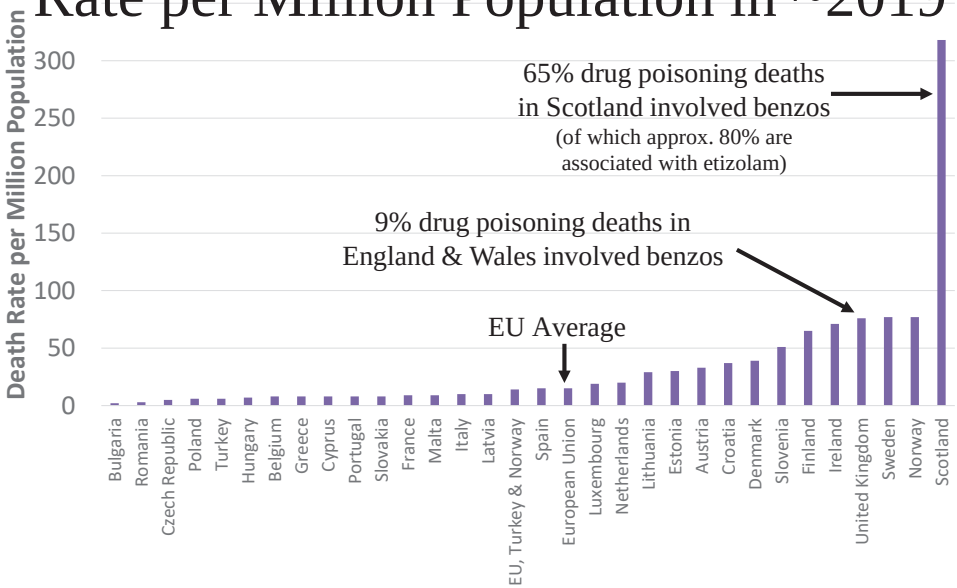
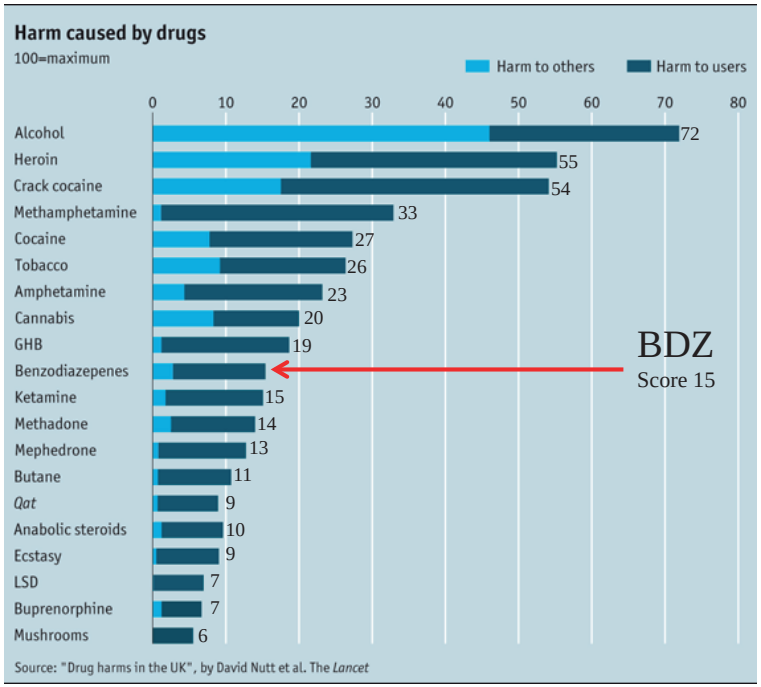
'Drug-Induced' Deaths Aged 15-64: Rate per Million Population in ~2019



European Monitoring Centre for Drugs & Drug Addiction - EMCDDA

How Harmful are BDZ Compared to Alcohol & Other Drugs in the UK?



Drug Harms in the UK: A Multicriteria Decision Analysis. Nutt, King and Phillips. Lancet 2010;376(9752):1558-65

Understanding Benzos – Tolerance, Misuse, Overdose Risk and Withdrawal

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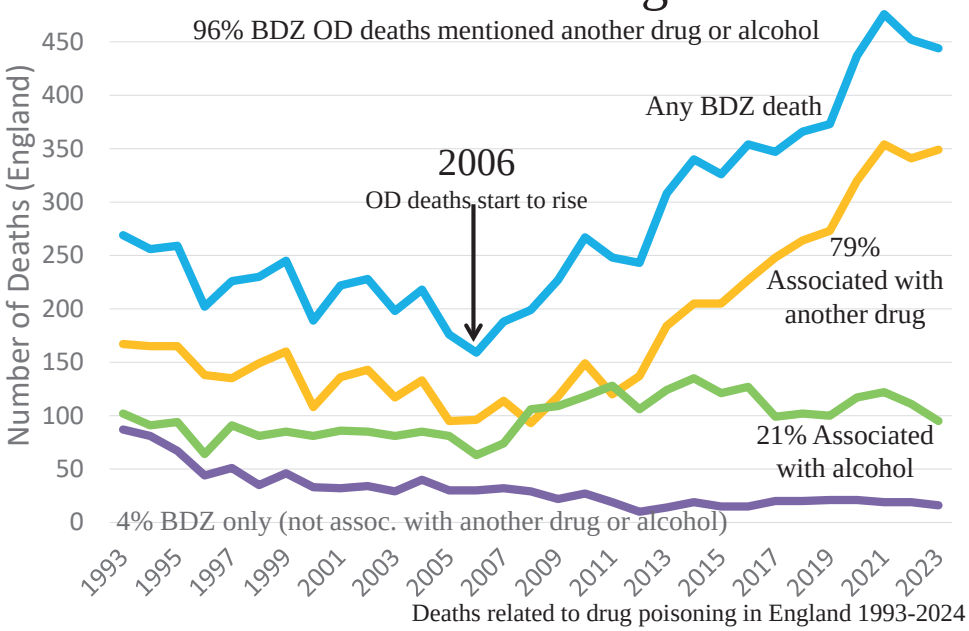
UKESAD Conference, London 31 Jun 2015

Learning Outcomes

1. Overdose on BDZ almost always occurs in combination with other drugs and/or alcohol
2. High dose use of BDZ typically occurs when the effects sought after are ones to which rapid tolerance develops
3. Tolerance to BDZ does not necessarily develop when they are used purely for anxiety

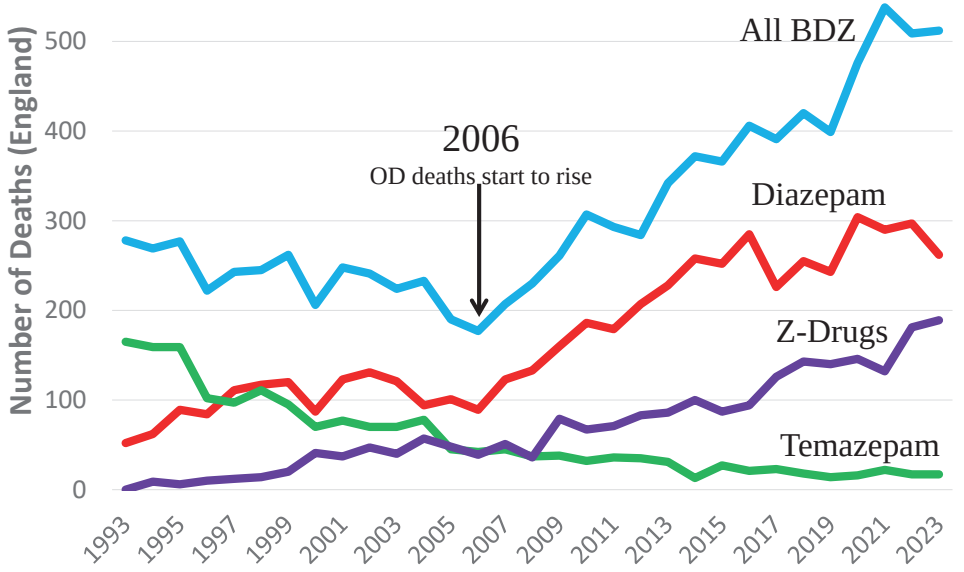
Increase in BDZ OD Deaths in Last Decade is Associated with Other Drug/Alcohol Use



Deaths related to drug poisoning in England 1993-2024

OD Deaths Associated with BDZ & Z-Drugs

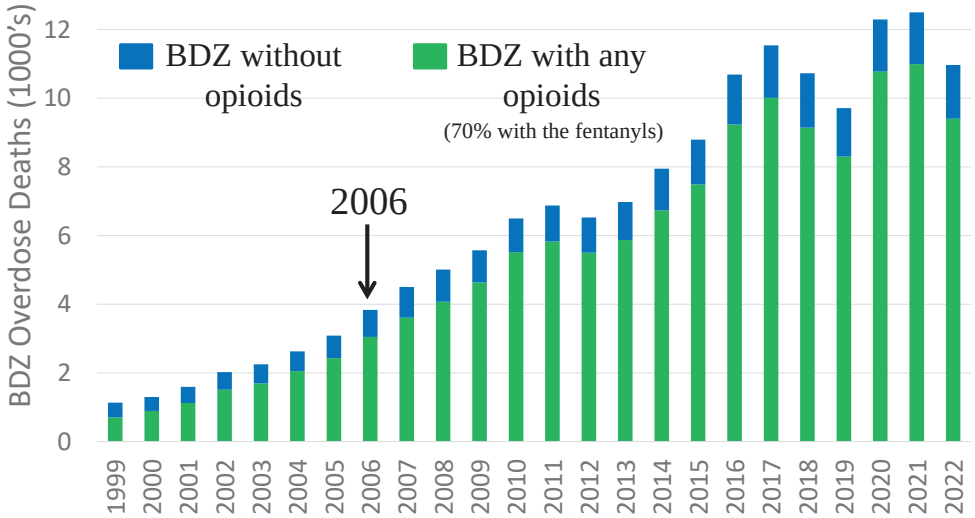
9.4% of 5448 drug OD deaths included BDZ on death certificates in England



Deaths related to drug poisoning in England 1993-2024

BDZ Overdose Deaths in USA

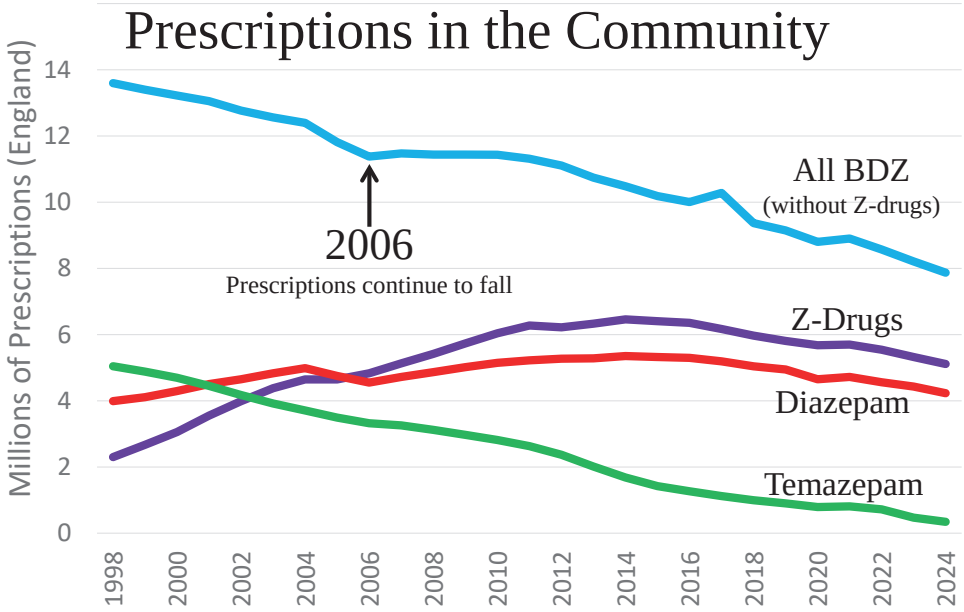
(% involving opioids increased from 62% to 88% of deaths)



% Opioid	62	69	70	75	75	78	79	79	80	81	83	85	85	84	84	85	85	86	87	85	85	**88**	**88**	86

National Centre on Health Statistics, CDC Wonder, USA

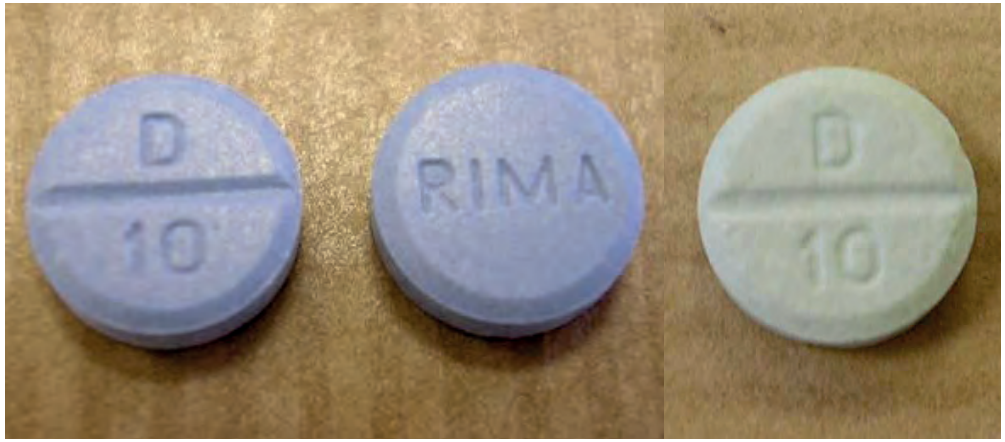
All BDZ, Diazepam, Z-drug & Temazepam Prescriptions in the Community



Based on ePACT data in England 1998 to 2024

Illicitly Manufactured Diazepam 10mg

(the blue one is identical to the pharmaceutical diazepam)



Blue Lime Green

Pictures kindly provided by Kenny Simpson

Heath Ledger

Died 22nd Jan 2008 aged 28, from an accidental overdose of 2 or 3 benzodiazepines, 2 opiate drugs, and a sedative antihistamine (diazepam, temazepam, alprazolam, oxycodone, hydrocodone, doxylamine)

NHS and Street Cost of Diazepam

- NHS price for diazepam (drug tariff price):
  - Blues (10mg) drug tariff price 3.0 pence per tablet
  - Yellows (5mg) drug tariff price 2.7 pence
  - Whites (2mg) drug tariff price 2.5 pence
- Street cost for illicit diazepam:
  - 'Blues' 10mg diazepam is £1, i.e. mark up 34x
  - White '10mg diazepam' is 50 pence, as uncertain if really is diazepam. Will often contain other BDZ, not diazepam
  - Other colours proportionally less

BDZ Use/Dependence in England

- 3% of general population have ever used BDZ
- 30% remand, 25% sentenced prisoners ever used
- 0.5-1.5 m people are dependent on BDZ in UK
- If entering addiction treatment in England:
  - 54% non-prescribed BDZ use in last 3 months
  - 34% weekly or more frequent BDZ use
  - 22% are BDZ dependent

Evidence for BDZ Effectiveness?

- RCT evidence for BDZ and Z-drugs in acute insomnia
- RCT evidence for acute treatment with BDZ for:
  - Generalised anxiety disorder (GAD)
  - Panic disorder ± agoraphobia
  - Social phobia
- No good evidence for treatment with BDZ for:
  - OCD
  - PTSD core symptoms

But use of BDZ only recommended in acute crises, or 4th line in treatment resistant anxiety disorders
(or 5th line for GAD) i.e. after psychological treatment(s), SSRI, SNRI, Gabapentinoids (& after Buspirone in GAD)

BAP Anxiety Disorder Consensus guidelines, Baldwin et al. J Psychopharm 2014: 28(5),403-39.
https://www.bap.org.uk/pdfs/BAP_Guidelines-Anxiety.pdf

Benzodiazepines: Risks & Benefits. A Reconsideration

Joint report of working group from BAP and RCPsych SIG

- "Benzodiazepine anxiolytics should be prescribed primarily either for the:
  - Short-term relief of severe anxiety symptoms or
  - Where anxiety disorders are:
    - Disabling and severe
    - And causing both significant personal distress and substantial impairment in daily activities"
- If not meeting the above criteria:
  - More suitable to use psychological or pharmacological treatments with an evidence base for long-term use

Baldwin et al. J Psychopharm 2013:27(11),967-971.
https://www.bap.org.uk/pdfs/BAP_Guidelines-Benzodiazepines.pdf

Good Quality UK Counterfeit BDZ & Packaging Looking Like Legitimate BDZ

Pictures kindly provided by Kenny Simpson

Illicit BDZ Manufacture & Import is Big Organised Business

Pictures kindly provided by Kenny Simpson

Subtle Longer Term Effects of BDZ

- Memory problems
- Emotional suppression and reduced mental clarity
- Reduced coping ability
- Reduced assertiveness with ones desires
- Delaying recovery from emotional disorders
- Reduced ability to engage in counselling
- Reduced outcome compared to antidepressants or psychological work for anxiety disorders
- Aggravate anxiety and low mood
- Protracted withdrawal symptoms

Why do People Use Illicit BDZ

- Self-medication:
  - Low dose – BDZ for anxiety or sleep
  - High dose – BDZ for intrusive thoughts, feelings or memories
- Numbing use:
  - BDZ for mind numbing/ oblivion, i.e. not using minimum dose to manage issues
- Fun use:
  - BDZ for positive mood change – for 'fun' or 'comfort', buzz/rush/high

Just Because BDZ are Efficacious in Most Anxiety Disorders Doesn't Mean they Should be Used to Treat Them

Associations Between BDZ Use & Morbidity/Mortality

Accidents, Injuries & Hangovers	Mental Health	Drug & Alcohol Use	Physical Health
RTAs/accidents	Suicide	Injecting use	Dementia
Falls & broken hips	Depression	Smoking	Cancers
Hangover effects	Stress and anxiety	Alcohol and opiate use	Infections
Impaired motor skills	Short & long sleep	Other risks of overdose	Reduced activity
Poor judgement	Sleep apnea	Polydrug use	CVD*

* Cardiovascular disease

Effect of Speed of Onset & Elimination Half-life on Abuse Potential and Onset of Withdrawal Symptoms

	Rapid Onset	Intermediate Onset	Slow Onset
Ultra-short half-life (< 8 hrs)	Early Onset Withdrawal Symptoms		
Short half-life (8-24 hrs)	Better High / More Abused		Less High / Less Abused (unless used with rapid onset drugs)
Long half-life (≥ 24 hrs)	Late Onset Withdrawal Symptoms		

Drugs by Rate of Onset and Half-Life

	Rapid Onset	Intermediate Onset	Slow Onset
Ultra short half-life (< 8 hours)	Midazolam Zopiclone Zolpidem Zaleplon		
Short half-life (8-24 hours)	Flunitrazepam Temazepam (oral solution or caps)	Lormetazepam Lorazepam Temazepam (tabs)	Oxazepam Loprazolam
Long half-life (≥ 24 hours)	Diazepam Nitrazepam Flurazepam	Alprazolam	Chlordiazepoxide Clonazepam Clobazam

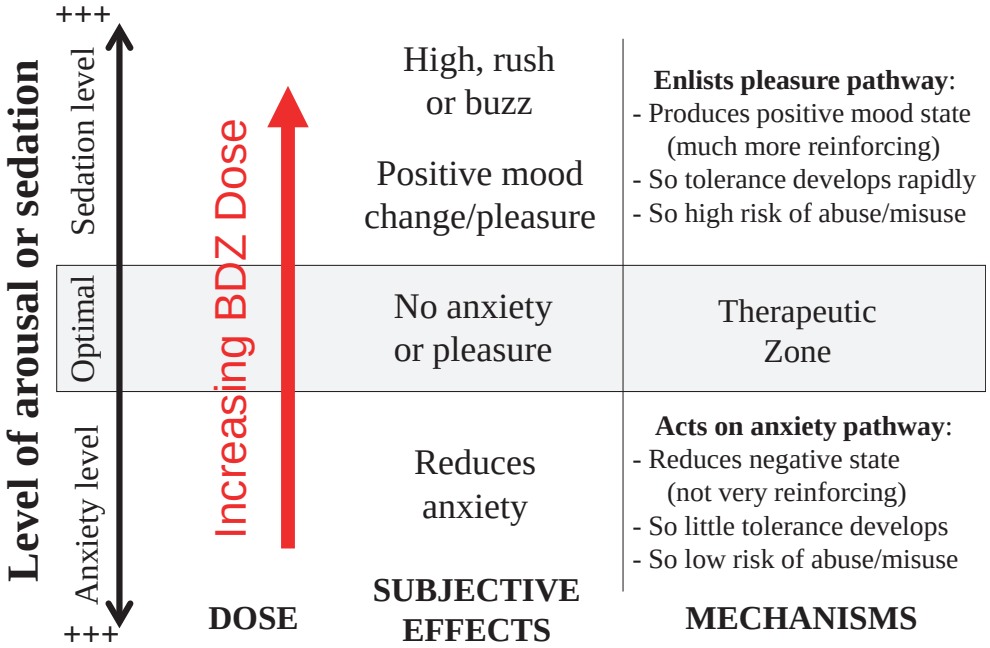
Treatment Objectives for the 3 Groups

- Self-medication:
  - Low dose for anxiety/sleep – treat the anxiety/sllep
  - High dose for intrusions – treat the anger, trauma or underlying psychiatric disorder
- Numbing use:
  - Use psychosocial interventions to develop psychological stability and encourage to use the minimum dose required that gives the self-medicating benefits
- Use for fun/buzz/high/rush:
  - Use motivational interviewing (MI) to draw out and help the person assess the benefits and adverse effects of BDZ use, and assist them to think about other ways to have fun

Most Important Clinical Factors Associated with Fun Use of BDZ

- Speed of onset of effects (at brain receptors):
  - Rapid onset - most abuse, whether long acting (e.g. diazepam) or shorter acting (e.g. flunitrazepam)
  - Slow onset - least abuse e.g. oxazepam is BDZ of choice in addicts misusing BDZ (unless pregnant)
- Rapid onset associated with “good” effects (buzz) & thus psychological reinforcement every time BDZ is taken, strengthening the psychological aspect of the addiction

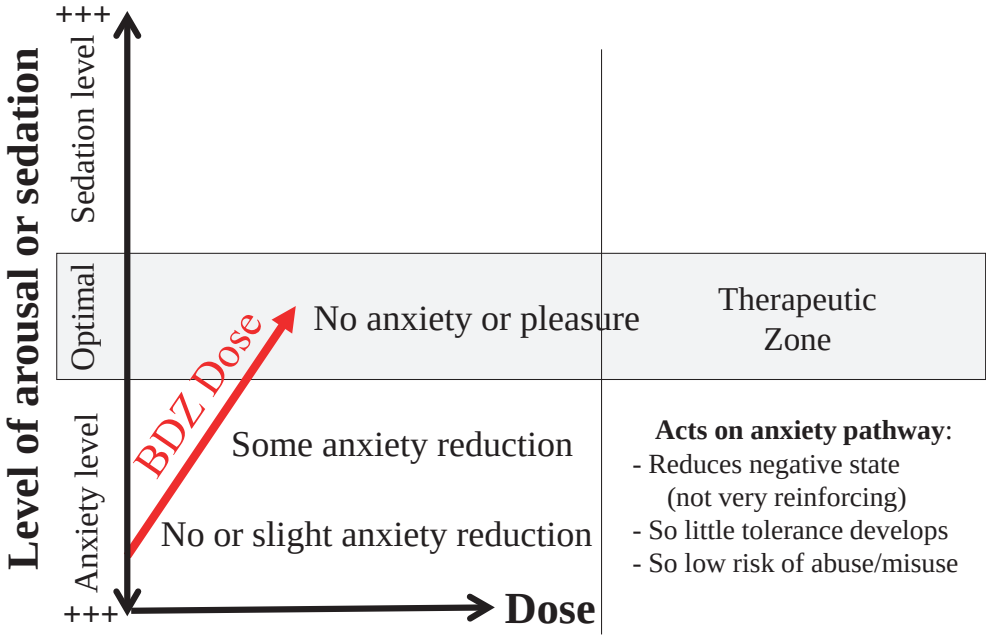
Model of BDZ Tolerance



Tolerance to BDZ Effects

- **Rapid tolerance to:**
  - Positive mood change: buzz / rush / high
  - Sedation: gauch / nodding
  - Cognition effects: amnesia / cognitive impairment
  - Motor effects: ataxia / muscle relaxation
- **Little tolerance to:**
  - Anxiolytic and anti-panic effects

Low Dose BDZ in an Anxious Person



Effect of Tolerance on Behaviour

- **If seek high/sedation** (rapid tolerance):
  - Escalate dose and **use as a single high dose in the day** to maximise the positive mood change
  - Use in binges
  - Use in combination with other drugs that potentiate drug effects e.g. opiates, alcohol, pregabalin etc.
  - Use route with more rapid speed on onset e.g. crunch up tablets, inject
  - Use in novel situations (less conditioned tolerance)
- **If seek anxiolytic effects** (little tolerance):
  - **Use repeated small doses 3-4 times a day** to maximise effect against the chronic anxiety
  - No need to engage in any of the above behaviours

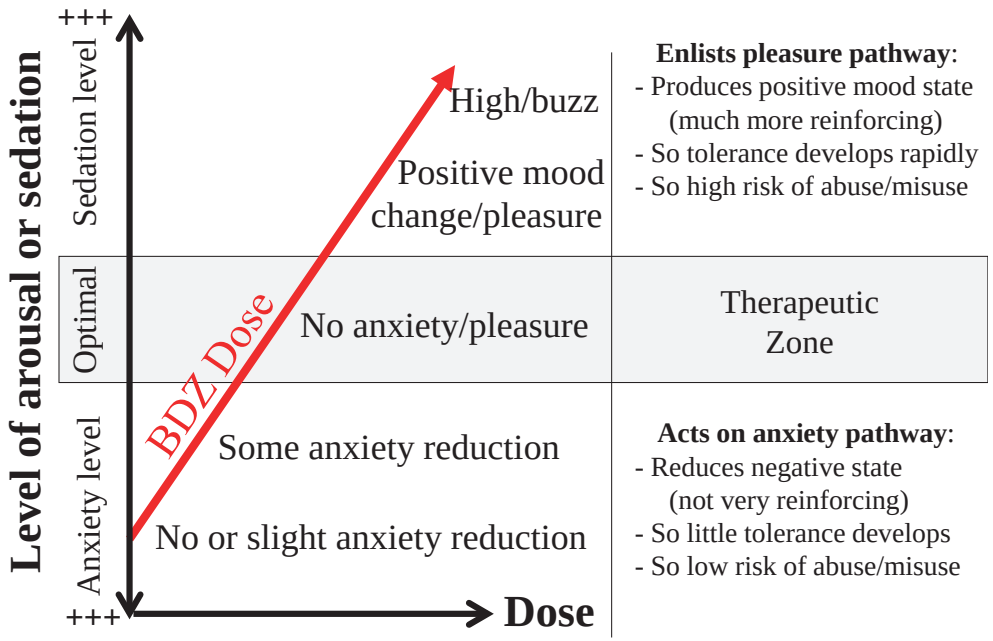
Strategies to Minimise Tolerance

- Use BDZ selectively, reserving them for crises and treatment resistant anxiety or insomnia
- Avoid use for positive mood change /fun
- Avoid excess doses - if causing sedation or dose more than the minimum to treat anxiety symptoms
- Use a dosing frequency that is less than 4-5 half-lives of the BDZ
- For night sedation, use intermittently (or use Z-drugs as tolerance develops more slowly)

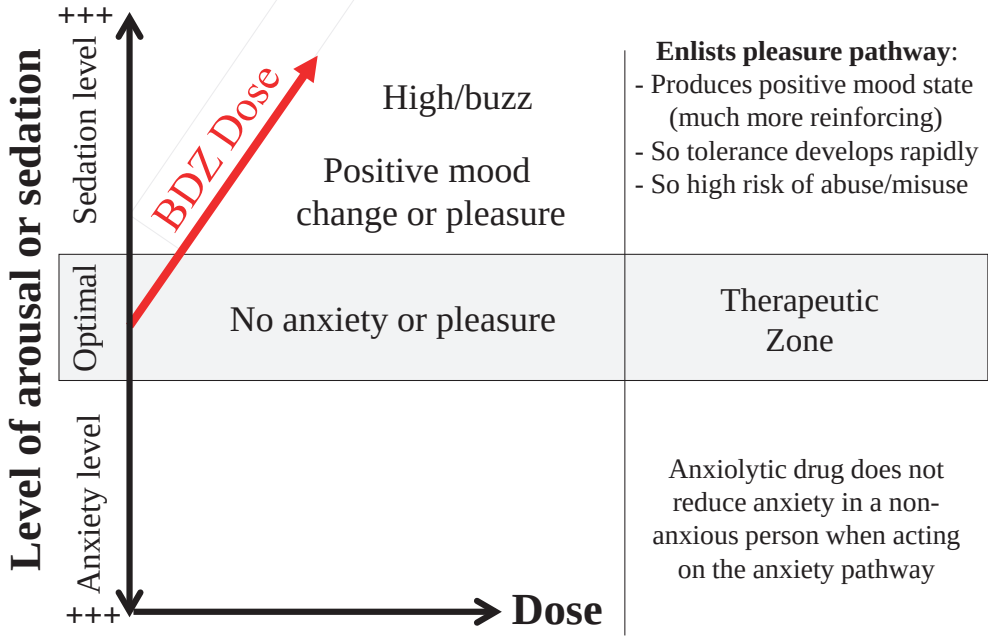
How "Addictive" Are BDZs? - Depends on Population Considered

- Normal populations:
  - Risk in moderate social drinkers higher than minimal drinkers (12 vs 4 units/week)
- Populations with a history of addiction:
  - Risk much higher, strong links with alcohol problems and opiate use
- Psychiatric populations:
  - Intermediate risk: BDZ are one of the safest of all drugs commonly prescribed in mental health
  - Higher risk: poor copers, chronic stress, anxious personality disorders (dependent, avoidant, obsessional-compulsive)

High Dose BDZ in an Anxious Person



BDZ in a Non-Anxious Person

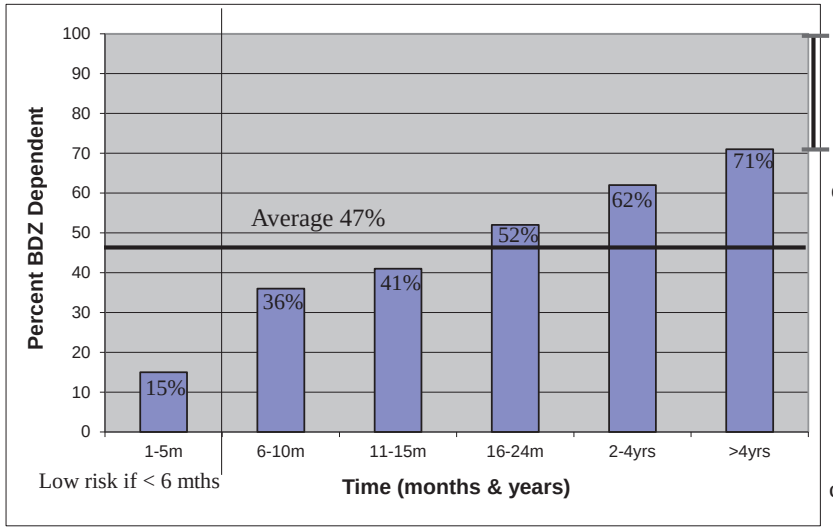


BAP Recommendations for Therapeutic Dose BDZ Users

- Depends on severity of BDZ dependence:
  - Early/mild dependence: minimal interventions e.g. info, GP advice and letters
  - Established dependence: gradual reduction
- Effectiveness of gradual reduction with BDZ:
  - Increased with additional psychological therapies esp. panic disorder, insomnia
  - Medication does not improve outcomes, but consider antidepressants, melatonin, valproate, flumazenil
- Switching from short to long half-life BDZ:
  - If having problematic withdrawal symptoms on reduction

British Association for Psychopharmacology Addiction Consensus Guidelines, Lingford-Hughes et al 2012. https://www.bap.org.uk/pdfs/BAP_Guidelines-Addiction.pdf

Rates of BDZ Dependence by Length of Use in People Using BDZ Daily in Primary Care



29% not dependent after > 4 yrs i.e. not just a drug effect – e.g. due to Tx for anxiety and a lack of conditioning, i.e. use of BDZ as a medicine independent of mental state and circumstances

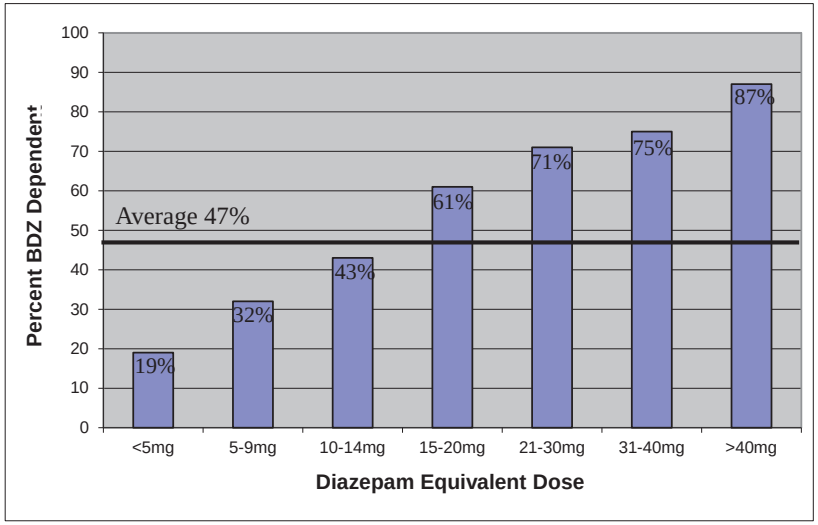
De las Cuevas et al. (2003). Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology 167:297-303

BAP Recommendations for Illicit or High Dose BDZ Misusers

- Can't recommend maintenance BDZ (as poor evidence), but may reduce illicit BDZ use in some people
- Doses > 30mg diazepam rarely necessary, and 30mg prevents withdrawal seizures in very high BDZ users
- Use drug screens to monitor BDZ/other drug use
- Carbamazepine may be used instead of BDZ to control withdrawal symptoms
- Reducing from a high to BNF doses may be useful
- Increased risks if dependent on opioids or alcohol

British Association for Psychopharmacology Addiction Consensus Guidelines, Lingford-Hughes et al 2012. https://www.bap.org.uk/pdfs/BAP_Guidelines-Addiction.pdf

Rates of BDZ Dependence by Dose Used in People Using BDZ Daily in Primary Care



De las Cuevas et al. (2003). Benzodiazepines: more "behavioural" addiction than dependence. Psychopharmacology 167:297-303

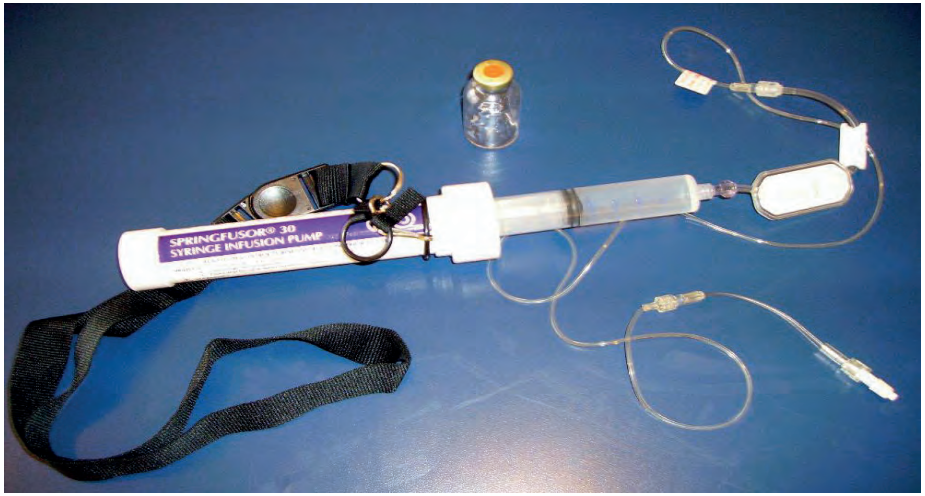
Conclusions on BDZ

- Problems from BDZ use/misuse are largely predictable
- Overdose deaths linked to other drug use, esp. opiates
- Tolerance develops at different rates to the different effects, which affects how people behave
- Tolerance may not develop if purely used for anxiety
- Evidence supports the gradual reduction of BDZ once dependent (very little evidence for maintenance dosing)
- Flumazenil infusions may be the future of BDZ detox

Flumazenil: ? The Future of BDZ Detox

- **Very slow** infusions of flumazenil (1mg/ 6 hours) for 7-14 days (5 half-lives of the BDZ being detoxed from)
- Current licensed formulation can be given IV (but S/C infusion of unlicenced formulation also used)
- Low severity of withdrawal even for high dose users or long term BDZ users
- Use anti-epileptic if high risk of seizures
- Abstinence success rate doubled in RCT at one month post detox (60% flumazenil vs 30% for gradual detox)
- Terminates protracted BDZ withdrawal symptoms

Flumazenil 12mg/30ml Filtered Infusion System Given over 96 Hours



Slide kindly provided by Dr George O'Neil of the Fresh Start Clinic, Perth, Australia
https://www.freshstart.org.au/