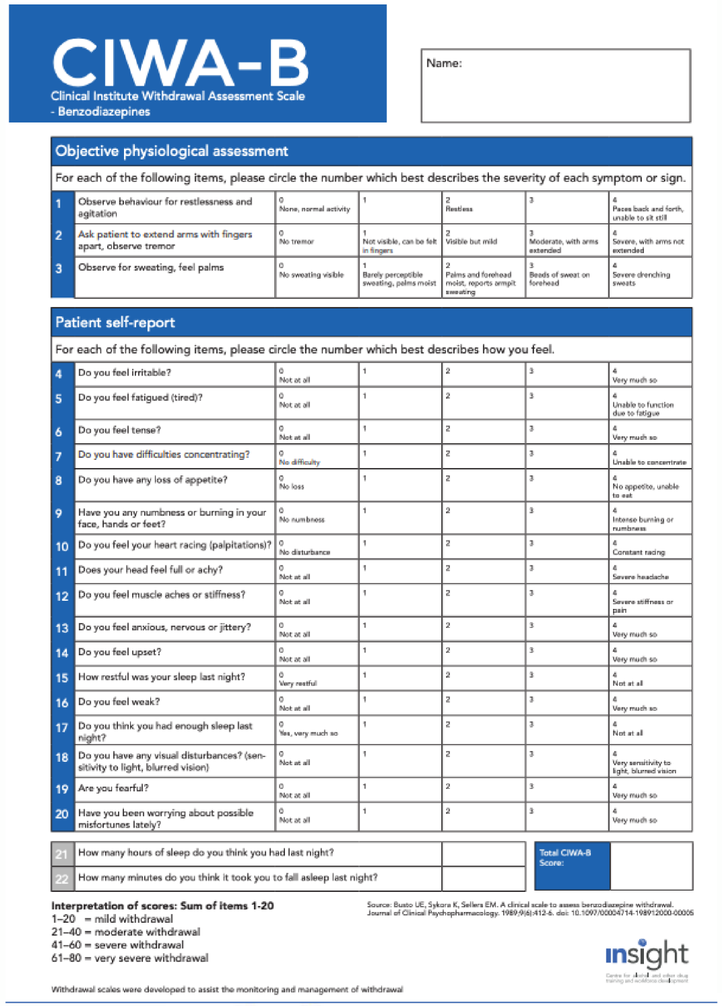
Duration:
- can last a few weeks - months (15%)

Risk:
- chronic use of high doses of short acting benzodiazepines (i.e. Alprazolam)

Setting:
- Inpatient vs Outpatient

Table 20: Benzodiazepine withdrawal symptoms

Stage	Psychological Symptoms	Physiological Symptoms
Intoxication	Drowsiness, relaxation, and sleepiness	Sedation and decreases in alertness and concentration
Acute withdrawal	Anxiety, panic attacks, depression, insomnia, poor memory and concentration, anger, irritability, and distorted perceptions	Agitation, tremor, headaches, weakness, dizziness, nausea, vomiting, diarrhoea, constipation, palpitations, fatigue, and flu-like symptoms
Protracted withdrawal	Anxiety, depression, insomnia, irritability, muscle aches, restlessness, poor concentration, and memory problems	Diarrhoea, constipation, and bloating,
Potential withdrawal complications	Transient hallucinations (visual, tactile, and auditory) and, rarely, delirium and psychosis	Withdrawal seizures (in 1-2% of patients)



CIWA-B
Clinical Institute Withdrawal Assessment Scale - Benzodiazepines

Name:

Objective physiological assessment

For each of the following items, please circle the number which best describes the severity of each symptom or sign.

1	Observe behaviour for restlessness and agitation	0 None, normal activity	1	2 Restless	3	4 Paces back and forth, unable to sit still
2	Ask patient to extend arms with fingers apart, observe tremor	0 No tremor	1 Not visible, can be felt in fingers	2 Visible but mild	3 Moderate, with arms extended	4 Severe, with arms not extended
3	Observe for sweating, feel palms	0 No sweating visible	1 Barely perceptible sweating, palms moist	2 Palms and forehead moist, reports armpit sweating	3 Beads of sweat on forehead	4 Severe drenching sweats

Patient self-report

For each of the following items, please circle the number which best describes how you feel.

4	Do you feel irritable?	0 Not at all	1	2	3	4 Very much so
5	Do you feel fatigued (tired)?	0 Not at all	1	2	3	4 Unable to function due to fatigue
6	Do you feel tense?	0 Not at all	1	2	3	4 Very much so
7	Do you have difficulties concentrating?	0 No difficulty	1	2	3	4 Unable to concentrate
8	Do you have any loss of appetite?	0 No loss	1	2	3	4 No appetite, unable to eat
9	Have you any numbness or burning in your face, hands or feet?	0 No numbness	1	2	3	4 Intense burning or numbness
10	Do you feel your heart racing (palpitations)?	0 No disturbance	1	2	3	4 Constant racing
11	Does your head feel full or achy?	0 Not at all	1	2	3	4 Severe headache
12	Do you feel muscle aches or stiffness?	0 Not at all	1	2	3	4 Severe stiffness or pain
13	Do you feel anxious, nervous or jittery?	0 Not at all	1	2	3	4 Very much so
14	Do you feel upset?	0 Not at all	1	2	3	4 Very much so
15	How restful was your sleep last night?	0 Very restful	1	2	3	4 Not at all
16	Do you feel weak?	0 Not at all	1	2	3	4 Very much so
17	Do you think you had enough sleep last night?	0 Yes, very much so	1	2	3	4 Not at all
18	Do you have any visual disturbances? (sensitivity to light, blurred vision)	0 Not at all	1	2	3	4 Very sensitivity to light, blurred vision
19	Are you fearful?	0 Not at all	1	2	3	4 Very much so
20	Have you been worrying about possible misfortunes lately?	0 Not at all	1	2	3	4 Very much so

21	How many hours of sleep do you think you had last night?		Total CIWA-B Score:
22	How many minutes do you think it took you to fall asleep last night?		

Interpretation of scores: Sum of items 1-20
1–20 = mild withdrawal
21–40 = moderate withdrawal
41–60 = severe withdrawal
61–80 = very severe withdrawal

Source: Busto UE, Sykora K, Sellers EM. A clinical scale to assess benzodiazepine withdrawal. Journal of Clinical Psychopharmacology. 1989;9(6):412-6. doi: 10.1097/00004714-198912000-00005

insight

Withdrawal scales were developed to assist the monitoring and management of withdrawal

DACAS - Alcohol and Drug Withdrawal Guidelines -2018

CIWA - B - Insight QLD

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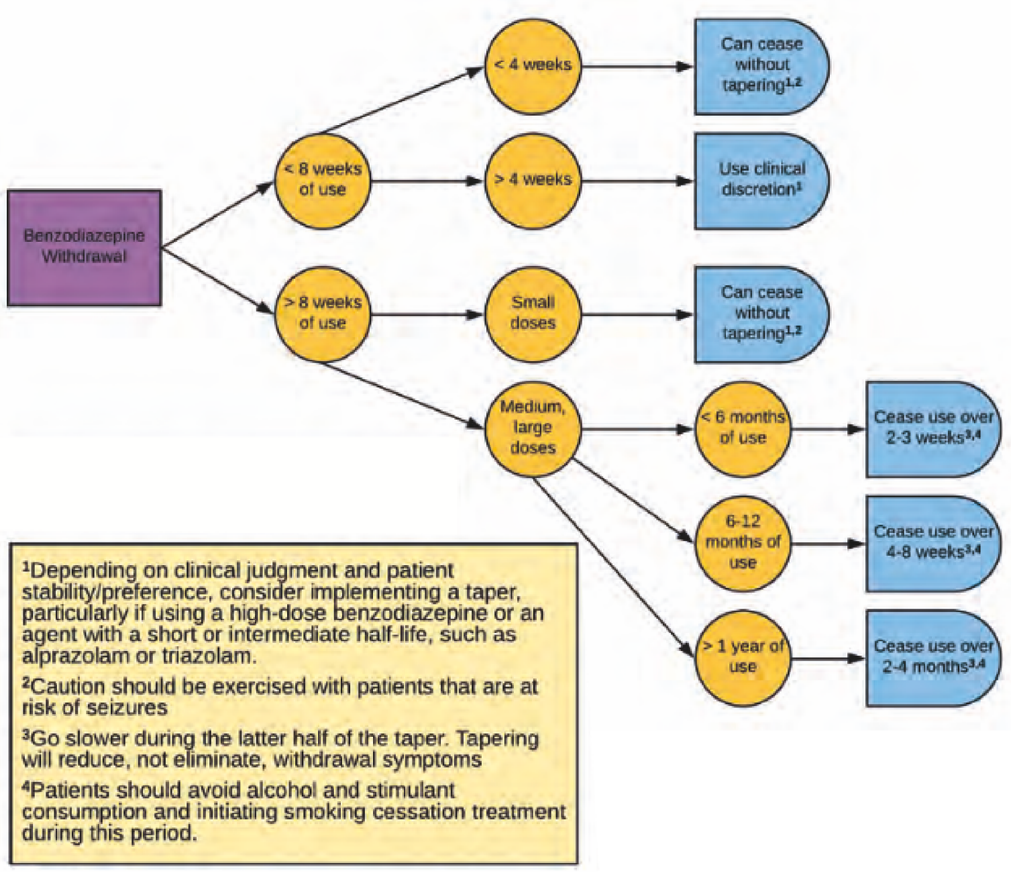
BZD Withdrawal Syndrome

Figure 10: Benzodiazepine dose tapering (Source: RACGP, 2015)



[1]Depending on clinical judgment and patient stability/preference, consider implementing a taper, particularly if using a high-dose benzodiazepine or an agent with a short or intermediate half-life, such as alprazolam or triazolam.

[2]Caution should be exercised with patients that are at risk of seizures

[3]Go slower during the latter half of the taper. Tapering will reduce, not eliminate, withdrawal symptoms

[4]Patients should avoid alcohol and stimulant consumption and initiating smoking cessation treatment during this period.

Table 21: Dosing regimen for people dependent on benzodiazepines

Setting	Withdrawal Goal	Recommended Regimen
Outpatient withdrawal	Reduction or stabilisation	» Convert benzodiazepine to diazepam and reduce by 10% every 1–2 weeks » When dose is at around 5mg, reduce by 1mg » Provide ongoing review, support, and reassurance » Manage therapeutic issues underlying the benzodiazepine dependence » Supervised pick-up of doses should be based on a management plan in conjunction with a community prescribing doctor » Consider use of a benzodiazepine treatment agreement or contract, outlining terms of ongoing prescribing as set out above, e.g., frequency of medication dispensing, frequency of review, frequency of use of urine drug assays, etc.
Inpatient withdrawal	Reduction or stabilisation	» Convert to diazepam and provide equivalent benzodiazepine dose in divided daily dosing » Specialist input may be required for higher doses, e.g., higher than 80mg total per day. Higher doses should be given with a higher level of nursing observation and doses withheld if patients are not easily roused. Clients should not be awoken to receive a dose. After establishing the dose required, on days 1-2 there should not be provision of PRN doses. Dose can then be reduced by 10mg daily without significant withdrawal symptoms. Below 50-40mg the rate of reduction will need to be slowed on par with an outpatient regimen

Source: RACGP, 2015

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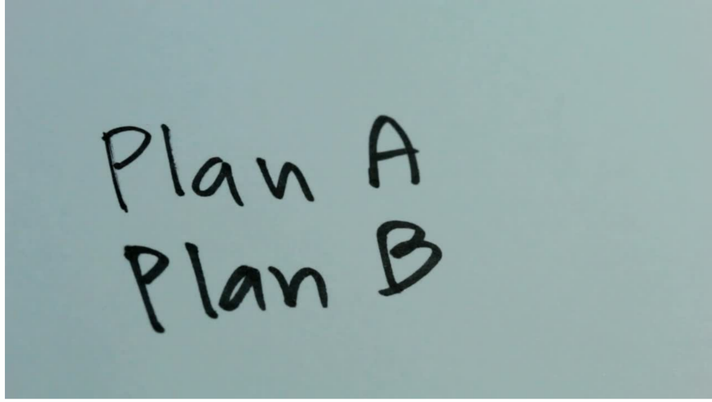
BZD Withdrawal Syndrome

Dont fail to Plan!



BZD Withdrawal Principles

Plan:

- Setting
- Symptoms and potential complications
- Consider:
  - Cross titrating to longer acting BZD
  - Use of symptomatic medications
  - patient/dose/rate of reduction/duration/lifestyle
  - motivation/risks/history of complicated withdrawal

- Scaffold & Support
  - Discussion with consumer/carer
  - Adequate psychological support (i.e. distress tolerance techniques/CBT)

- Legal
  - Medicare/PBS notification

Table 23: Symptomatic medications for use in benzodiazepine withdrawal

Symptom(s)	Symptomatic Medication(s)
Anxiety or Depression	If anxiety or insomnia is prominent in benzodiazepine withdrawal, consideration may need to be given to rate of dose reduction Sedating atypical antipsychotics are sometimes prescribed as benzodiazepine sparing agents but carry some risk and are not approved for this use Persisting anxiety or depressive symptoms may be managed with antidepressant medications & SSRIs
History of seizures	Anticonvulsants
Physical symptoms such as tremors	Beta-blockers
Insomnia	Melatonin

Source: NSW Department of Health (2008a); Murray et al, (2002)

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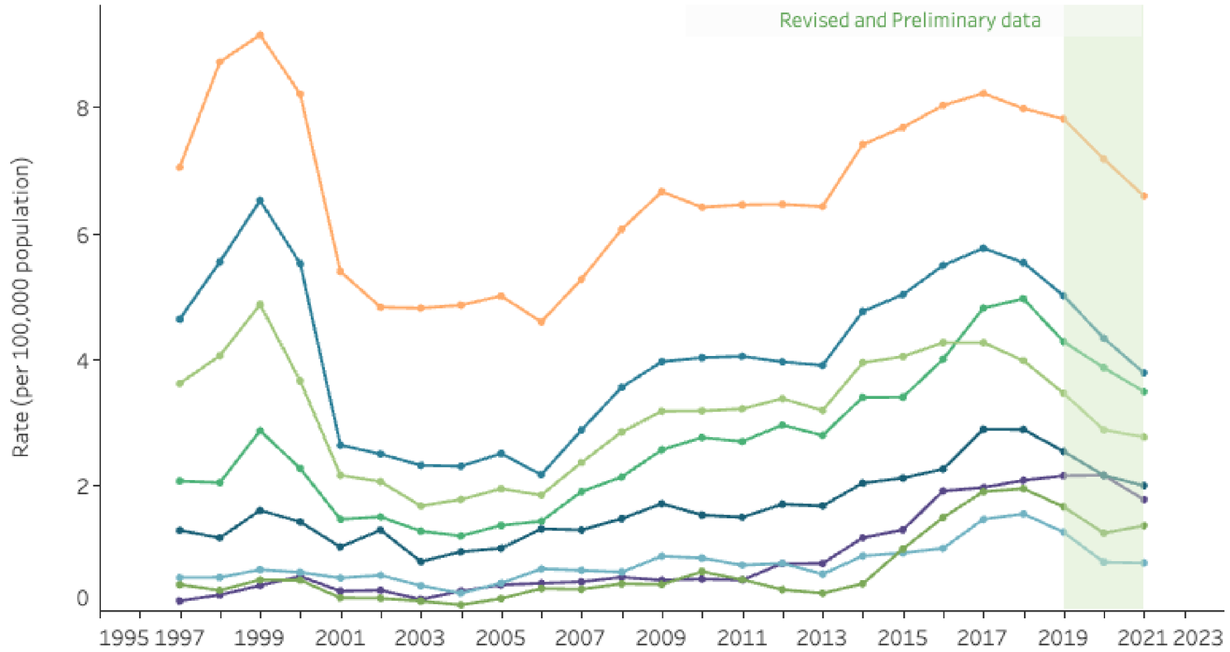
Impact on Patient Care

What does the data show?

AIHW Drug Induced Deaths - 2021

Figure IMPACT1: Number or age-standardised rate (per 100,000 population) of drug-induced deaths[a], by drug type or drug class, 1997 to 2021



The trend of sum of Estimate for Year broken down by Measure. Colour shows details about Drug type. The marks are labelled by sum of Estimate. Details are shown for Figure number (Figure notes (Data for figures))andTitle (Figure notes (Data for figures)).The data is filtered on Category, which keeps Drug class.The view is filtered on Drug type,MeasureandYear.The Drug type filter keeps 15 of 15 members.The Measure filter keeps Rate (per 100,000 population).The Year filter ranges from 1997 to 2021.

Drug type or drug class

- All drug-induced deaths[a]
- All opioids
- All opioids excluding heroin
- All antidepressants
- All antipsychotics
- All non-opioid analgesics
- All depressants[b]
- All psychostimulants[c]

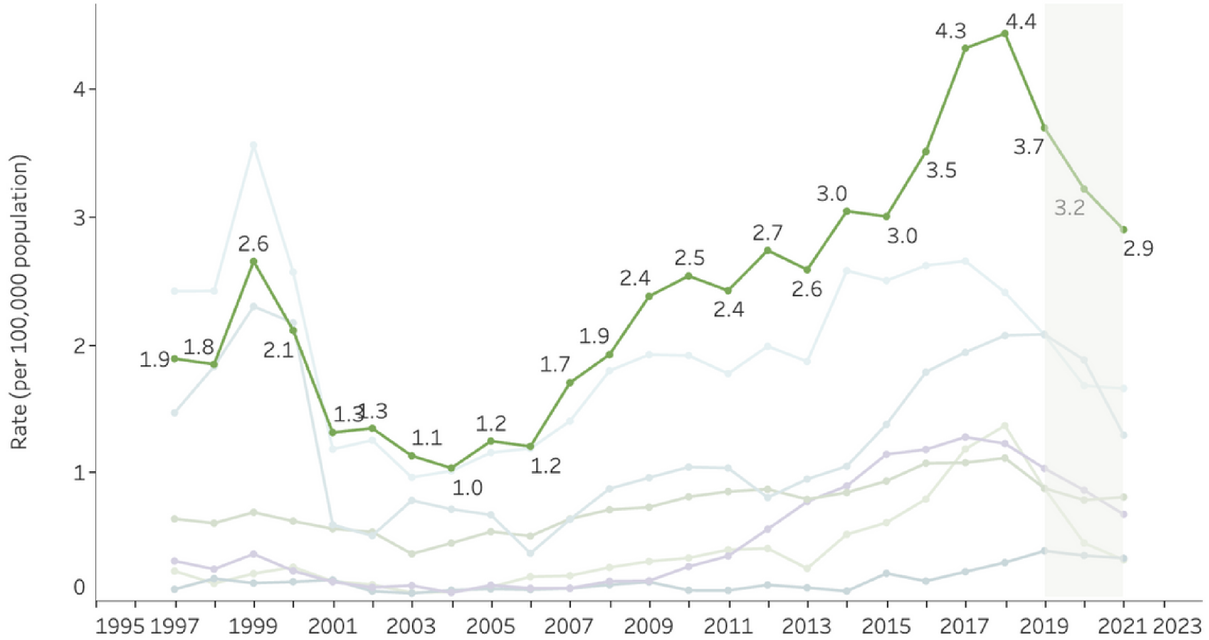
Australian Institute of Health and Welfare (AIHW) . Alcohol, tobacco & other drugs in Australia. AIHW 2021. Drug Induced Deaths

Drug induced Deaths 2021

- **1,704** drug-induced deaths
- This is the **fourth consecutive decrease** in the number of drug-induced deaths, (2,005 in 2017)
- Higher rate of deaths in **Major cities** c.f regional/remote areas (has been fluctuating)
- Higher rate of OD deaths involving **pharmaceutical medicines c.f. illicit drugs**
- ~ **Two-thirds** (65%) of drug-induced deaths were considered **accidental** (1,113 deaths) and 27% (460 deaths) were considered intentional.
- Other drug types **commonly identified in drug-induced deaths included depressants** excluding alcohol (53% or 901 deaths) and antidepressants (31% or 520 deaths).

BZD related hospitalisations/deaths - AIHW 2021

Figure IMPACT1: Number or age-standardised rate (per 100,000 population) of drug-induced deaths[a], by drug type or drug class, 1997 to 2021



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Drug type or drug class

- Heroin
- Methadone
- Natural and semi-synthetic opioids
- Synthetic opioids
- Benzodiazepines
- Cocaine
- Cannabinoids

Hospitalisations

- > 2 in 5 hospitalisations were for benzodiazepines (18.2 hospitalisations per 100,000)
- number of BZD related hospitalisations has declined since 2006 (26.1 - 18.2 per 100,000)
- highest in major cities + outer regional areas

Deaths

- Benzodiazepines continued to be the largest contributor to drug-induced deaths.
- In 2021, there were 744 drug-induced deaths involving benzodiazepines (2.9 per 100,000 population).
- Benzodiazepine related deaths have decreased since 2017.

Australian Institute of Health and Welfare (AIHW) . Alcohol, tobacco & other drugs in Australia. AIHW 2021.

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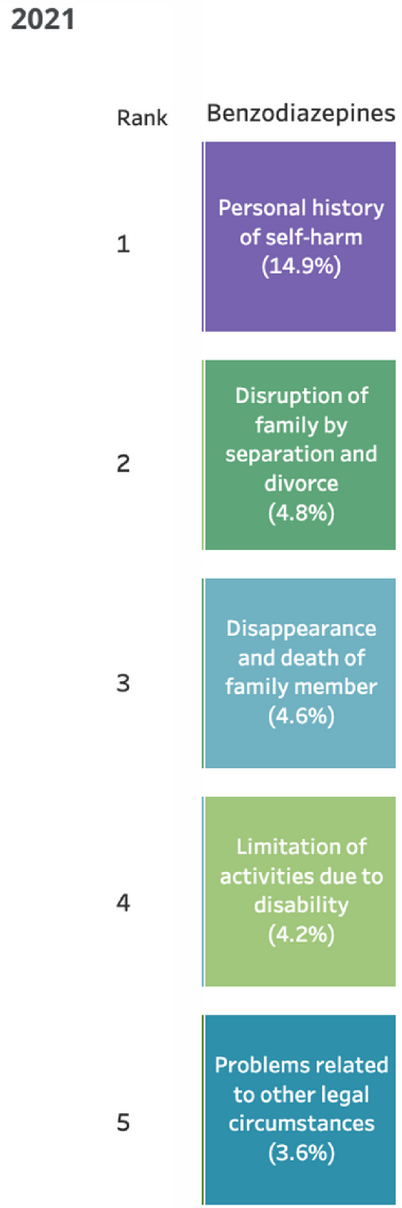
Psychosocial risk factors

Benzodiazepine

1. Personal history of self harm (14.9%)
2. Disruption of family by seperation & divorce (4.8%)
3. Disappearance & death of family member (4.6%)
4. Limitation of activities due to disability (4.2%)
5. Problems related to other legal circumstances (3.6 %)



Australian Institute of Health and Welfare (AIHW) . Alcohol, tobacco & other drugs in Australia. AIHW 2021. Drug Induced Deaths

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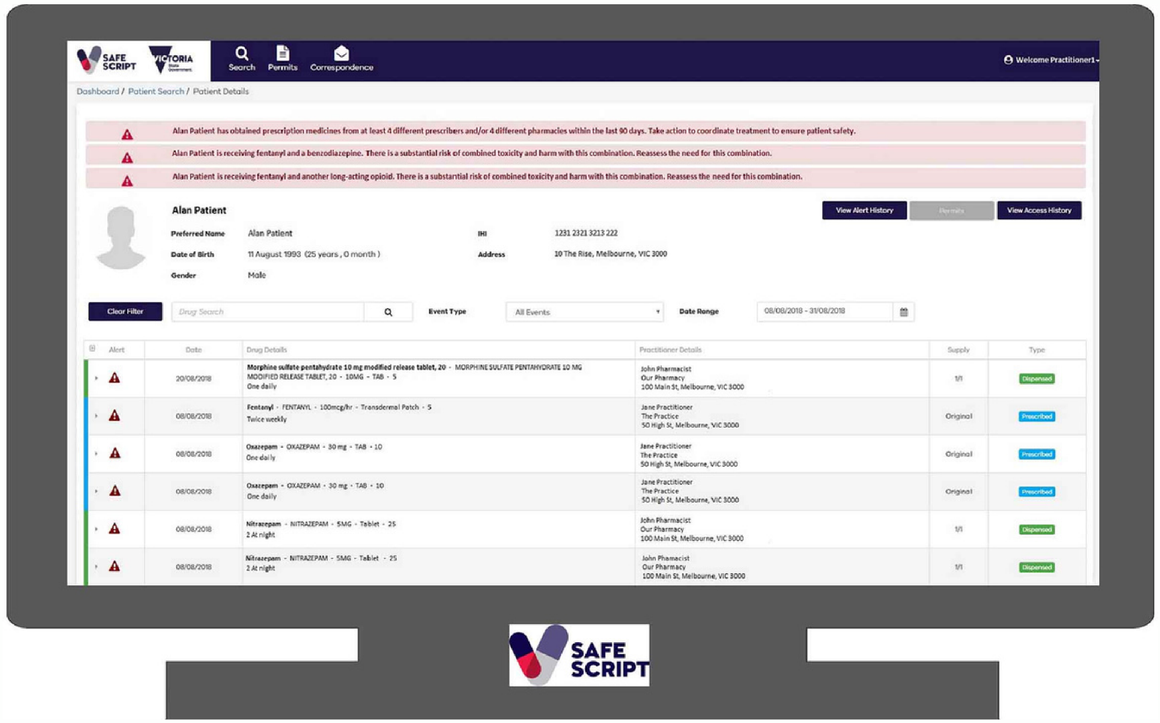
Monitoring BZD Prescriptions - Safescript



Medicines that are monitored include:

- all Schedule 8 medicines
- benzodiazepines, such as diazepam
- ‘Z-drugs’ (zolpidem, zopiclone)
- quetiapine
- codeine containing products
- pregabalin, gabapentin, tramadol

SafeScript monitors all prescriptions for these medicines regardless of whether they receive a PBS subsidy or are private, non-PBS prescriptions.

VicGov Department of Health: Safescript
https://www.health.vic.gov.au/safescript

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Summary

Benzodiazepines

- Lots of different types and formulations
- multiple effects on the brain and body
- Remain as important therapeutic options in Mental Health/AOD + others
- Understand risk factors for long term use/dependence
- BZD related mortality is decreasing but still significant

Questions to consider

- Indication
- Risk vs Benefit ratio
- Co-morbid physical health mental health/SUD/personality structure
- Sociocultural elements (i.e. support/environment)
- Type/Formulation/Dose/Duration
- Other medications (i.e. Methadone/Buprenorphine)
- Monitoring/Communication - Safescript, single prescriber, pharmacy etc.
- Other practical considerations:
  - testing: UDS vs GCMS

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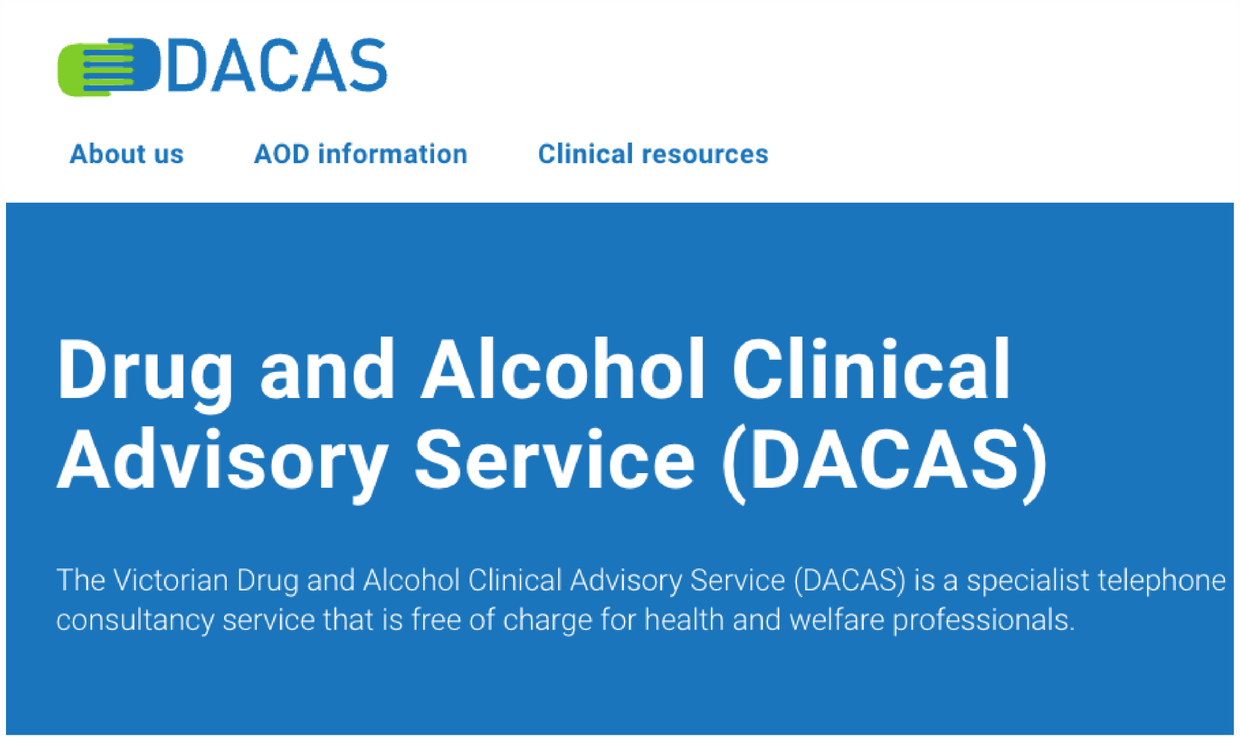
Where to go for more?

- Reconnexion (Vic)
- DACAS GP Fact Sheet: Benzodiazepine withdrawal
- RACGP Clinical Guidelines 2015: Prescribing drugs of dependence in general practice: Benzodiazepines
- The Royal Women's Hospital. Medicines, drugs and breast feeding



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Thank You