



**Guidance on Prescribing Benzodiazepines to
Drug Users in Primary Care
Updated October 2005
Dr Chris Ford, Kay Roberts & Jean-Claude Barjolin**

Introduction

Benzodiazepines were first introduced in clinical practice in the 1960's and soon became the treatment of choice for anxiety and insomnia. They have replaced barbiturates because they were thought to be reliable, with fewer unwanted effects, be less addictive and safer in overdose. During the 1970's & 80's they were widely prescribed by clinicians, although addiction problems were rapidly being recognised. More recently, it has become clear that illicit benzodiazepine use, particularly by opioid users, is prevalent and a major problem for users in and out of drug treatment. This group is now the largest group of users of benzodiazepines that need help with this problem (1). Up to 90% of people attending drug treatment centres reported benzodiazepine use in a one-year period (2) and almost half had injected them (4). It is a problem in many countries with high lifetime use and a high prevalence of benzodiazepine abuse in methadone maintenance patients (3). High doses of prescribed and illicit benzodiazepines are taken and users become extremely tolerant to the sedative effects (5). They are taken because of their own effects of intoxication, to enhance a primary drug or in order to counter early withdrawal symptoms from other drugs. Several studies found that a large majority of patients reported that diazepam increased or boosted the effects of their methadone dose (6, 7). Studies have found no evidence of any pharmacokinetic interaction between methadone and diazepam, one study however, found a measurable increase in some physiologic and subjective opioid effects when the two drugs were administered concurrently in methadone maintenance subjects (8)

Methadone maintenance patients using non-prescribed benzodiazepines have been reported to be on higher methadone doses, as well as exhibiting more HIV/HCV risk-taking behaviour, greater poly-drug use, higher levels of psychopathology and social dysfunction (4, 9, 10). However, attending treatment has been effective in reducing non-prescribed benzodiazepine use (11). Some GPs are still more comfortable with prescribing benzodiazepines than methadone to problem drug users, whereas the reverse should be true. The evidence for the value of methadone maintenance prescribing in heroin / opioid dependency is overwhelming. There is still no 'gold standard' treatment for benzodiazepine dependency and no such evidence for the value of substitute prescribing of benzodiazepines (12). Short term prescribing of benzodiazepines may have some benefit in supporting drug users to control their intake of benzodiazepines and stabilise their lives. The benefits of long term prescribing of benzodiazepines to drug users are less certain. Drug users in treatment often continue to buy benzodiazepines in addition to their prescribed drugs and often continue to use these chaotically regardless of how much is prescribed. We can offer support and advice to benzodiazepine users so they can control and reduce their use. This does not always need to include the prescribing of substitute benzodiazepines.

Possible Harm of prescribing benzodiazepines to drug users:

- There is some evidence that long term prescribing of benzodiazepines may lead to increased risk taking and cause harm (9).
- There is a little evidence of cognitive impairment in those using high (greater than 30mgs of diazepam or equivalent) doses of benzodiazepines.
- Benzodiazepines have also been sited as important in combination with methadone and buprenorphine and / or alcohol in drug related deaths.
- There is evidence that many people continue to buy BZs on top of any prescription given
- Use of benzodiazepines in methadone maintenance patients are associated with adverse factors: poor physical and physiological health, increased injecting, increased risk behaviours, poor social functioning (4, 9, 10), but this may be to do with the people who take them, rather than the drug itself

Possible Value of prescribing benzodiazepines to drug users:

- Benzodiazepine use is a large problem in many drug users
- Many people presenting to services have a long-term dependence problem with benzodiazepines and ignoring it does not make it go away
- Some practitioners feel that some people settle better on combination of methadone and diazepam because of the 'opiate-enhancing' effect yet there is only a little evidence to support this
- It may reduce alcohol relapse in a few individuals

For and against prescribing long-term benzodiazepines prescribing to poly drug users

FOR

Too dependent to stop – relieves withdrawal problems
Control existing BZ usage, long-acting substitute available
May help avoidance of street drugs- encourage into treatment
Reduced contact with illicit drug markets
May have some effect as symptomatic treatment in people with poor coping skills
Tolerance occurs to all adverse effects with chronic use (except memory impairment at peak plasma levels)

AGAINST

Little evidence to promote its prescribing
Promotes dependence – most withdrawal problems can be overcome
Risk of erratic or dangerous usage (BBV more common in poly-BZ use)
Associated with worse outcomes in some studies
Prescribing can set unsatisfactory precedent
Memory impairment occurs at time of peak plasma level
Use of rapid onset BZ (e.g. diazepam) gives a high, which promotes addiction processes

Substitute prescribing of benzodiazepines:

The available evidence is poor as most research on the use of benzodiazepines has been undertaken on psychiatric patients:

- Short term (less than 6 months) prescribing of 30mgs or less may have some benefit in supporting drug users to control their intake
- Long term prescribing of BZ is of uncertain benefit and may actually be harmful
- Long term of more than 30mgs may cause cognitive impairment
- Support can help the patient to control their benzodiazepine use
- Not all users become dependent
- But many do exhibit classical withdrawal symptoms when benzodiazepines are stopped, less than 50% in one in-patient study (13, 14)
- Detoxification can start at much lower doses than reported use without ill effect
- Reduction from 60mgs over 6 days – no fits, even if had fits previously (15)
- As yet no controlled studies of additional BZ prescribing in drug users to guide us (16)

Why drug users use benzodiazepines?

1. Anxiety.
2. Insomnia (a real problem when trying to stabilise or reduce drug use).
3. To potentiate the effect of methadone or other opiates – 'opiate-enhancing' effect (8) increasing the buzz from use. Typically BZ taken at same time as the opiate to get this effect.
4. To counteract the non-euphoric effect of methadone.
5. Depression, many drug users feel they 'help' their mood.
6. To help come down from amphetamines, ecstasy, crack cocaine or cocaine.
7. To reduce 'voices in the head'.

Before starting a prescription for benzodiazepines

In the absence of evidence of benefit and with increasing concern about the possible harm of prescribing benzodiazepines in the long term:

- Great care should be taken before deciding to initiate a prescription for substitute benzodiazepines
- A full assessment, including at least two urine tests must be undertaken
- Identify clear goals e.g. stopping use on top, stopping contact with illicit markets, stabilising, reducing to therapeutic dose levels

- Should normally be for a short time (no more than 6 months) and with a clear goal in mind of what is to be achieved by prescribing.
- Identify a clear way in which progress towards these goals can be assessed, e.g. goal reached within an agreed time frame

Only consider prescribing benzodiazepines if (17):

1. The patient has been stabilised on substitute opioid first.
2. The patient has attempted some control of their illicit benzodiazepines and they want to address their drug use.
3. The goals of the prescribing have been established e.g.:
 - a) What changes the drug user wishes to make to the way they use drugs
 - b) What changes they want to make to other areas of their life
 - c) How do they think a prescription might help them achieve these changes (e.g. to stop using street drugs, to improve relationship with partner / family)
4. Both doctor and patient are clear that substitute prescribing could help to achieve these goals
5. Benzodiazepines are taken daily. If misuse/running out early occurs, use daily scripts.
6. At least two positive urine drug screens confirming the presence of benzodiazepines. (With heavy use these can stay in the urine for 3-4 weeks).
7. Confirmation of dependence from history (drug diary) and withdrawal symptoms.

PROBLEMS (to the prescriber and to the using patient)

1. There is a high risk of dependence - benzodiazepines are addictive (18).
2. Coming off benzodiazepines is potentially more difficult than opioids (due to multiple withdrawal symptoms, which often resemble the original symptoms they were taken for, such as anxiety, restlessness and insomnia).
3. Withdrawal symptoms occur in daily chronic users. About a third of drug users have significant symptoms for between 10 months and 3.5 years. Many users are binge users and tend to suffer less frequent withdrawal symptoms.
4. Risk of withdrawal symptoms increases with length of use.
5. Withdrawals worse if high doses have been used (13).
6. Withdrawals less severe if tapered withdrawal.
7. Tablets can be crushed and injected - risk of tissue damage and risk of death.
8. Some evidence of (reversible?) cognitive damage from high dose prescribing (>30mgs diazepam) over a long period.
9. Unwanted effects and long-term problems need to be explained to the patient, especially emotional suppression and the development of a learning deficit/reduced coping ability.
10. Can be used to exchange for other drugs. They have 'street' value.
11. They are not licensed for maintenance treatment, only for detoxification.

Some GPs are more willing to prescribe benzodiazepines than methadone:

- BUT:** Methadone or buprenorphine may be what patient wants and needs.
 Substituting opioids with benzodiazepines does not prevent illicit opioid use.
 Doctors should be **LESS** willing to initiate benzodiazepine prescribing than opioids.
- BUT:** Many drug services, both primary and secondary services will not prescribe any benzodiazepines – ignoring the problem does not make it go away.

WHAT TO PRESCRIBE? (19)

1. Only prescribe one benzodiazepine at a time.
2. If established benzodiazepine problem, diazepam is the drug of choice.
3. If the patient is using more than one benzodiazepine change to one preparation.
4. Change all benzodiazepines to **diazepam** – It is harder to achieve stability on shorter acting drugs (such as temazepam).
5. Always start low and work up to a maximum of 30mgs of diazepam

How to change one benzodiazepine to another

1. Convert all other benzodiazepines to the equivalent of diazepam.
2. Make the change all in one go, very rarely, if the patient is very anxious, it can be done over 1-2 weeks.
3. Prescribing of any other benzodiazepines is actively discouraged and should only be done in very rare instances.

Conversion of equivalent BZ

Diazepam 10 mgs = (e.g. Valium)	Temazepam 20mgs Nitrazepam 10mgs Lorazepam 1mg (Ativan) Oxazepam 30mgs (Serenid-D) Chlordiazepoxide 20-30mgs (Librium) Flurazepam 30mgs (Dalmane) – not on NHS prescriptions Flunitrazepam 1mg (Rohypnol) – not on NHS prescriptions
------------------------------------	--

How Much to Prescribe?

- Aim at the lowest dose possible that will prevent withdrawal symptoms.
- Start at 10-30mgs daily of diazepam.
- Doses above 30mgs diazepam daily should rarely be used.
- All changes should be done working with the patient as lack of prescribing flexibility can reduce success for some patients in this difficult area (20).
- May need in-patient stabilisation or detox for large doses.
- Divide the daily dose, keeping some of the dose for helping to sleep at night.
- The patient should not be intoxicated, 'stoned' or drowsy during the day.

Benzodiazepine reductions:

- Usually short-term (maximum 6 months).
- Give the evidence to the patient and explain the risks of long-term prescribing.
- Establish at the beginning that this is short term and will be reduced and stopped.

How to reduce:

1. Change to the equivalent dose of diazepam
2. Reduction can be quicker if shorter use
3. If on more than 60 mg of diazepam, working with the patient, reduce by 5-10mgs/fortnightly
4. If on between 30-60mgs reduce by 5mgs/fortnightly
5. If on between 20-30mgs reduce by 2-5mgs/fortnightly
6. If on less than 20mgs reduce by 2 mgs/fortnightly
7. When down to 5 mgs reduce by 1 mg every 2 weeks. (NB can use ½ of 2mg tablet or oral solution of diazepam 2mg/5ml or 5mg/5ml)
8. Reduction may need to be slower if experiencing withdrawals.
9. While reducing, counselling, support groups, relaxation techniques and herbal teas can be helpful

Dispensing

1. Always begin with daily dispensing – as of April 2005 in England, can prescribe for instalment dispensing on FP10(MDA). This is already available in Scotland and Wales.
2. While patients continue on daily substitute opioids then remain on daily benzodiazepines.
3. Once stable can consider move to x3 weekly if appropriate.
4. If prescriptions have been lost or if the drugs have been used before the next prescription is due patients should be moved to daily scripting. If this is recurrent, then the scripts should not be repeated.

Other Drugs

If insomnia continues to be a problem first try all natural methods, such as herbal teas, hot drinks and relaxation techniques before. Taking part of the opioid substitute at night can also help.

Anti-depressants should only be used if underlying depression and not for sleep alone. However they must be used with extreme care as they, particularly amitriptyline and dosulepin, have been frequently found as an additional drug in drug-related deaths.

- Preferred antidepressant drugs: trazodone 150mgs nocte or mirtazepine 15mg.
- There are increasing reports of misuse with zopiclone (also zaleplon and zolpidem). All of these are more expensive than the benzodiazepines and should not be used. NB Zolpidem has been added to Schedule 4 Part 1 of Misuse of Drugs Regulations because of world-wide (especially in Europe) misuse, zopiclone and zaleplon are not controlled

MAINTENANCE PRESCRIBING

Maintenance prescribing of benzodiazepines has not been shown to have any definite medical value (unlike methadone) and is rarely justified (12).

It was hoped that it would help the drug user to achieve goals such as stabilisation of drug use and lifestyle and removal from the illicit drug market, but there is little evidence for this. There is poor evidence of harm reduction and may be some evidence of increased risk:

1. Dependence and tolerance are significant problems with these drugs
2. Withdrawal symptoms are worse with longer use (13)
3. HIV and other infections are more common in people using opioids plus benzodiazepines and there is little evidence that these risks reduce if all drugs being used are prescribed (18).
4. Using benzodiazepines prescribed or not appears to lead to higher rates of risk behaviour (9,10)
5. Real risk of diversion onto the illicit market
6. Preparations (especially temazepam) not meant for injecting may be injected

But it has to be remembered that:

1. Benzodiazepine use is a large problem, especially for poly drug users: 90% of attendees at treatment reported use in a 1 year period (2).
2. Many people presenting to services have a long-term dependence problem with benzodiazepines and ignoring this problem will not make it go away.
3. They may well have been self-medicating using benzodiazepines to improve their mood or improve their coping skills (16). These are however not appropriate reasons to use benzodiazepines – psychological treatment is the treatment of choice.
4. There is a long-acting variety available (diazepam).
5. It may reduce alcohol relapse in a few individuals.

Who might benefit from longer-term benzodiazepine prescribing?

A few people may benefit from being left on a small dose (*no more than 30mgs diazepam daily*) and this may include:

- Those with alcohol problems who have come off alcohol using benzodiazepines and who find it difficult to stay off alcohol unless they are on a small dose of benzodiazepines. In this case continuing to prescribe e.g. diazepam may cause less harm than stopping the prescription. The benzodiazepine script should however be stopped if the patient continues to drink on top of the script, for safety reasons.
- A few people who have a long-term opioid and benzodiazepine problem and do not stabilize on opioid substitution medication alone.

REDUCTION

Because of the long-term effects reducing off benzodiazepines must be considered in regular reviews. Concurrent psychiatric problems may come to light when the dose is reduced. Co-morbidity (dual diagnosis) is increasingly recognised in poly-drug users and needs to be considered and managed appropriately.

SUMMARY: Benzodiazepine use is a large problem in poly-drug users. They are often used to reduce anxiety, help sleep or counter the negative effects of other drugs. They are addictive and when coming off can cause significant withdrawal symptoms. Short term prescribing of benzodiazepines may have some benefit in supporting drug users control their intake of benzodiazepines when first coming into treatment and stabilise their lives. The benefit of long term prescribing of benzodiazepines to drug users is more questionable. Greater than 30mgs of diazepam has been shown to risk increased harm and may cause cognitive impairment. We need to think carefully about the goals that we hope to achieve before starting a prescription of benzodiazepine, even a short-term reduction.

References:

1. Oyefeso A, Ghodse H, Williams H 1996 Prevalence and Pattern of benzodiazepine abuse and dependence among patients in a methadone maintenance detoxification programme. A repeated cross-sectional analysis. *Addiction Research* 4 (1): 57-64
2. Perera KM, Tulley M, Jenner FA 1987 The use of benzodiazepine amongst drug addicts. *British Journal of Addiction*, 82, 511-515.
3. Strang J, Griffiths P, Abbey J, Gossop M 1994 Survey of use of injected benzodiazepines amongst drug users in Britain *British Medical Journal* 308, 1082
4. Gelkopf M, Bleich A, Hayward R, Bodner G, and Adelson M 1999 Characteristics of benzodiazepine abuse in methadone maintenance treatment patients: a 1 year prospective study in an Israeli clinic. *Drug and Alcohol Dependence* 55: 63-68
5. Seivewright N & Dougal W. Withdrawal Symptoms from High Dose Benzodiazepines in Poly Drug Users'. *Drug & Alcohol Dependence* 1993 32:15-23.
6. Budd R.D., Walkin, E., Jain, N.C. and Sneath, T.C. (1979) Frequency of use of diazepam in individuals on probation and in methadone maintenance programs. *Am. J. Drug Alcohol Abuse*, 6, pp.511-514.
7. Stitzer M L, Griffiths R R, McLellan T A, Grabowski J and Hawthorne J W 1981 Diazepam use among methadone maintenance patients: patterns and dosage. *Drug and Alcohol Dependence* 8: 189-199
8. Preston K L, Griffiths R R, Stitzer M L, Bigelow G E and Liebson I A 1984 Diazepam and methadone interactions in methadone maintenance. *Clinical Pharmacology and Therapeutics* 36: 534-541
9. Bleich A, Gelkopf M, Schmidt V, Hayward R, Bodner G and Adelson M 1999 Correlates of benzodiazepine abuse in methadone maintenance treatment. A 1 year prospective study in an Israeli clinic. *Addiction* 94 (10): 1533-1540
10. Darke S, Swift W, Hall W and Ross M 1993 Drug use, HIV risk-taking and psychosocial correlates of benzodiazepine use among methadone maintenance clients. *Drug and Alcohol Dependence* 34: 67-70
11. Gossop M, Marsden J, Stewart D and Rolfe A 1999 NTORS: Two year outcomes. The National Treatment Outcome Research Study: Changes in substance use, health and crime: Fourth Bulletin. Department of Health: London
12. Drug Misuse and Dependence Guidelines on Clinical Management, Department of Health, 1999.
13. Seivewright N, Dougal W, Withdrawal symptoms from high dose benzodiazepines in poly drug users. *Journal of Substance Misuse*, 3, 170-177
14. Williams H, Oyefeso A, Ghodse AH 1996 Benzodiazepine misuse and dependence amongst opiate addicts in treatment. *Irish Journal of Psychological Medicine*, 13, 62-4
15. Scott R 1990 The prevention of convulsions during benzodiazepine withdrawals. *British Journal of General Practice*, 40, 261
16. Seivewright N 2000 Community treatment of drug misuse: more than methadone Cambridge Press 70 -9
17. Landry M.J., Smitt D.E., McDuff D.R., Baughmann O.L., Benzodiazepine Dependence and Withdrawal: Identification and Medical Management. *Journal of the American Board of Family Practitioners* 1992; 5:167-75.
18. Darke S. The Use of Benzodiazepines amongst Injecting Drug Users'. *Drug & Alcohol Review*. 1995 13:63-9.
19. Primary Care Facilitator Team (HIV/Drugs) Managing Drug Users in General Practice 4th Edition, 2003
20. Vorma H. et al. 2002, Treatment of out-patients with complicated benzodiazepine dependence: comparison of two approaches. *Addiction* 97:851-859

Dr Chris Ford SMMGP GP Advisor chrishelen.ford@virgin.net

SMMGP Production www.smmgp.org.uk

**SMMGP, c/o Bolton, Salford and Trafford Mental Health NHS Trust, Bury New Road,
Prestwich, Manchester M25 3BL**

Currently a group of practitioners is being formed to write more extensive guidance on the prescribing of benzodiazepines in all groups of patients in primary care. As this is an extensive piece of work it is expected to take at least 2 years. If you wish any evidence to be considered or you wish to see drafts please let us know
chrishelen.ford@virgin.net or Mark Birtwistle on mark@smmgp2.demon.co.uk