

# What is the Size, Prevalence & Evidence of Misuse of Benzodiazepines and How do we Treat this in General Practice?

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# Plan of Talk

- Who misuses BDZ
- Prevalence of BDZ misuse
- Problems from BDZ misuse
- Treatment of BDZ misuse

Who is at Risk of Misusing  
BDZ & Why do They do it?

# How Benzodiazepines are Obtained

- Diversion of prescribed medications:
  - Sold by one user to another
  - May be obtained for this purpose ('an earner')
- Bought on internet – delivered by post
  - Increasingly common
- Brought in or smuggled in from abroad
- Diversion of prescriptions:
  - Forged scripts
- Warehouse/pharmacy thefts

# Cost of Diazepam

- Cost of a BNF 10mg diazepam tablet:
  - £1 on 'black market' for a blue 10mg tablet
  - Cost from abroad over the web from India 8-13 pence for a 10mg tablet (may be white, so cost 50 p as uncertainty re its identity, usually BDZ but ? type), much cheaper from China but often not BDZ)
  - 3.9 p BNF cost (3.5p for 5mg)
- Not breaking the law if buying BDZ from abroad without a prescription or in large quantities
- May be arrested for 'supplying' once BDZ in your possession. Need to prove obtained from abroad and for your personal use
- The website selling the BDZ is breaking the law if it is based in the UK

# Which Diazepam 10mg is Illicit?



Blue

Lime Green

Pictures kindly provided by Kenny Simpson

# Good Quality UK Counterfeit BDZ & Packaging Looking Like Legitimate BDZ



Pictures kindly provided by Kenny Simpson

# Illicitly Manufactured Zopiclone Imported into UK Masquerading as Temazepam



Pictures kindly provided by Kenny Simpson



# Illicit BDZ Manufacture & Import is Big Organised Business



Pictures kindly provided by Kenny Simpson

# Why do People Abuse BDZs?: Three Types of (Subjective) Reasons

- Fun/pleasure (buzz, high, rush and sedation or gauch):
  - Intoxication or using with other drugs to potentiate buzz e.g. opiates, alcohol
- Numb the mind:
  - Seek oblivion, escape (emotional suppression), so don't feel part of the world
- Self-medication:
  - Psychological issues:
    - Sleep, relax, improve confidence, low mood, worries & any other distress
  - Psychiatric issues:
    - Anxiety, depression, reduce voices, medication side-effects
  - Drug use (withdrawal, come down and 'substitution'):
    - To prevent withdrawal from BDZ & other cross tolerant drugs e.g. alcohol
    - To combat opiate withdrawal symptoms
    - To help come down from stimulants (amphetamines, XTC, crack/cocaine)
    - To limit the level/frequency of use or to keep going until obtain a supply
    - Top up script from doctor or as feel reducing dose too quickly

# Why People Combine BDZ with Other Drugs

- All drugs
  - Reduce withdrawal
  - Emotional suppression (escape, reduce worries)
- Stimulants:
  - Comedown (esp crack)
  - Sleep
- Opiates, alcohol & other sedatives:
  - Enhance buzz
  - Reduce withdrawal (esp alcohol), reduce cost of high (esp alcohol)
- Cannabis
  - Alternative type of sedation

# Preference For BDZ in Humans

- Generally no preference for BDZ over placebo in:
  - Normal subjects in general
  - Anxious subjects in general
- Increased liking for BDZ:
  - Normal subjects who are moderate drinkers (av. 12 units/wk) have an increased preference for diazepam over placebo than minimal drinkers (av. 4 units/wk)
  - Minority of anxious subjects have a clear preference for BDZ
  - Non-anxious former alcoholics (but not controls) have a rapid positive mood change with single doses of BDZ
  - F/H of substance use a risk factor for BDZ liking in some studies

# Most Important Clinical Factors Associated with Abuse of BDZ

- Speed of onset of effects:
  - 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, & thus psychological reinforcement every time drug is taken, strengthening the psychological aspect of tendency to addiction

- Dose of BDZ - higher dose leads to better buzz

# Tolerance to BDZ Effects

- Rapid tolerance to buzz, sedation & cognitive-motor effects (but may never be complete):
  - Buzz/rush/high, sedation/gouch
  - Amnesia, cognitive effects, ataxia, muscle relaxation
- Partial tolerance to antiepileptic effects:
  - Break through seizures may occur
- Little tolerance to other therapeutic effects, especially at lower/therapeutic dose levels:
  - Anxiolytic & antipanic effects

Note: Differential rates of development of tolerance indicates different mechanisms of action for the various effects

# Effect of Tolerance on Behaviour

- If rapid tolerance occurs (high doses & sedation):
  - Escalate dose
  - Use in binges (with gaps in between)
  - Use route with more rapid speed on onset e.g. crush up tablets, inject rather than oral
  - Use in combination with other drugs that potentiate each others effects e.g. opiates
  - Use in novel situations (to offset effects of conditioned tolerance = ‘context dependent tolerance’)
- If little tolerance occurs (lower doses & anxiety):
  - No need to increase dose or increase speed of onset, binge, polydrug use or use in novel situations

# Who Escalates Their BDZ Dose?

## **Fun & Sedation Seeking**

- Assoc abuse of BDZ
- Seeking positive effects
- Often escalate BDZ dose
- Lower doses not enough
- Typically take BDZ as single dose in day
- Includes bingers & those who use to potentiate drug effects

## **Self-Medicating for Anxiety**

- Not assoc BDZ abuse
- Seek relief from neg Sx
- Rarely escalate BDZ dose
- Lower doses efficacious
- Typically take BDZ 3-4 times a day
- Includes regular BDZ users & illicit use to help with problems



# How “Addictive” Are BDZs?

## - Depends on Population Considered

- Normal pops:
  - Acute toxicity very low (moderate > minimal drinkers  
? Due to GABA subunit change)
- Psychiatric patients:
  - Intermediate risk. BDZ said to be one of the safest of all drugs prescribed for psychiatric problems
- Addict populations:
  - Risk higher. Strong links with alcohol problems, opiate misuse & dependent personality disorder

# Adults at Risk of Using BDZ

(Data from Raistrick et al 2006, Singleton et al 2001)

	<b>Men</b> (%)	<b>Women</b> (%)	<b>Both</b> (%)
*Alcohol use disorder	38	16	26
Short term insomnia	24	34	29
Neurotic disorder in the last week	13	19	16

\*Figures don't include at risk population of social drinkers

# Prevalence in Various Populations

# Prevalence of BDZ Use & Misuse

- 12 million scripts issued per year, esp women
- 1.5 million people addicted in UK (Prof H. Ashton evidence to APPDMG inquiry, p. 18):
  - Mostly prescribed by qualified doctors
  - A disgrace to the medical profession
- Estimated 0.2 million illicit benzodiazepine users
  - Males > females

APPDMG inquiry = The All-Party Parliamentary Drugs Misuse Group” report “An Inquiry into Physical Dependence and Addiction to Prescription and Over-the-Counter Medication” By G Reay, Jan 2009

# Evidence of Misuse: UK Surveys

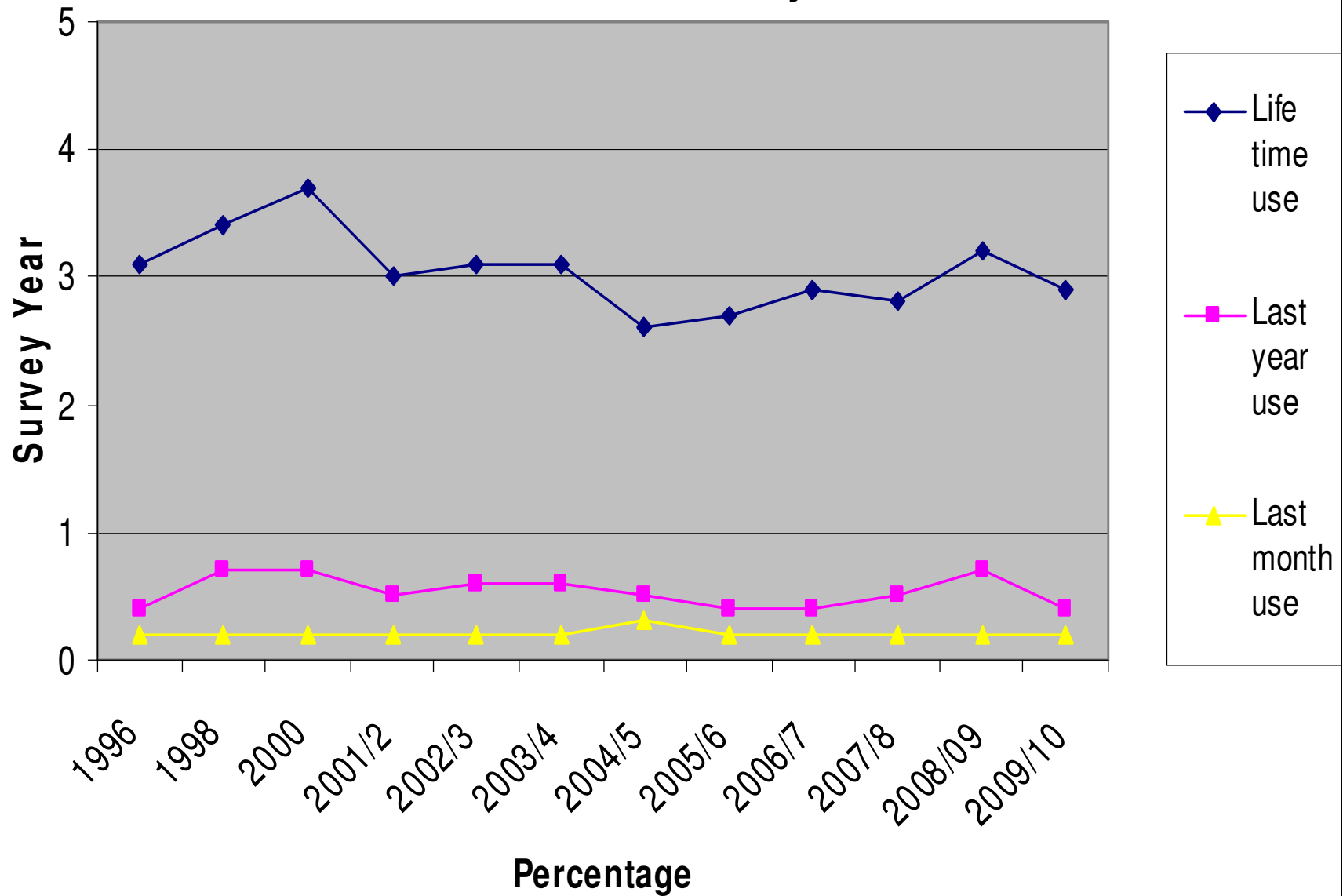
- British Crime Survey ([www.homeoffice.gov.uk](http://www.homeoffice.gov.uk))
  - Annually in England & Wales with 16-59 year olds
  - Asks about “tranquillisers such as temazepam or Valium, not prescribed by a doctor”
- ONS National Survey of Psychiatric Morbidity in Adults in Great Britain 1997
- Young people: European Schools Project on Alcohol & Other Drugs ([www.ESPAD.org](http://www.ESPAD.org)):
  - Surveys every 4 years (1995, 1999, 2003, 2007), 15-16 year old in 26 European countries. Asks about use of non-prescribed tranquilliser & sedatives
- Addiction treatment pop: National Treatment Outcome Research Study (NTORS, Gossop et al 2001)

# General Population

Numbers Using Non-Prescribed  
Tranquillisers Aged 16-59 years in  
England & Wales  
from British Crime Survey 2009/10

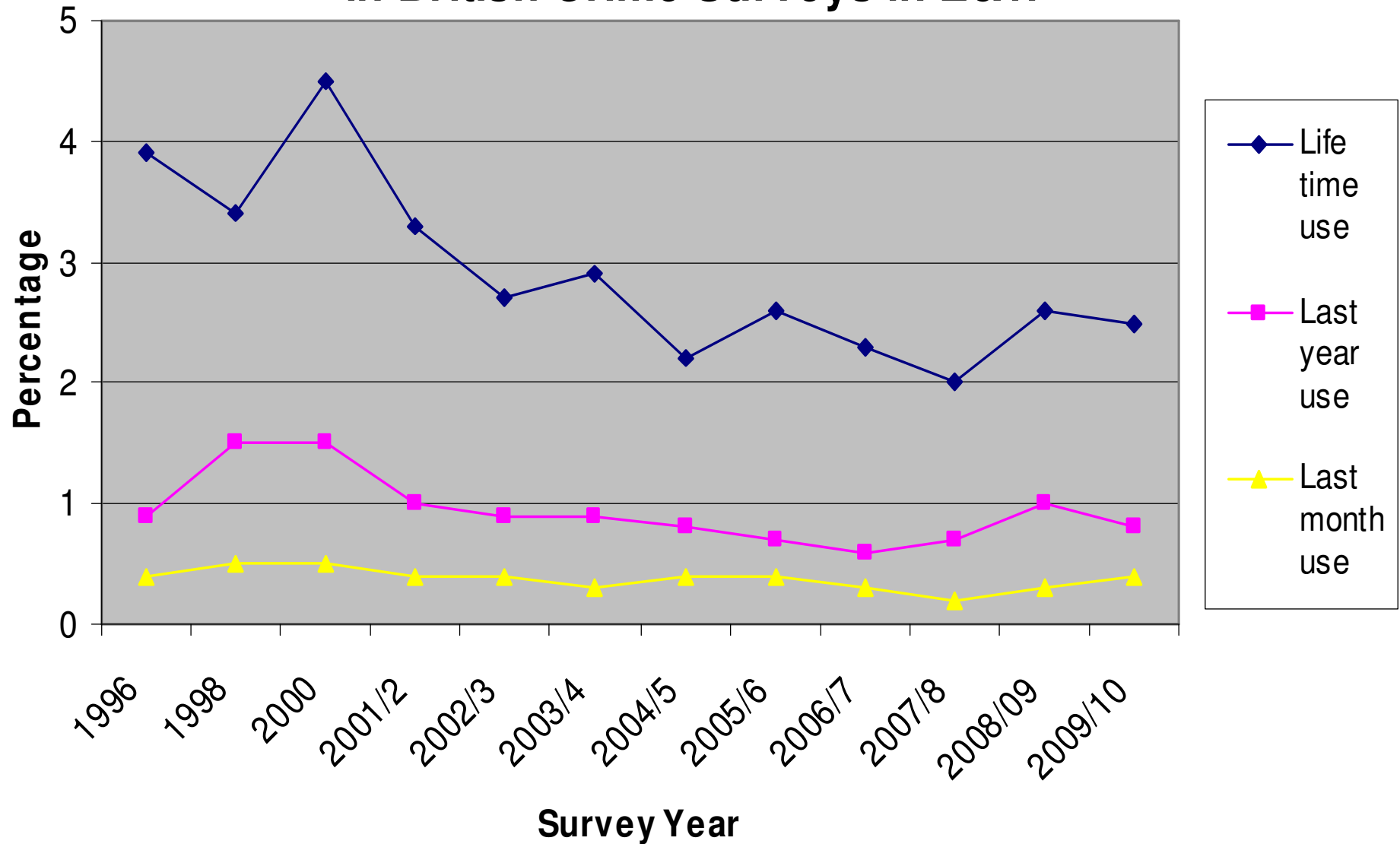
- Ever used: 948,000 (range 872-1030k)
- Last Year use: 145,000 (range 117-180k)
- Last month use: 73,000 (range 54-99k)

# Non-Prescribed Tranquilliser Use in 16-59 Year Olds in British Crime Surveys in E&W

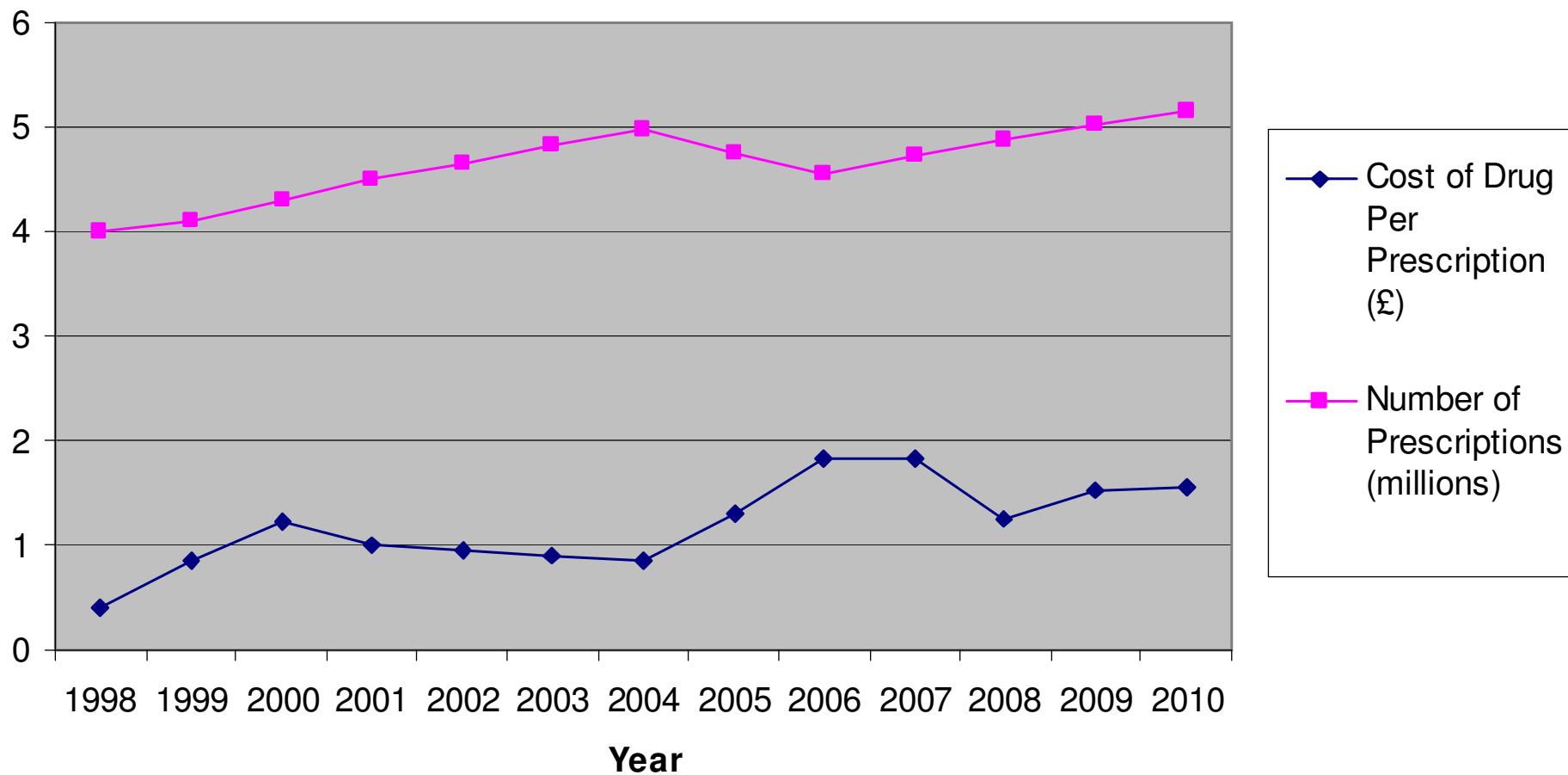




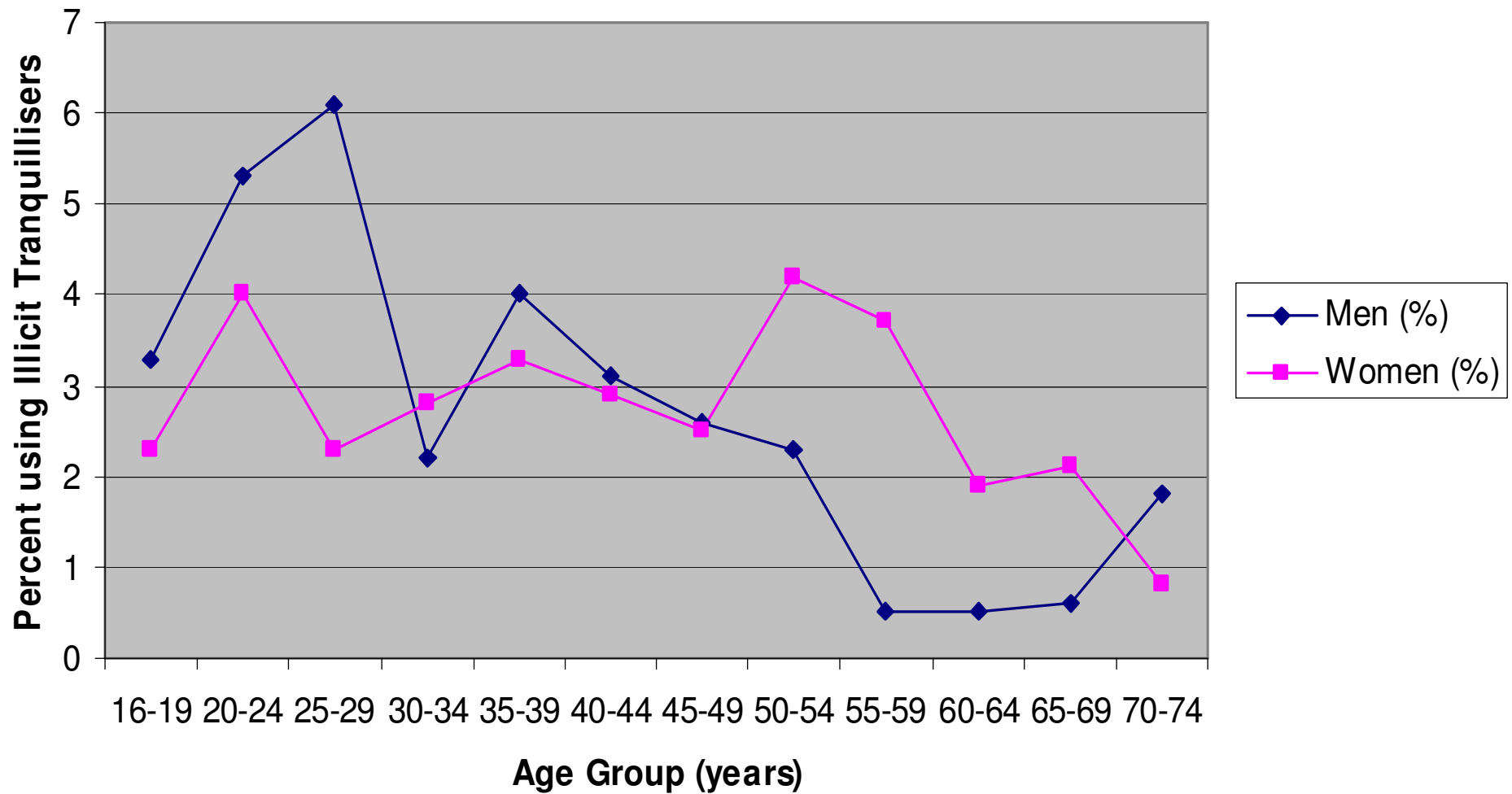
# Non-Prescribed Tranquilliser Use in 16-24 Year Olds in British Crime Surveys in E&W



## Number of Diazepam Prescriptions Issued Annually and Average Cost Per Prescription



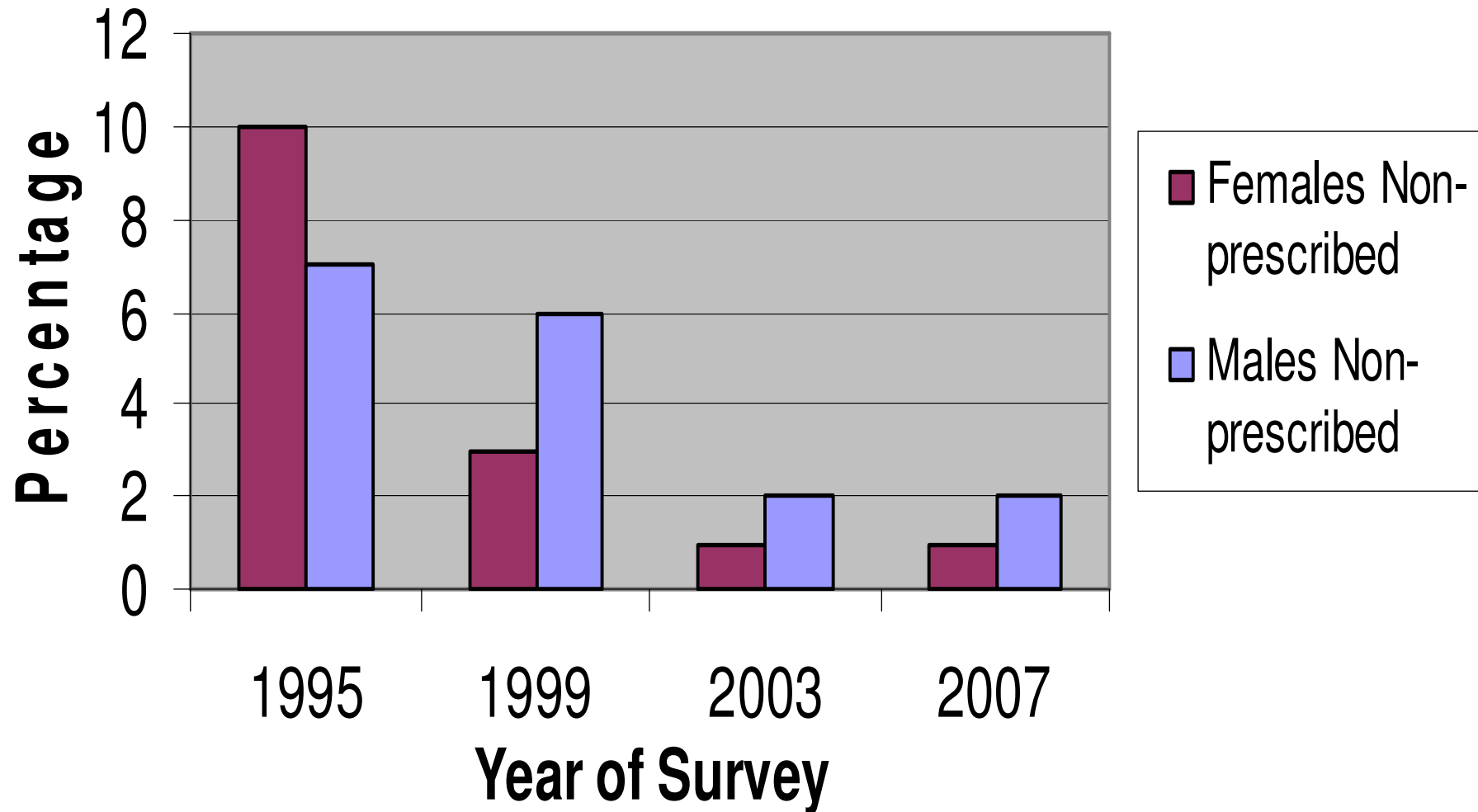
# Rates of Illicit Tranquilliser Use by Age Group from the ONS Survey of Psychiatric Morbidity among Adults in Great Britain (Coulthard et al 2002)



Adolescents 15-16 Years Old

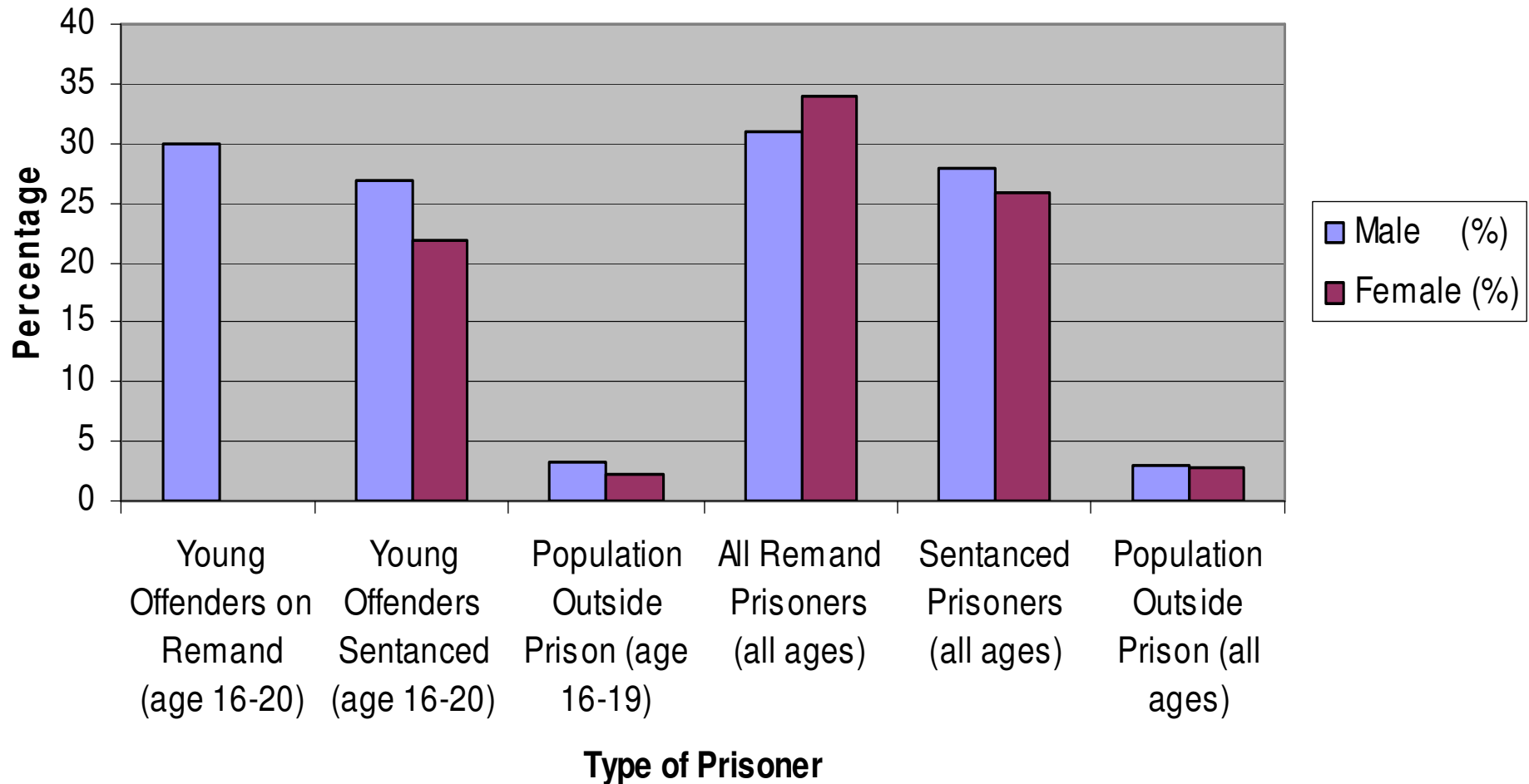
# Percent of Male & Female 15-16 Year Olds in UK Taking Non-Prescribed Sedatives & Tranquillisers

(ESPAD - European Schools Project on Alcohol & Other Drugs)



# Prison Populations

## Lifetime Use of Non-Prescribed Tranquillisers by Gender and prisoner Type from the 1997 Survey of Psychiatric Morbidity Among Prisoners (Singleton et al 1999, Lader et al 2000)



# Poly Drug Use & Addiction Populations



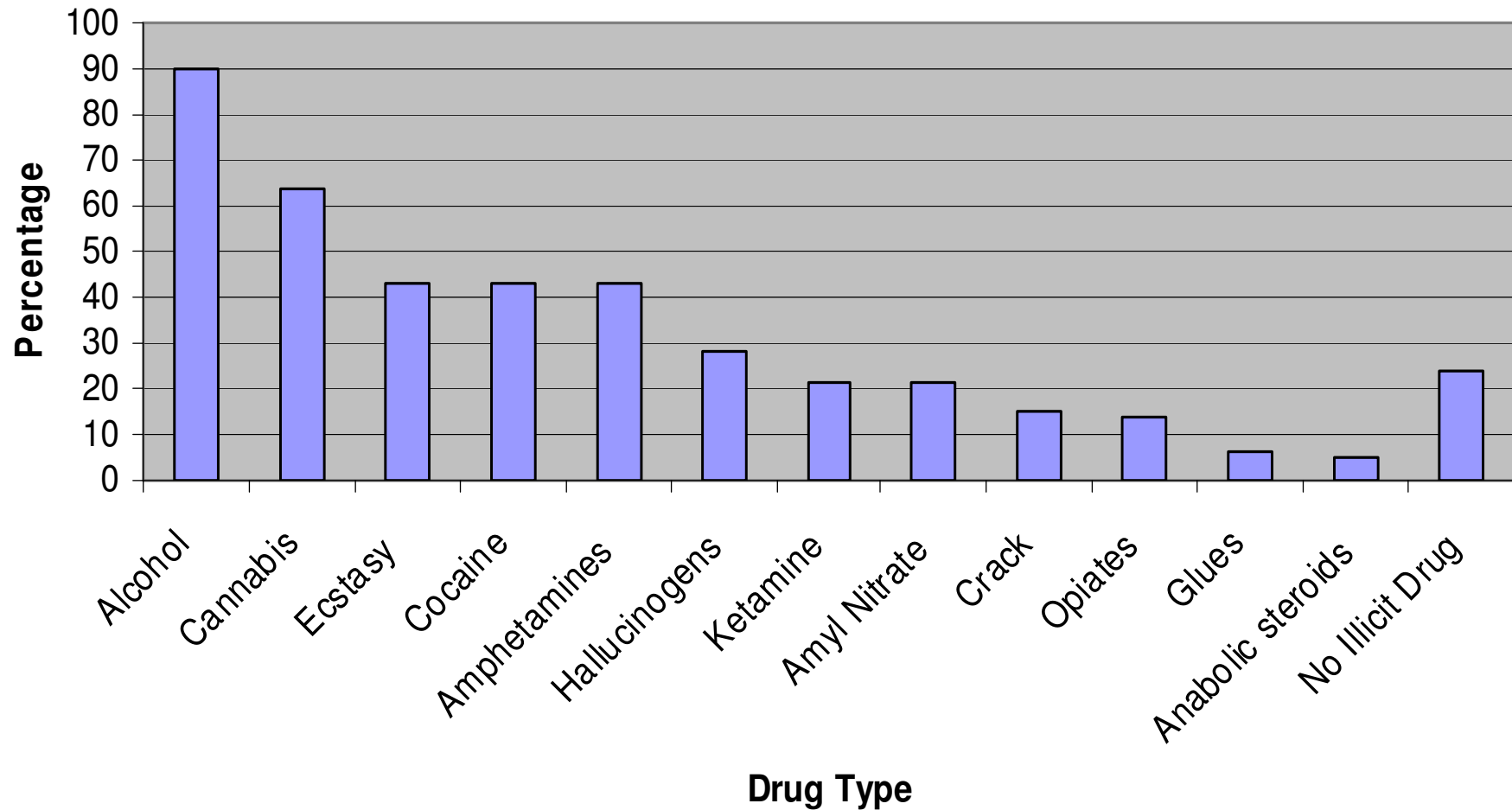
# National Treatment Outcome Research Study (NTORS, UK)

(Gossop et al 2001, [www.dh.gov.uk](http://www.dh.gov.uk))

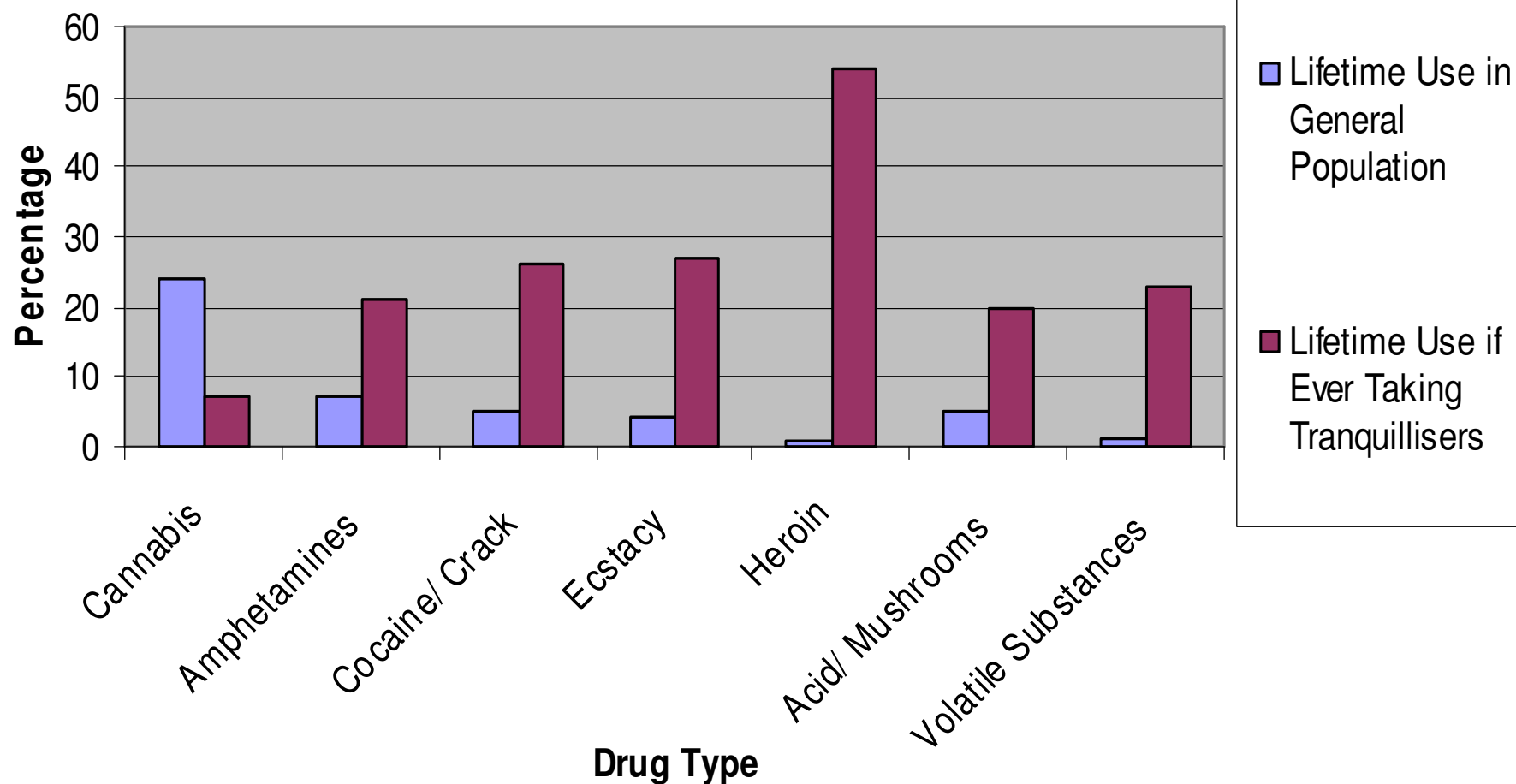
Population entering addiction Tx in England:

- 54% non-prescribed BDZ use in last 3 mths
- 34% weekly or more frequent BDZ use
  - Reducing to 12% 4-5 yrs after start of treatment
- 22% BDZ dependent
- 4% were injecting benzodiazepines
- BDZ Rates higher if a worse alcohol problem

# Percentage Using Tranquillisers with Other Drugs in the Last Year in 16-59 Year Olds in the British Crime Survey 2009/10



# Comparison of Rates of Use of Various Drugs in General Population and Those Having Used Tranquillisers in the 2000 National Survey of Psychiatric Morbidity in GB (Coulthard et al 2002)



Z-Drugs (zopiclone,  
zolpidem, zaleplon)

# NICE (2004) View on the Use of Z-Drugs in the Majority of Patients

- “The committee concluded that currently there was no compelling evidence of a clinically useful difference between the Z-drugs and shorter-acting BDZ hypnotics [temazepam, loperazolam, lorazepam] from the point of view of their effectiveness, adverse effects, **or potential for dependence or abuse**” ( § 4.3.8)
- “... the drug with the lowest purchase cost (taking into account daily required dose & product price per dose) should be prescribed.” ( § 1.2)

# GP Attitudes to Z-drugs vs BDZ

(Siriwardena et al, BrJGP Dec 2006, pp.964-7)

Feeling rested on waking (p<0.001)	<b>Less tolerance</b> (p<0.001)
Better daytime functioning (p<0.001)	<b>Less withdrawal effects</b> (p<0.001)
Less daytime sleepiness (p<0.03)	<b>Less dependence risk</b> (p<0.001)
Total sleep time (p<0.001)	Less risk of RTA (p<0.018)
Less falls (p<0.08)	Less SE in elderly (p<0.001)

# Abuse of Z-Drugs

(Law 2005, How abusable are the Z drugs? *PharMAGazine* 6(1):1-3)

- Zopiclone and zolpidem now cheaper than temazepam (Zopiclone 7.5mg < zopiclone 3.75mg < zolpidem 5mg = temazepam 20mg < zolpidem 10mg < temazepam 10mg)
- Z-drugs less abused in UK than BDZ:
  - Zopiclone abused at 2-4x typical dose level, zolpidem abused at 40x typical dose level, zaleplon not abused for subjective effects
  - Addicts typically don't like the sedative effects they get from Z-drugs (so lower abuse potential), as tend to 'knock them out', awake alert, don't feel relaxed
  - Little or no tolerance to Z-drugs as dosing interval >> functional half life (Z-drugs have shorter half-life than any oral BDZ)

# Problems from BDZ Misuse



# Acute Toxicity Problems from Illicit and High Dose BDZ Use

- Increased risk of overdose
- Memory problems
- Risk of BDZ dependence, including fits
- BDZ seeking behaviour:
  - ‘I’ve run out & can’t get any more’
  - ‘I’ve run out and will have a fit’
  - Demanding, intimidating ...
- Dilemma for the doctor:
  - ‘To prescribe or not to prescribe’

# Overdose Risk

- Low risk if BDZ taken alone:
  - Increased if respiratory compromise
- Increased risk if taken with other sedatives e.g. amitriptyline, opioids (synergistic effect):
  - More with methadone than buprenorphine
  - PM reveals that among those who died on buprenorphine, 80% had BDZ, 50% cannabis, 50% psychotropics, 30% alcohol, 20% narcotics & 4% cocaine detected in their blood

# Memory Problems Associated with Therapeutic BDZ Use

(Lucki and Rickels 1986, 1988)

- Memory problems routinely occur in people who take BDZ
- Incomplete tolerance occurs to memory effects even after long term use
- Difficulty acquiring new information at therapeutic doses of BDZ:
  - Occurs with every dose taken
  - A specific deficit in remembering recent events
  - Also interferes with concentration & attention

# Transient Global Amnesia with High Dose BDZ Use

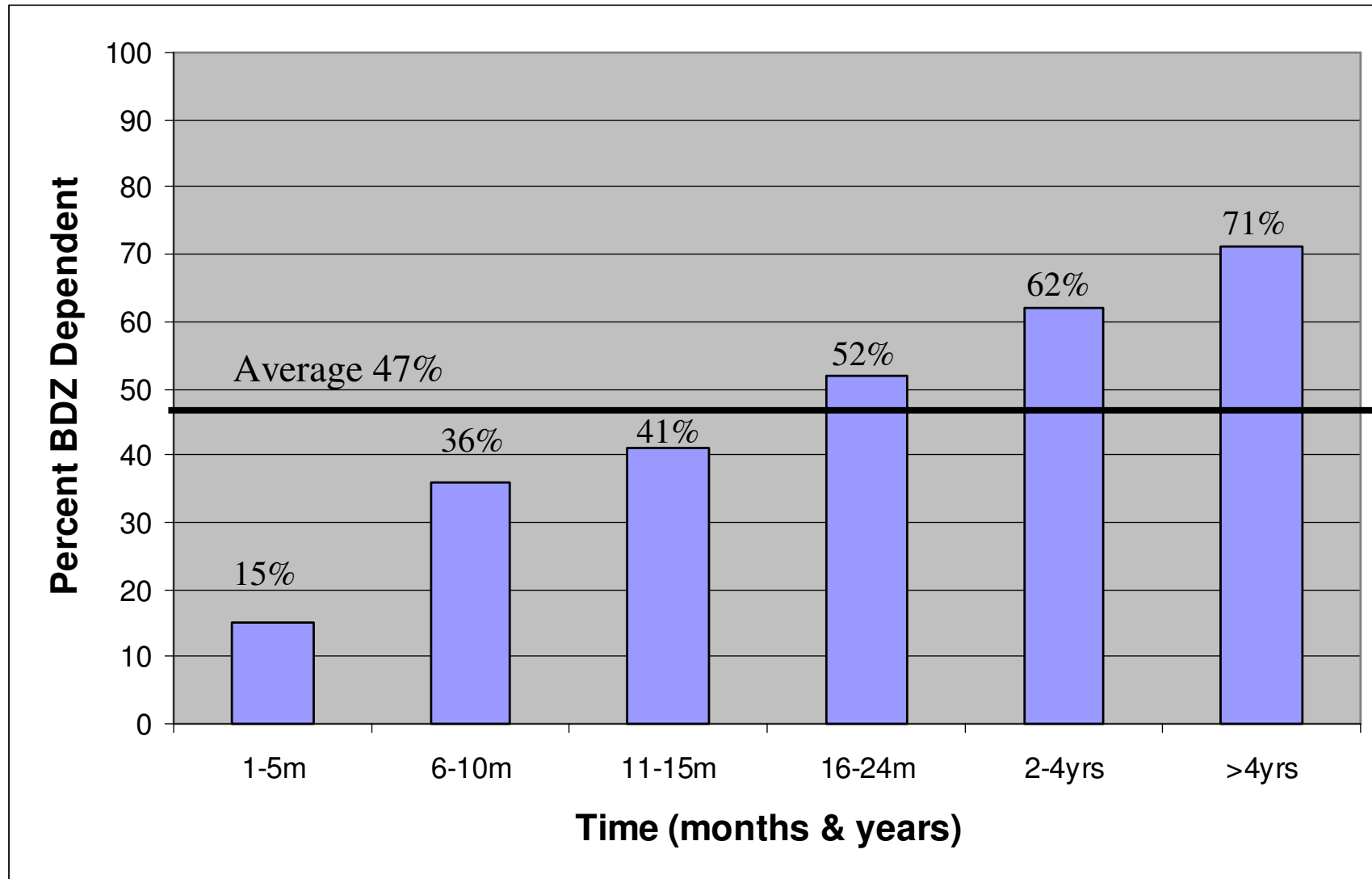
- Loss of memory for previous day's events, although behaving normally at the time:
  - Feel 'floaty', warm & comfortable with no worries
  - Feel invincible & invisible, so may commit crimes openly but not remember ('Rambo syndrome')
  - Pt may decide to stop BDZ use because of it
  - Flunitrazepam (Rohypnol) used in date rape
- Similarly with high dose zopiclone (30mg+)
- ? Similar to 'alcoholic blackouts'
- Utilised for premedication & anaesthesia

# Fits/Seizures

- May occur if high doses stopped abruptly
  - Only if physically dependent
- Assess cause of fits:
  - Medical cause – epilepsy etc
  - Alcohol withdrawal
  - Stimulant use – crack, amphetamines
  - BDZ use – have high doses been stopped abruptly
- Withdrawal symptoms develop 3-5 days after stopping diazepam due to long half-life (diazepam 2+ days):
  - Client complaining of ‘withdrawal’ within a few hours must be complaining of lack of high, anxiolytic or sedative effect
  - Look for signs of BDZ withdrawal e.g. sensitivity to light
- If physically dependent and fits:
  - Up to 30mg daily to prevent withdrawal or fits (No need to give equivalent ‘replacement’ doses to prevent withdrawal)

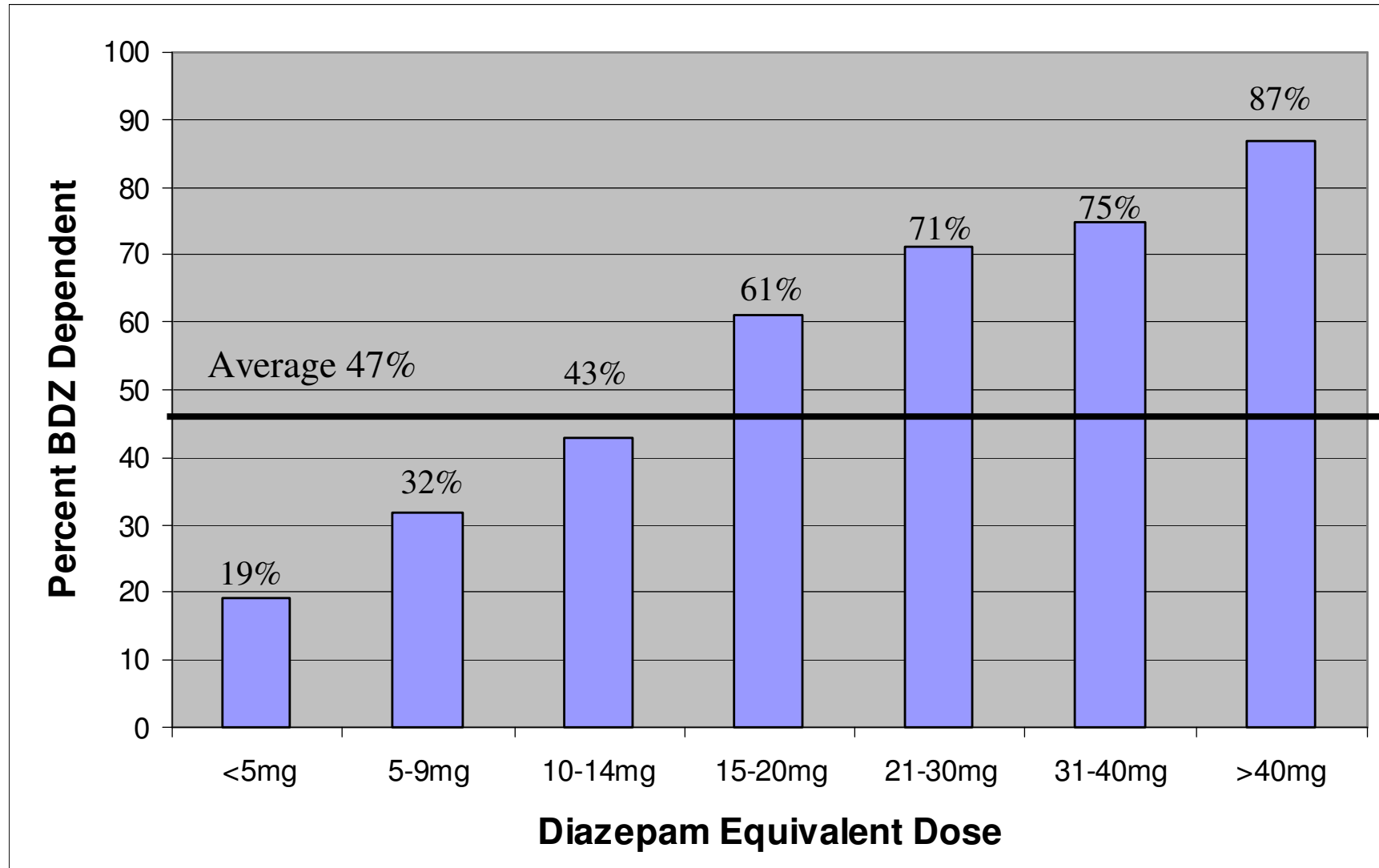
# Rates of BDZ Dependence & Length of Use

(De las Cuevas et al 2003, Canary Islands, N=1048)



# Rates of BDZ Dependence by Dose Used

(De las Cuevas et al 2003, Canary Islands, N=1048)



Treatment  
of High Dose &  
Illicit BDZ Users



# British Assoc for Psychopharmacology

## Recommendations: Illicit BDZ Misusers

(Lingford-Hughes, Welch & Nutt 2004, [www.BAP.org.uk](http://www.BAP.org.uk))

- Management less clear than therapeutic users.  
No robust evidence supporting maintenance
- Cannot recommend maintenance (D), but may reduce illicit BDZ use in some clients (D)
- Appropriate studies have yet to be performed
- Carbamazepine may be used instead of BDZ for withdrawal symptoms from high doses of BDZ (C) based on descriptive studies (inpatients)

Recommendations from descriptive studies (C) or expert opinion (D) or extrapolated from higher level evidence

# Prescribing to Illicit BDZ Users

The DH Orange Guidelines 2007

- “Many drug misusers misuse BDZs but the majority do not require long-term replacement prescribing or high doses.” ( § 5.9.1, p.60)
- “Clinicians may be faced with request to continue a prescription for maintenance BDZs. To prevent symptoms of BDZ withdrawal, the clinician should continue the prescription but the dose should be gradually reduced to zero. Only very rarely should doses of more than 30mg diazepam equivalent per day be prescribed.” ( § 5.9.2, p.60)

# Prescribing to Illicit BDZ Users

The DH Orange Guidelines 2007

- “Good assessment & care planning – & adherence to local protocols – are prerequisites for considering prescribing BDZs. Prescribing BDZ to drug misusers requires competencies in this form of Tx & appropriate supervision. It is therefore more likely to be considered an appropriate approach in secondary rather than in primary care.”  
( § 5.9.1, p.60)
- “Longer-term prescribing of BDZs should adhere to the general principles of management, including clear indications of BDZ dependence, clear intermediate Tx goals and milestones, regular review & methods to prevent diversion.” ( § 5.9.2, p.60)

# Risks-Benefits of BDZ Prescribing in Illicit BDZ Users

- Possible problems:
  - Lack of evidence that it does any good & may do harm
  - Difficulty monitoring - urine screens don't help
  - Adding to supply on the street & risk of O/D
  - Promoting or prolonging use & dependence
- Possible benefits:
  - Helps users too dependent to stop on own:
    - Engagement, stabilisation, detox
  - Reduces contact with illicit markets
  - Diazepam can be given by daily PU (FP10MDA)

# Assessing BDZ Misusers

- Are they seeking fun or self-medication?
  - Look at pattern of use, e.g. use once daily, binge
  - Treat psychiatric problem if present
- Are they dependent on other drugs too?
  - Treat opioid addiction first, and see what happens to BDZ use
- Are they physically dependent & committed to stopping?
  - Consider a reducing BDZ script

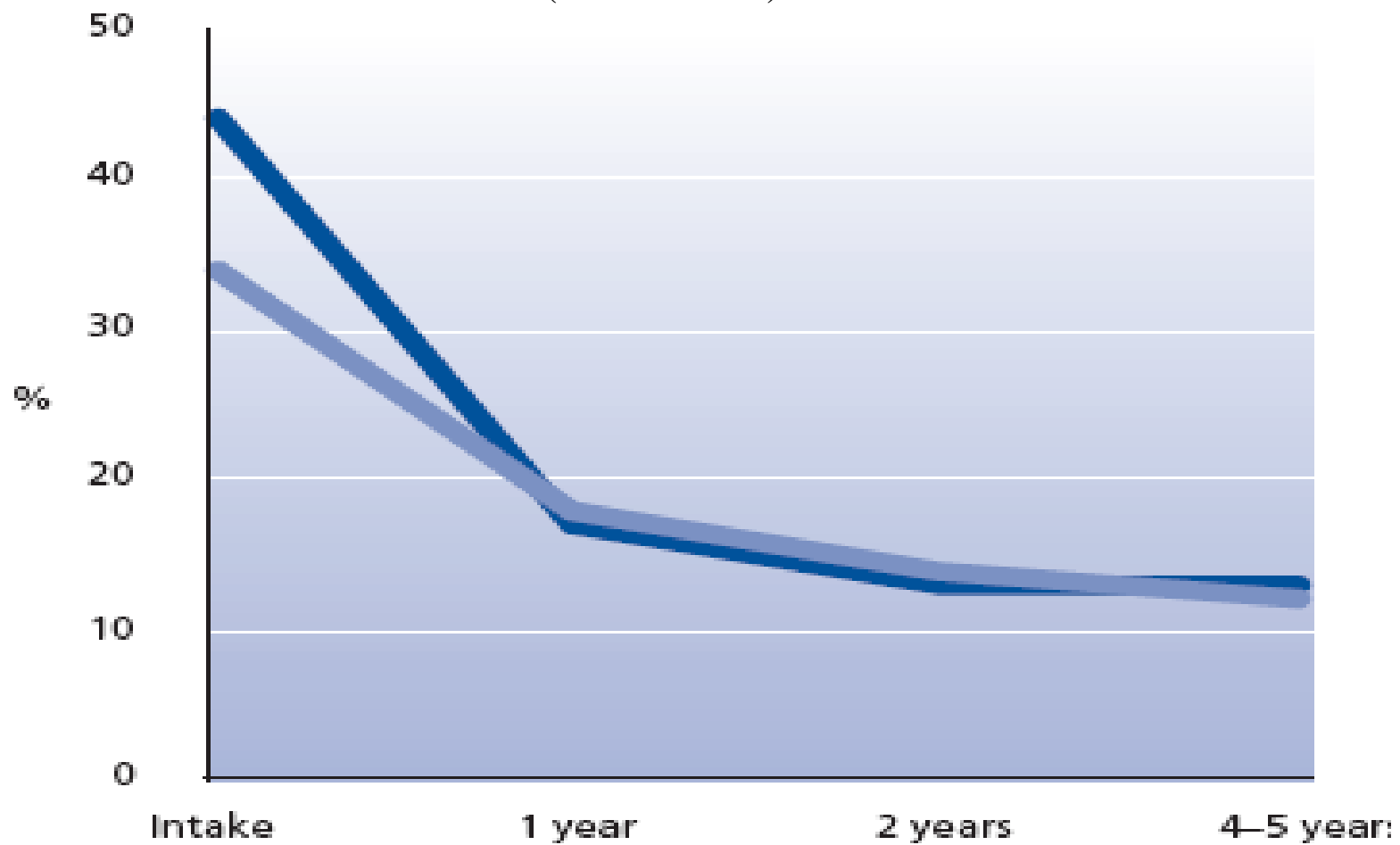
# Avoid Prescribing BDZ to Certain Patients

- Pattern of BDZ use:
  - Non-dependent users
  - Fun seekers, mind numbers, bingers
- Type of poly-drug user:
  - Opiate users not stable on opioid treatment
  - Drinkers
  - Poly-drug users, where BDZ just part of the mix
- Type of psychiatric problem:
  - Poor copers, general stress, dependent personality
  - Just for sleep or anxiety

# Evidence for Treating High Dose BDZ Users & Addiction Populations

- Rates of BDZ use decline when patients in treatment
- Few treatment studies:
  - 2 studies of maintenance (no RCT's), & 2 RCTs of detox
  - 15-30% successfully detox (½ rate of low dose users)
  - Evidence that can reduce BDZ dose effectively, but abstinence often not sustained at follow-up
- Suggests different Tx strategy required:
  - Brief stabilisation on BDZ followed by partial detox
  - Complete detox once Pts life becomes more stable
- However lack of evidence:
  - Is stabilisation helpful? Is a 2 stage process helpful?

## Regular non-prescribed benzodiazepine use (NTORS 2001)



### Key

- Residential\*
- Community\*



# Prescribing to BDZ & Opiate Users

Provide opiate prescribing only initially  
as evidence based treatment (& discuss how to control BDZ use)



Optimise opiate treatment  
counselling & psycho-social interventions, self-help, pharmacology



Reassess whether need for BDZ still exists



? Prescribe BDZ - initial stabilisation & reduction  
over 6 weeks to 6 months if controlling use & wants to stop



? Stabilise at BNF levels before completing detox

## Need to Meet FIVE Criteria Before Prescribing to Illicit BDZ Users

1. You have a least 2 BDZ positive urine screens
2. No BDZ negative urine screens in last 4 mths
3. Evidence from the history & symptoms that the Pt is physically dependent on BDZ or has the BDZ dependency syndrome
4. You believe that the benefits of treatment will outweigh the adverse effects & risks (e.g. diversion)
5. You are happy to take the clinical responsibility

# Detox of High Dose BDZ/Z-drug Users

- BDZ:
  - Start script (e.g. 20-30mg diazepam) & stabilise
  - Do not need to give equivalent dose to that used
  - Reduce gradually over say 6 months to minimise withdrawal symptoms
- Z-drugs:
  - Reduce gradually where possible
  - Expect some rebound insomnia
  - Physical withdrawal very unlikely
  - Manage psychological aspect of care (explain, reassure, support)

# The Goals of BDZ Detoxification

- Therapeutic dose users - Use a one stage process:
  - Full detoxification. 50-75% of BDZ dependent clients can be successfully tapered in the short term
- High dose Users – Use a two stage process:
  - 1<sup>st</sup> do a partial detox - High dose users typically unable to comply with detox regime. It is a clinically important treatment objective to reduce to therapeutic dose levels (30-40mg diazepam or equivalent), and allow the client to adapt to this state
  - 2<sup>nd</sup> complete the detoxification when client ready

# Determining the BDZ Starting Dose

- Convert all other BDZ to a single BDZ:
  - BDZ of choice or preferably a long acting BDZ: e.g. diazepam (D), but widely abused/rapid onset (good buzz)
  - Slower onset long acting BDZ is better, e.g. oxazepam, clonazepam, clobazam
- Dose offered is typically (after negotiation!):
  - Therapeutic & low dose users: 50-100% of stated dose
  - Moderately high dose users: 30-50%, e.g 30-40mg D
  - Very high dose users: 10-30%, e.g. rarely give up to 60mg D
- Doses > 60mg diazepam only if exceptional indications e.g. fits, already prescribed this dose daily

# Strategy for Starting a BDZ Dose in High Dose & Illicit Users

- Biological step: If physical dependence give minimum dose to prevent BDZ physical withdrawal - negotiate
  - Only requires a moderate dose even if high usage claimed
  - Give none if not physically dependent
- Psychological step: Give dose to achieve psychosocial goal. Even if not dependent, may occ. give BDZ to achieve stopping contact with illicit drug markets etc.
  - Negotiate rough dose level with the client, as the minimum they can get away with to avoid having to buy illicit supplies
  - After a day or so negotiate a small increment (5-10mg diazepam) to terminate on top use and contact with illicit markets and ensure client feels “happy”/engaged in Tx

# Dealing with BDZ Detox Problems

- Difficulty coping with BDZ withdrawal Sx:
  - Use longer  $\frac{1}{2}$ -life BDZ e.g. diazepam, clonazepam
- Liking BDZ too much to reduce it:
  - Use slow onset BDZ e.g. oxazepam
- Using different amounts each day or binging:
  - Increase frequency of pickup, even to daily pickup on interval FP10 scripts (or increase supervision by relatives, or pharmacists if willing)

# Dealing with BDZ Detox Problems 2

- Rebound anxiety/insomnia:
  - Reassure (and prepare at start of treatment)
- Continuing anxiety/depression:
  - Treat psychiatric problems more effectively
- Difficulty coping with stress:
  - Increase psychosocial support
- Difficulty sleeping:
  - Short term → Reassure/zopiclone
  - Long term → Sleep hygiene etc



# Conclusions

- Limited evidence on prevalence rates & how best to treat
- Prevalence higher in adolescents, young men, older women, opiate users, prisoners
- A challenging group to treat
- Assess users carefully before considering prescribing
- Prescribe reducing BDZ prescriptions in limited situations & if highly motivated:
  - May need 2 stage detox