Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice

Chris Ford and Fergus Law

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Acknowledgement

The development of the *Guidance for the use and reduction of misuse of benzodiazepines and other hypnotics and anxiolytics in general practice*

It has been a long, often difficult and winding road to get to the point of this guidance seeing the light of day. It is perhaps unsurprising because benzodiazepines are probably the drugs that cause more disagreement between different health professionals and different users and also between these groups. Moreover, there are very large holes in the evidence base - which were even bigger at the time of more common use 30 years ago - when benzodiazepines were found to work well in the short term and offered a "quick fix" for some patients.

In October 2005 I co-wrote and released a brief paper "*Guidance on prescribing benzodiazepines to drug users in primary care*". It was very well received in the UK and internationally. Requests poured in asking us to extend the guidance to all patients in general practice, as benzodiazepines were causing (and still cause) many headaches to both prescribers and users.

A working party was formed to take on the task of expanding the scope of the guidance in late 2006. But as many of you will know - writing coherent guidance by committee is virtually impossible! Many drafts were circulated but differences in style and lack of consensus dragged matters out. More and more time elapsed between each draft, the guidance got longer and more repetitive. Also, negative interest from some groups who felt they were misrepresented in the guidance diverted our attention and for a while we lost focus.

A new way forward was found and after a complete re-write in 2010 Fergus Law and I had a working draft that could be shared. Slowly over the next 3 years we continued to work on the guidance. Because it is such a difficult area, many compromises have had to be made. Where there is no - or conflicting - evidence we have had to use clinical experience.

Many wonderful people have helped us on the way, some acknowledged, others not wanting to be acknowledged. We have tried for the past year to have the guidance endorsed by various bodies but so far we have not been successful. In the meanwhile, once again many people have asked for copies, which we have provided. It has been well received overall, so rather than let it go out of date at this stage we have decided to make it available on the internet. You may not agree with it all, but we hope you find it helpful.

Dr Chris Ford, July 2014

SUMMARY

Section 1: Introduction

- Benzodiazepines and similar drugs such as Z-drugs are widely prescribed in clinical practice short-term for a variety of conditions and their anxiolytic and hypnotic efficacy has been well established
- The combination of effectiveness and risks of long-term use is the reason why benzodiazepines and similar drugs are so exasperating to deal with in clinical practice.
- With benzodiazepines, there is often a wide divergence between published guidelines and clinical practice, which says they should only be prescribed for maximum of 2-4 weeks but many people are prescribed for much longer
- The number of people taking prescribed benzodiazepines worldwide is enormous and over 1 million people in the UK are on long-term
- Up to half of long-term users have difficulties in stopping benzodiazepines because of withdrawal symptoms
- Over the last decade the level of combined benzodiazepine and Z-drug prescribing has remained stable but that of benzodiazepines used for anxiety has steadily risen, as has Z drugs replacing BZ for sleep disturbances

Section 2.1 Properties and clinical actions

- There are a large number of benzodiazepines available, all have similar properties, although their potency greatly varies
- Benzodiazepines are rapidly and fully absorbed orally, leading to peak effects within a half-hour to 2 hours of ingestion
- The more fat-soluble drugs (e.g. diazepam) are absorbed faster and enter the central nervous system more rapidly hence are generally associated with increased abuse potential.
- Those with long half-lives such as diazepam and nitrazepam are more likely to produce residual effects such as sedation and falls the next day.
- Rapid-onset drugs are associated with 'good' subjective effects, and therefore result in psychological reinforcement every time they are taken and higher dose leads to a better 'buzz'.
- The actions of benzodiazepines are mediated by enhancing the activity of gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter that transmits messages from one neuron to another. Benzodiazepines bind to receptors on the GABA-A receptor complex and can directly or indirectly affect almost every part of brain function unselectively. This "inhibitory" effect is responsible for the characteristic effects of sedation, amnesia and motor incoordination.
- Tolerance is a physiological reaction and the body responds so the original dose of the drug has progressively less effect and a higher dose is required to obtain the original effect.
- The rate of development of tolerance may vary for different drug effects, such as relief of anxiety, sedation and pleasure, can develop at different speeds, and can vary between individuals.
- Many different people of all ages and both genders use benzodiazepines. They cover a spectrum of people ranging from therapeutic users to pleasure-seekers.

Section 3 Treatment of insomnia, anxiety

- Insomnia is an important, common, usually long-term health problem that requires accurate diagnosis and effective treatment and anxiety symptoms may range from mild and transient without daytime functional impairment, to severe and persistent causing significant distress.
- Treatment for both should start with addressing underlying problems and then using: talking therapies, cognitive behavioural therapies and self-help.
- Drug treatment can include benzodiazepines, Z-drugs and SSRIs but drugs should not be first-line treatment for most occasions.
- They may be indicated in very few specific situations such as an acute crisis with a clear endpoint or a predicted acute crisis.
- Benzodiazepines should be used in the lowest dose and for the shortest time, maximum 2-4 weeks.
- Benzodiazepines and other similar drugs are not indicated for the long-term treatment of anxiety or insomnia, unless in rare cases where the patient has been proven to have treatment-resistant anxiety or insomnia.
- The use of benzodiazepines is inappropriate to treat short-term mild anxiety.
- Benzodiazepines primarily relieve and suppress symptoms, rather than being curative for any disorder.
- The “Z” drugs were developed as hypnotics to overcome the side effects associated with benzodiazepine therapy, although their potential to cause tolerance, dependence and withdrawal symptoms was known from the beginning
- Melatonin can be used for insomnia in adults aged 55 and over for up to13 weeks.
- Caution must be used when prescribing benzodiazepines, Z-drugs and other related drugs to any patient, but more so when there is a current or past history of substance abuse or personality disorder.
- Having once started it is harder to stop and hence the prescriber and the patient must have a plan for not using longer than 2 – 4 weeks or use very intermittently.
- Discuss fully before issuing short-term that it is one-off, the risks of driving etc, and explain long-term risks
- Prescribing for patients with established benzodiazepine dependence, is more controversial, and abrupt withdrawal of prescribed benzodiazepines carries significant risks

Section 4 Adverse effects and specific problems with long-term use

- Benzodiazepines and related drugs are usually effective when first prescribed and nearly all the disadvantages and problems come from long-term use.
- These can be associated with considerable physical, mental and social health problems and hence long-term use should be avoided.
- Relapse can occur with all drugs of dependence, but is low with benzodiazepines.
- With slow reduction and psychological support, most patients lose their anxiety, panics, agoraphobia etc.
- Increased anxiety can be caused by the benzodiazepines or when reducing long-term use.
- Long-term use of benzodiazepines has been associated with long-term cognitive effects, memory impairment, emotional blunting, weakening of coping skills and amnesia, which gradually disappear in most people 6-12 months after stopping.
- Long-term benzodiazepine users will sometimes develop depression, for the first time after prolonged use, which will resolve within 6 months or a year of stopping the drug.
- Benzodiazepines may also aggravate depression and can precipitate suicidal tendencies in depressed patients

- Benzodiazepines occasionally cause paradoxical excitement with increased anxiety, insomnia, nightmares, and hallucinations at the onset of sleep, irritability, hyperactivity or aggressive behaviour.
- Use of benzodiazepine and Z-drug hypnotics is associated with an increased risk of many physical health conditions and death.
- Long-term use can cause withdrawal symptoms in many people – between 30 and 45%.
- Withdrawal symptoms can take almost any psychological and / or somatic form, but can be considered as falling into three main groups: anxiety symptoms, such as anxiety and agitation; distorted perceptions such as abnormal body sensation and major incidents such as fits, which are all rare.
- The risk of withdrawal symptoms increases with longer use and higher doses and use of high-potency benzodiazepines, in patients with chronic psychiatric and personality problems and those with chronic physical health problems.
- A history of current or past alcohol or other sedative-hypnotic dependence, or a family history of these is also significant.
- The protracted withdrawal syndrome occurs in a minority (up to 15%) of patients who develop a post-withdrawal syndrome on detoxifying from benzodiazepines. Most have taken benzodiazepines for many years.
- Withdrawal is possible in most patients who are dependent on benzodiazepines once problems related to prolonged use of benzodiazepines and other drugs are explained and discussed. Consideration needs to be given as to when and how to detoxify and extra help and services may be needed.
- Remember to ask about alcohol, as some patients may simply substitute alcohol for the benzodiazepine
- Before starting a reduction tackle any underlying problems, ensure any physical or psychiatric health problems treated and give the patient information about the problems of long-term benzodiazepine use and explain the process of withdrawal and possible effects.
- Tailor the dose reduction to the individual and taper it. There should be no hurry
- Assess the need for additional support and therapies and monitor frequently enquiring about general progress and withdrawal and rebound symptoms.
- If patients experience difficulties with a dose reduction, encourage them to persevere and suggest delaying the next step down. Do not revert to a higher dosage.
- If withdrawal symptoms might be a problem, consider substitution of short- or medium-acting benzodiazepines by long-acting compounds (diazepam)
- There are no drugs that can act as a substitute for benzodiazepines and are generally best avoided. Rarely and in certain circumstances antidepressants, beta-blockers, mood stabilizers, melatonin can help with some symptoms.
- The decision to prescribe longer-term benzodiazepines should be rare and made with care. If patients are prescribed long-term benzodiazepines, they are inevitably put at risk of all the negative effects including cognitive impairment etc.
- Unfortunately, most often, long-term benzodiazepine use results from inadvertent continuation of short-term prescriptions and started many years ago before all problems of their long-term use were known

Part 2 Section 5

- People of all ages and both genders use and misuse benzodiazepines, for many different reasons and there is much commonality of use and treatment for long-term use but there are some specific problems in specific groups including: patients with a mental health problem, the “therapeutic dose” users and people who tend to use high-doses, may use illicit benzodiazepines and other illicit drugs and / or alcohol are seeking pleasure.

- About half of the population does not find the effects of benzodiazepines either positive or reinforcing.
- Benzodiazepines are used much less in the treatment of mental illness than they used to be but are still prescribed extensively, particularly at the time of acute admission. Benzodiazepines are used in the treatment of acute agitation or behavioural disturbance, whether due to psychosis, delirium or other causes.
- Benzodiazepines have proven value in alcohol detoxification. The use of benzodiazepines in people who drink outside of the detoxification context is less clear. But care is needed as their use is higher in alcohol problems.
- We also know that people who drink moderately or harmfully but not light drinkers, have an increased liking for the effects of benzodiazepines hence care needs to be taken in all people who use about 4 units / week
- Benzodiazepine use / abuse are a serious problem in people who use drugs, especially for polydrug users and there is little evidence to guide practitioners.
- As well as taken orally, they can be snorted and / or injected.
- Up to 90% of attendees at drug treatment services reported their use in a 1-year period and over half report using illicit benzodiazepines in the last 3 months.
- People who use benzodiazepines, along with other illicit drugs and / or alcohol generally are using them for a different reason that is reward. They tend to increase rather than dampen activity in the brain reward centres.
- They are also used to alleviate withdrawal symptoms from other drugs, especially crack and / or heroin. They are more likely to be taken in binges.
- But people who use drugs may also use benzodiazepines as self-medication to improve their mood or their coping skills.
- Benzodiazepine use leads to higher rates of risk behaviour and social dysfunction, and problems may lead to fatal overdose.
- Prescribing for people who are using high doses and those who use illicit drugs develop tolerance quickly and will often escalate their dose.
- It is important to use psychological interventions and not prescribing in patients who binge-use benzodiazepines.
- In high-dose users all benzodiazepines are converted to diazepam and it is rarely appropriate to start a dose of more than 30 mg diazepam daily.
- All patients should be offered detoxification in the same way as other patients. Trials show that high-dose users are equally successful as others,
- A few people have a long-term opioid and benzodiazepine problem and do not stabilize on opioid substitution medication alone.
- When considering longer-term prescribing this must always be balanced against the risks, especially the negative effects on memory and cognitive skills.
- Women are more often prescribed than men, in pregnancy it is best to detox and this can be done at any stage.
- Older people are prescribed more and about 15% over 65 years take regularly, which is not recommended, as they are more sensitive to side-effects, pseudo-dementia, cognitive changes and increased falls.

PART 1 SECTION 1: INTRODUCTION

1.1 Background

This guidance has been produced to aid all clinicians and other practitioners in the use of, and reduction of misuse of benzodiazepines (BZ) aimed at primary care. Other hypnotics and anxiolytics, including the 'Z-drugs' (zopiclone, zolpidem, zaleplon, eszopiclone) are mentioned briefly.

There is a selection of other helpful guidance documents but these have not been specifically aimed at primary care.

There is:
1) BAP (British Association for Psychopharmacology, www.bap.org.uk) which have provided guidance on:

- Anxiety: Evidence-based guidelines for the pharmacological treatment of anxiety disorders: recommendations from the British Association for Psychopharmacology (Baldwin, Anderson et al. 2005)
- Insomnia: British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders (Wilson, Nutt et al. 2010)
- Substance misuse: Evidence-based guidelines for the pharmacological management of substance abuse, harmful use, addiction and comorbidity (Lingford-Hughes, Welch et al. 2012)

2) National Institute for Health and Care Excellence on: Insomnia (NICE 2004) and Anxiety (NICE 2011)
3) NICE Clinical Knowledge Summaries (CKS) on: Benzodiazepine and z-drug withdrawal (NICE July 2013)
4) Department of Health on: Drug Misuse and Dependence (Department of Health 2007)
5) Royal College of Psychiatrists (2013)
www.rcpsych.ac.uk/expertadvice/treatmentswellbeing/benzodiazepines.aspx
6) Educational pack to support the appropriate prescribing of hypnotics and anxiolytics across Wales (January 2011) www.awmsg.org

This guidance briefly mentions prisons in part 2, but it does not cover these in depth and we would advise readers to consult specific guidance for secure environments (Safer Prescribing in Prisons, 2011).
www.emcdda.europa.eu/attachements.cfm/att_146300_EN_UK51_Safer_Prescribing_in_Prison%20(2011).pdf

Benzodiazepines are widely prescribed in clinical practice short-term for a variety of conditions and their anxiolytic and hypnotic efficacy has been well established in numerous placebo-controlled studies (American Psychiatric Association 1990). The combination of effectiveness and risks of long-term use is the reason why benzodiazepines are so exasperating to deal with in clinical practice.

In part 1 of this guidance, the commonality of treating people will be discussed and then in part 2 it will attempt to cover most groups of patients who are taking benzodiazepines in more detail, including those who have been prescribed long-term, in people who use other illicit drugs and / or alcohol, women and in people with mental health problems.

Evidence base and practice-based guidance
Where possible, these present guidelines draw on the evidence base: available research literature and experience, both in the UK and internationally. The evidence base for use of benzodiazepines and other hypnotics and anxiolytics is extensive in clinical populations, particularly psychiatric patients, although much of it is now quite dated and even less on dual-diagnosis patients. Unfortunately, there is relatively little quality information on the group who use benzodiazepines illicitly, often in combination with other illicit drugs. Hence we will also draw on practice-based experience and by offering recommendations from experts in the field.

This guidance is part of a series that also includes prescribing for opioid dependence treatment in primary care (Ford, Halliday et al. 2011) and working with cocaine and crack users in primary care (Ford 2004). The detection and treatment of hepatitis C is currently

being updated (RCGP 2007). These documents are available online at www.smmgp.org.uk and www.rcgp.org.uk.

1.2 History of benzodiazepines and other hypnotics and anxiolytics

When they were first introduced into clinical practice in the 1960s, benzodiazepines were recognised to have distinct advantages over other available hypnotics. After brief clinical trials at the University of Texas in 1959, chlordiazepoxide (Librium) became the first of the benzodiazepines to be marketed for insomnia and anxiety (Lopez-Munoz, Alamo et al. 2011).

It took less than a decade for benzodiazepines to acquire more than a 90% share of a market previously dominated by barbiturates. Another decade was to pass, however, before it became generally accepted that they brought many problems of their own, greatly limiting their usefulness. Compared to barbiturates, they had initially appeared to have a much-improved safety profile and less toxicity, were relatively safe in overdose, and greater anxiety reduction in therapeutic dose. Benzodiazepines were originally thought to have no physical dependence potential but this was soon found to be untrue and tolerance, dependence and withdrawal symptoms emerged (Tyrer, Owen et al. 1983).

During the 1970s and 1980s the volume of overall benzodiazepine prescribing by doctors increased dramatically. Over the last decade the level of combined benzodiazepine and Z-drug prescribing has remained stable but that of benzodiazepines used for anxiety has steadily risen (figure 1).

1.3 Prevalence of benzodiazepine use and other hypnotics and anxiolytics

In the most recent Office for National Statistics General Household Survey in 2007, 0.5% of the population reported tranquillizer use in the last year. This figure varied with geographic area, being higher in the North East (0.8%) and Wales (1%) and lower in the East Midlands (0.2%), North West (0.3%) and East of England (0.3%). Non-white populations are much less likely to have used tranquillizers than the white population, while mixed-heritage people use tranquillizers even more commonly than whites. The British Crime Surveys look at illicit tranquilliser use annually, and gets rates of 0.4% in 16-59 year olds (est 155-177,000 people) and 2.3% in 16-24 year olds (est 30-75,000).

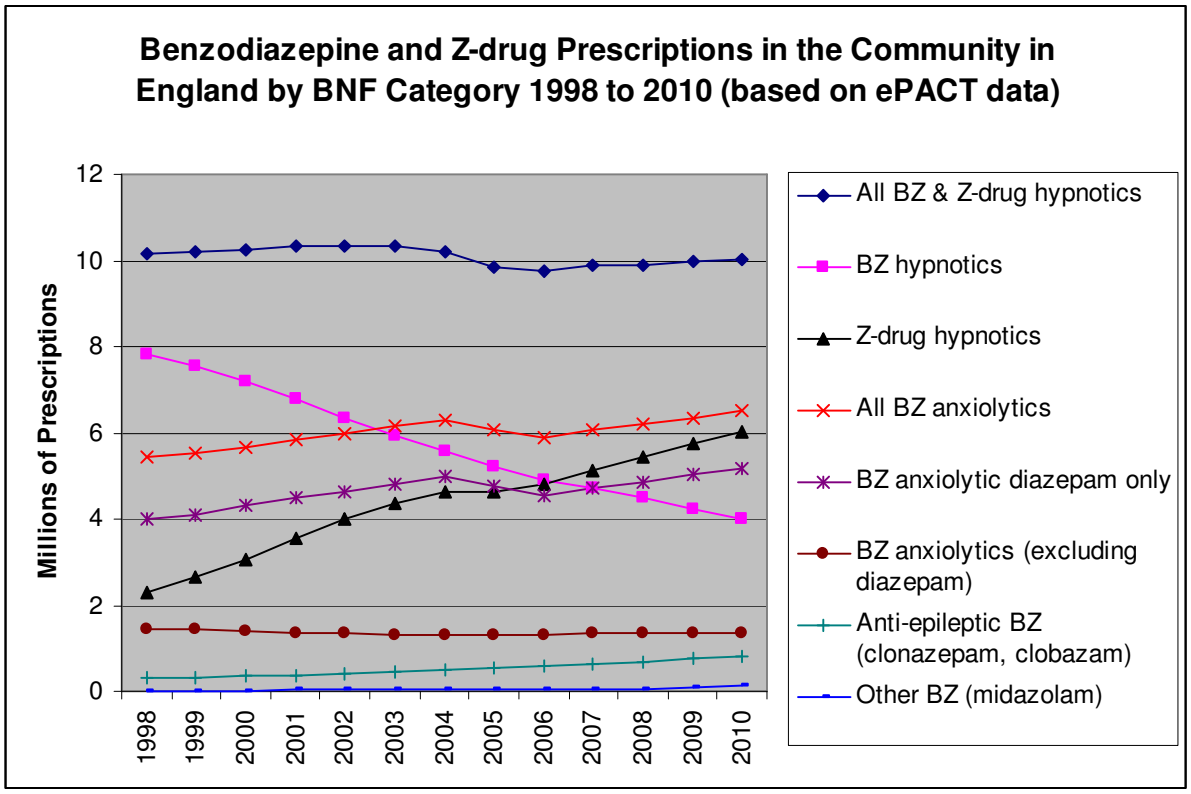
The number of people taking prescribed benzodiazepines worldwide is enormous. For example, in the US about 2% of the adult population (around 4 million people) appear to have used prescribed benzodiazepine hypnotics or tranquillizers regularly for 5–10 years or more. Similar figures apply for most of Europe and some Asian countries.

The number of people who are dependent on benzodiazepines in UK is unknown, as it has never been calculated but may be between 0.5 and 1.0 million people. A survey in 2004 undertaken in 7 GP practices found 1297 long-term (6 months or longer) benzodiazepine users, which is approximately 185 patients per practice (Heather, Bowie et al. 2004). Extrapolating this figure nationwide one gets over 1 million long- term benzodiazepine users in the UK (Ashton 2004). The All Party Parliamentary Report (2007/8) has quoted higher figures (up to 1.5 million) but hard evidence is not available. www.seroxatusergroup.org.uk/parliamentary-drugs-misuse-OTC.pdf

In 1988 the Committee on Safety of Medicines recommended limiting the length of treatment to 2-4 weeks. This recommendation was reiterated by the Chief Medical Officer in January 2004, based on Department of Health data from 2002 (Chief Medical Officer 2004) which showed that 30% of prescriptions written by general practitioners (GPs) were for 56 or more tablets, and 56% were for people over 65 years of age. While the number of prescriptions for benzodiazepine hypnotics has been steadily reducing, the numbers of Z-drugs have been increasing to compensate. In contrast the numbers of benzodiazepine

anxiolytics, particularly diazepam, have been slowly increasing. Taking both together the numbers of prescriptions are now about 16 million per year, and are currently slowly increasing by about 100,000 per year (Figure 1).

Figure 1 Benzodiazepine and Z-drug prescriptions in the community in England by *British National Formulary* (BNF) category, 1998–2010



SECTION 2: CLINICAL PHARMACOLOGY OF BENZODIAZEPINES

If we have some knowledge of how hypnotics and anxiolytics work, it may be possible for prescribers and patients to understand why they should be started rarely and some of the problems of long-term use.
NB: Clinical pharmacology of other drugs will be discussed under each section.

2.1 Properties and clinical actions

Benzodiazepines have six main clinically relevant actions:

1. **Anxiolytic**
2. **Hypnotic**
3. Anticonvulsant
4. Muscle relaxant
5. Anterograde and retrograde amnesia
6. Alcohol withdrawal.

This guidance focuses only on their anxiolytic and hypnotic actions.

There are a large number of benzodiazepines available. Their pharmacokinetics (what the body does to the drug e.g. how long the effects last) show wide variability. But they have similar pharmacodynamic (what the drug does to the body) properties, although their potency also greatly varies (see table 1). Benzodiazepines can be classified according to main use, speed of onset, duration of action and drug half-life, which gives an indication of when withdrawal symptoms are likely to begin.

2.2 Speed of onset and peak effects

Benzodiazepines are rapidly and fully absorbed orally, leading to peak effects within a half-hour to 2 hours of ingestion. The more fat-soluble drugs (e.g. diazepam) are absorbed faster and enter the central nervous system (CNS) more rapidly than the less fat-soluble drugs (e.g. oxazepam), hence the more fat-soluble agents are generally associated with increased abuse potential (Robertson and Treasure 1996). Temazepam has also been previously widely misused both because it was commonly prescribed, and because it was available until 1993 as easily injectable capsules (Ashton 2002). Those with long half-lives such as diazepam and nitrazepam are more likely to produce residual effects such as sedation and falls the day after the dose.

Rapid-onset drugs are associated with 'good' subjective effects, and therefore result in psychological reinforcement every time they are taken; over time, this strengthens the psychological component of any dependence process. The second most important factor related to risk of abuse is dose, as a higher dose leads to a better 'buzz'.

2.3 Duration of action

The duration of clinical action of most benzodiazepines is usually considerably shorter than their elimination half-life because once absorbed, they are rapidly redistributed into fatty tissue. With repeated daily dosing, accumulation occurs and high concentrations can build up in the body. With repeated dosing a steady state of blood concentration is reached in about five half-lives. After prolonged use, urine tests may remain positive for benzodiazepines for 4–6 weeks after cessation, as the drug slowly leaches out of the fatty tissues.

Although noticeable clinical effects usually wear off within a few hours, most benzodiazepines, as long as they are present, continue to exert subtle effects within the body, which may become apparent during continued use. Diazepam, for example, is typically given 2–4 times daily for anxiety, despite its elimination half-life being about two days and its active metabolite having an elimination half-life of 4 days.

2.4 Metabolism

Benzodiazepines differ markedly in the speed at which they are metabolized. They are converted to water-soluble compounds for renal excretion.

2.5 Mechanism of Action

The actions of benzodiazepines are mediated by enhancing the activity of gamma-aminobutyric acid (GABA), which is an inhibitory neurotransmitter that transmits messages from one neuron to another. Benzodiazepines bind to receptors on the GABA-A receptor complex and can directly or indirectly affect almost every part of brain function unselectively. This "inhibitory" effect is responsible for the characteristic effects of sedation, amnesia and lack of motor coordination. There is also evidence that they affect the mesolimbic dopamine system, which damps down all emotions including fear, anxiety, pleasure (from reward systems) and also cause 'emotional anaesthesia', apathy and depression. In the cerebral cortex they cause cognitive impairment and drowsiness; in the hippocampus they cause memory impairment and also have anticonvulsant actions and in

the cerebellum and motor areas such as corpus striatum they interfere with balance, motor control, muscle tone and coordination. These and other effects become more marked in with increasing age and in long-term use (personal communication Ashton H 2013).

2.6 Tolerance (Ashton 2002)

The development of tolerance is a physiological reaction (neuroadaptation) to all chronically used drugs of dependence, including opioids, alcohol, nicotine, cannabis and benzodiazepines. The body responds to the continued presence of the drug with a series of adjustments that tend to overcome the drug effects. In the case of benzodiazepines, compensatory changes occur in the GABA and benzodiazepine receptors, which become less responsive, so that the inhibitory actions of the GABA and benzodiazepines are decreased. As a result, the original dose of the drug has progressively less effect and a higher dose is required to obtain the original effect. The rate of development of tolerance may vary for different drug effects, such as relief of anxiety, sedation and pleasure depending on the number and complexity of the receptors involved. It can also develop at different speeds, which vary between individuals and can change in individuals over time.

Tolerance can develop rapidly and increased doses are required to maintain the same effect, especially for certain types of effect and can be rapid to sedation, cognitive and to motor effects (but may never be complete). The way tolerance develops to other therapeutic effects, such as anxiolytic, anti-panic and antiphobic effects is arguable, some such as Vinkers and Olivier in a review in 2012 state that “tolerance to anxiolytic and amnesic effects probably does not develop at all”, but few studies cited in this review continued for more than two years (Vinkers and Olivier 2012). Others have shown that tolerance has developed after months or even years of regular use, such as in the 1987 Ashton study patients had been taking benzodiazepines for 1-22 years (mean 9.76 years). The benzodiazepines had been effective at first, but the anxiety, agoraphobia, panics and other symptoms developed later – often over a year or two later, supporting the view that tolerance does develop. There is also a high degree of cross-tolerance between benzodiazepines and other sedatives / hypnotics and alcohol and we can conclude that tolerance is complex.

2.7 Equivalence

In March 2011 the BNF listed fourteen benzodiazepines and three Z-drugs; it is beyond the scope of this document to review them all and we have concentrated on the ones most commonly in use.

Equivalent doses of the hypnotic benzodiazepines are described in the BNF (Joint National Formulary Committee 2011) and in the 2007 National Clinical Guidelines (Department of Health 2007). These dose equivalents are approximate and used when making a transfer between drugs, and are primarily based on clinical experience and not agreed by all clinicians (Table 1).

Note that the clinical potency of the different drugs varies between individuals, that different sources provide different estimates of equivalence and that it is difficult to demonstrate equivalence with drugs having very different half-lives. The equivalent doses given above are only approximate but are representative of opinion in the literature.

Table 1: differences between benzodiazepines and z-drugs and equivalence to 5mg diazepam

Benzodiazepine agonist drug	**Half Life of Parent Drug** (hours)*	**Speed of onset**	**Equivalence to diazepam 5mg****	**Use**
Chlordiazepoxide	5-30	slow	15mg	Anxiety

Diazepam	20-100	rapid	**5mg**	Anxiety / Insomnia
Loprazolam	4-15	slow	0.5mg (to 1mg)	Insomnia
Lorazepam	10-20	intermediate	0.5mg ***	Anxiety / Insomnia
Lormetazepam	11	intermediate	0.5(to 1mg)	Insomnia
Nitrazepam	18-25	rapid	5mg	Insomnia
Oxazepam	4-15	slow	15mg	Anxiety
Temazepam	8-22	intermediate	10mg	Insomnia
Zaleplon	1	rapid	10mg	Insomnia
Zolpidem	2	rapid	10mg	Insomnia
Zopiclone	5-6	rapid	3.75mg	Insomnia

*Some variation between individuals
** Equivalence as BNF and Clinical guidelines
****Approximately equivalent oral dosage from other sources

NB: Use of clonazepam, licensed for use in epilepsy, has changed over the past 10 years and the drug is now much misused in the prison environment. Many prisoners report use in the community and claim to be epileptic to procure a continuous supply. The reasons for this are complex because clonazepam has a relatively slow onset of action therefore on its own causes little buzz but it can be used to help pass the time in prisons, and can enhance the effects of other rapid onset drugs used at the same time. Clonazepam 0.25mg is approximately equivalent to 5mg diazepam.

SECTION 3: TREATMENT OF INSOMNIA AND ANXIETY

It was difficult to decide whether to discuss the treatment of insomnia and anxiety in general or just benzodiazepines but we include here a short piece of the range of treatments for them.

3.1 Insomnia, anxiety, panic disorder and related disorders

Sleep is needed daily to restore the body and mind. Insomnia is an important, common, often poorly understood by patients and professionals, usually long-term health problem, that requires accurate diagnosis and effective treatment. It is can consist of poor sleep onset, sleep maintenance, early waking or a combination of these factors (Edinger, Bonnet et al. 2004).

Insomnia causes a reduction in quality of life and increased daytime function impairment. It also leads to the release of stress hormones, and may increase the risk of hypertension, cardiovascular disease and cancer, poor mental health, especially depression and anxiety disorders, loss of energy, irritability and poor memory.

A UK study showed that 75% of patients reported sleep disturbance symptoms lasting a year, plus chronic insomnia affects around 9-12% of UK adults every year, with the percentage increasing to 12-25% in those over 60 years of age (Morphy, Dunn et al. 2007; Montgomery and Shepard 2010).

Anxiety symptoms may range from mild and transient without daytime functional impairment, to severe and persistent causing significant distress and a general reduction in quality of life (Baldwin, Anderson et al. 2005).

Assessment

Before treatment a full assessment needs to be undertaken. Take a physical and mental health history including use of alcohol and caffeine, symptoms of pain, sleep history, depression and anxiety, daily exercise. Review all medication including over-the counter and check if any recent personal losses or illness.

Consider the use of a sleep diary and/or anxiety diary as appropriate and information leaflets on sleep hygiene and/or relaxation should be recommended.

Look for possible causes of sleep disturbance and / or anxiety symptoms, such as shift work, noise, room temperature, illness, psychological factors, drug withdrawal and where possible treat appropriately.

Treatment for insomnia and anxiety

i) Behavioural treatment for primary insomnia and anxiety

First-line interventions for insomnia and anxiety management need to be addressing underlying problems and then using: talking therapies, cognitive behavioural therapies or approaches and self-help (Wilson, Nutt et al. 2010).

Both NICE (NICE 2011) and the British Association for Psychopharmacology (BAP) have issued useful evidence-based guidance on anxiety (Baldwin, Anderson et al. 2005), and insomnia (Wilson, Nutt et al. 2010).

Cognitive behavioural therapy (CBT) is an effective treatment performed either individually or in small groups, and has been found in some cases not only to be as effective as short-term prescription medication but may last beyond the withdrawal from active treatment (Morgan, Dixon et al. 2004)

NB: Further discussion of these techniques is beyond the scope of this guidance.

ii) Drug treatment for insomnia and anxiety

Several classes of drugs, including benzodiazepines, Z-drugs and SSRIs, can be used to treat insomnia and / or anxiety but drugs should not be first-line treatment for most occasions. They may be indicated in very few specific situations such as an acute crisis (psychological or situational) with a clear endpoint or a predicted acute crisis such as attending a highly distressing or stressful event such as a funeral or interview.

Benzodiazepines: When prescribed for severe insomnia or disabling anxiety the guidance is clear that benzodiazepines should only be given for short-term relief (2–4 weeks), which may occur alone or in association with short-term psychosomatic, organic, or psychiatric illness. They should be used in the lowest dose and for the shortest time.
Benzodiazepines and other similar drugs are not indicated for the long-term treatment of anxiety or insomnia, unless in rare cases where the patient has been proven to have treatment-resistant anxiety or insomnia, i.e. resistant to psychological therapies and non-addictive medications. The decision to prescribe in these circumstances is usually made by a specialist. The use of benzodiazepines is inappropriate to treat short-term mild anxiety.

Benzodiazepines primarily relieve and suppress symptoms, rather than being curative for any disorder. So unless a condition in which benzodiazepines are used for treatment is self-limiting, or is otherwise effectively treated, the symptoms treated by the benzodiazepine will return when it is reduced or stopped. The evidence for this includes the high relapse rate when stopping benzodiazepines for anxiety disorders, compared to

stopping an antidepressant for the same disorder. Patients may not understand why benzodiazepines are being refused despite their apparent (short-term) efficacy, reduction in symptoms and why they are encouraged to take what seems to them to be less effective medications or treatments, such as antidepressants or counselling.

Z-drugs: zopiclone, zolpidem and zaleplon: The "Z" drugs were developed as hypnotics to overcome the side effects associated with benzodiazepine therapy, although their potential to cause tolerance, dependence and withdrawal symptoms was known from the beginning (Nutt 2005).

Zopiclone, zolpidem and zaleplon have been shown to be effective hypnotic treatments for insomnia in adults (Liverpool Reviews and Implementation Group 2003; Wilson, Nutt et al. 2010) and are comparable to benzodiazepines in hypnotic efficacy. Although biochemically distinct from benzodiazepines, Z-drugs have a very similar pharmacological action.

In 2004 NICE concluded that there was a lack of compelling evidence distinguishing between "Z" drugs and the shorter-acting benzodiazepine hypnotics, NICE advised that they should only be prescribed for short periods of time, because of the lack of evidence distinguishing between "Z" drugs and the shorter-acting benzodiazepine hypnotics, the drug with the lowest purchase cost and patients who have not responded to one of these hypnotic drugs should not be prescribed any of the others (NICE 2004)

Dependence and tolerance were not inevitable with zopiclone, even when used for up to 1 year (Wilson, Nutt et al. 2010). The evidence suggests that tolerance to sedative effects may not occur where the elimination half-life is much shorter (1/4 or 1/5th than the inter-dose interval, and this has been shown for the benzodiazepines midazolam (t½ = 2–7 hrs) and for the Z-drugs zopiclone (t½ = 5–6 hrs), zolpidem (t½ = 2 hrs) and zaleplon (t½ = 1 hr).

The number of prescriptions for Z-drugs has steadily risen since they became available, by about 300,000 per year, as the prescriptions for benzodiazepine hypnotics have decreased by the same number (figure 1). GPs have been shown to favour Z-drugs over benzodiazepine hypnotics on a whole range of issues (Siriwardena, Qureshi et al. 2006), while clinical experience suggests that Z-drugs have clinically relevant advantages in at least two subpopulations (Law 2005). Firstly the elderly where the short half-life have less 'hangover' effects and there is less drug accumulation. All oral benzodiazepines available in the UK have a longer half-life than Z-drugs. Secondly, where there is a risk of misuse as benzodiazepines appear to have a higher misuse potential than all the Z-drugs.

Melatonin: is an endogenous hormone produced by the body in response to darkness that helps regulate circadian rhythms. Levels are reduced in middle-age and elderly patients with insomnia. A licensed preparation of long-acting melatonin is available in the UK for the management of insomnia in adults aged 55 and over and the license does not include warnings of tolerance, dependence, rebound or withdrawal syndrome and treatment can be continued for 13 weeks. Melatonin does not appear to cause motor or memory problems but long-term adverse effects have not been thoroughly studied.

3.2 Practical prescribing

The decision to prescribe or not is often a complex difficult decision and we need to think very carefully before prescribing hypnotics or anxiolytics to any patient who has not used them before because there are treatments with better longer term outcomes available. Caution must be used when prescribing benzodiazepines, Z-drugs and other related drugs to any patient, but more so when there is a current or past history of using illicit drugs (Longo and Johnson 2000) or personality disorder. Having once started it is harder to stop and hence the prescriber and the patient must have a plan for short-term or use very intermittently.

There are three common starting points for discussions with patients:

1. The patient has acute self-limiting anxiety or insomnia, other treatments such as counselling and medication have failed and immediate relief is requested.
2. The patient has acute self-limiting anxiety or insomnia, has used benzodiazepines or other drug before to good effect and requests them again.
3. The patient has used benzodiazepines over a long period, has a dependence on them, may or may not be dependent on other drugs and / or alcohol too, and requests help.

These are very different discussions that none the less share some common ground, and each should be addressed appropriately.

In the first two situations, other treatments must be explored before starting a prescription, but this is difficult, particularly if help is needed immediately and / or benzodiazepines have worked before. Short courses prescribed to non-dependent individuals to 'alleviate acute conditions after causal conditions have been established' are the least contentious areas of prescribing (Joint National Formulary Committee 2011).

Discuss before issuing short-term:

a. Explain any prescription for benzodiazepines or Z-drug is one-off and must be short-term to suppress symptoms (2-4 weeks including final taper).
b. If a prescription is given, warn of risks of driving, operating heavy machinery etc., adverse effects and drug interactions (alcohol etc.).
c. Advise patients not to take benzodiazepines daily if they are intended for night sedation (and also for anxiety), and should be warned that the drugs are addictive.
d. Only initiate therapy after full discussion of risks and provide verbal and written information to patients regarding the complications of long-term use and associated side effects such as tolerance, dependence, memory, rebound and withdrawal.
e. Plan reduction and show how to manage rebound effects.
f. Generally use diazepam for anxiety and avoid potent, short-acting benzodiazepines such as lorazepam.
g. For insomnia, shorter-acting drugs such as the Z-drugs and temazepam are used in preference to the longer acting drugs such as nitrazepam, as they cause less 'hangover' effects in the morning.

Prescribing for patients with established benzodiazepine dependence is more controversial, and abrupt withdrawal of prescribed benzodiazepines carries significant risks and will be discussed in the next section. Where non-prescribed benzodiazepines are involved, the situation is more complex still. Many individuals taking illicit benzodiazepines operate in the context of poly-drug use, including alcohol. Prescribing to a dependent patient will be covered in Part 2.

SECTION 4: ADVERSE EFFECTS & PROBLEMS WITH, MANAGEMENT OF & WITHDRAWAL FROM LONG-TERM USE

Benzodiazepines and related drugs are usually effective when first prescribed and nearly all the disadvantages and problems come from long-term use, which can be associated with considerable physical, mental and social health problems . Problems include over-

sedation, which contributes to accidents on the roads, in the home and at work, anxiety, panic attacks, emotional blunting, suicidal thoughts, and agoraphobia**.** Benzodiazepine consumption has been estimated to approximately double the risk of motor vehicle accidents (Thomas 1998). All side effects are more pronounced in the elderly see section 5.9 for further information. These experiences have been confirmed in many studies, by thousands of patients attending tranquillizer support groups. It is interesting to note that it was the patients themselves, and not the medical profession, who were first to realize that long-term use of benzodiazepines can cause problems (Ashton 2002).

4.1 Specific problems with long-term use

Benzodiazepines may be started appropriately with a clear indication, but it is easy to slide into longer-term use. Relapse can occur with all drugs of dependence, but is low with benzodiazepines after withdrawal compared with most other drugs of dependence such as alcohol and opioids if benzodiazepines are withdrawn slowly. With slow reduction and psychological support, most patients lose their anxiety, panics, agoraphobia etc (Ashton 1987).

Mental Health
Increased anxiety
Anxiety can be caused by benzodiazepines themselves, as well as associated with reduction or cessation and long-term use. Anxiety may be reduced if benzodiazepines are stopped in 40–60% of patients (Rickels, Schweizer et al. 1990; Schweizer, Rickels et al. 1990; Rickels, Case et al. 1991).

After several years on benzodiazepines, patients may experience a gradual increase in anxiety symptoms over time, panic attacks and agoraphobia. The increase in anxiety may lead to a dose increase or the addition of another benzodiazepine but this is not the most appropriate treatment (Ashton 1987).

Patients may also develop a preoccupation with benzodiazepines and the dose they are taking (‘benzodiazepine neurosis’), which makes it difficult to implement appropriate changes. This typically resolves only once the drug is stopped.

Memory impairment and other cognitive effects
Benzodiazepines have long been known to cause memory impairment and amnesia, a desirable effect when they are used as pre-medication for surgery, but undesirable when the drugs are taken on a regular basis. Acquisition of new information is reduced because benzodiazepines cause a lack of concentration and attention and a because they provoke a specific deficit in the remembering of recent events (Curran 1991). This continues even after long-term use, even for therapeutic doses, which has led to the recommendation that these drugs should not be taken during the day but only at night and not in divided doses (Lucki and Rickels 1986; Lucki and Rickels 1988). Impairment of episodic memory may occasionally lead to memory lapses or ‘blackouts’, when patients may do something under the influence of benzodiazepines but not remember the next day (transient global amnesia).

Chronic effects on memory are likely to result in reduced social functioning over a period of time, e.g. reduced ability to remember new people or appointments. The question of whether long-term benzodiazepine use results in brain damage has never been adequately studied and remains controversial (2011 Supplement to Ashton Manual on www.benzo.org.uk).

Long-term use of benzodiazepines has been associated with long-term cognitive effects. Moderate to large deficits occur in all 12 cognitive domains in long-term benzodiazepine users compared with controls (Barker, Greenwood et al. 2004); these deficits may mimic dementia in the elderly (Lader 1992).

Depression, emotional blunting and reduced coping

Emotional blunting is a common complaint of benzodiazepine users (Ashton 2002). Inhibition of arousal results in an inability to feel normal emotional highs or lows, pleasure or sadness, and grief.

Emotional and cognitive suppression may account for the insidious development of psychological and physical symptoms with long-term use (Ashton 1987; Griffiths and Weerts 1997; Movig, Mathijssen et al. 2004; Walsh, Flegel et al. 2004), especially in the elderly (Gray, Penninx et al. 2003; Panneman, Goettsch et al. 2003; Madhusoodanan and Bogunovic 2004; Wagner, Zhang et al. 2004)

Long-term benzodiazepine users will sometimes develop depression after prolonged use. Typically it will resolve within 6 months or a year of stopping the drug (Olajide and Lader 1984; Ashton 1987). Benzodiazepines may also aggravate depression, possibly by reducing the brain's output of neurotransmitters such as serotonin and noradrenaline (norepinephrine). Sometimes the drugs seem to precipitate suicidal tendencies in depressed patients (Committee on the Safety of Medicines 1988) (http://www.benzo.org.uk/commit.htm).

Long-term use also typically results in a weakening of coping skills because patients use them as part of their coping mechanisms. The effects of emotional suppression and reduced coping ability may become prominent when the benzodiazepine dose is reduced or stopped. An increased intensity of emotions occurs on reduction and continues even after rebound and withdrawal symptoms have resolved. Patients commonly talk of emotions ‘bubbling to the surface’, which may be sufficiently severe to cause panic attacks.

Traumatic issues, such as abuse and other difficulties, may be reactivated and result in the emergence of PTSD. Symptoms related to emotional suppression and poor coping gradually disappear in most cases within 6–12 months after successful tapering and withdrawal of benzodiazepines, as the patient learns to cope better with stress (Ashton 1987).

Disinhibition / paradoxical stimulation

Benzodiazepines occasionally cause paradoxical excitement with increased anxiety, insomnia, nightmares, hallucinations at the onset of sleep, irritability, hyperactivity or aggressive behaviour, and exacerbation of seizures in epileptics. Attacks of rage and violent behaviour have been reported, particularly after intravenous administration. Less dramatic increases in irritability and argumentativeness are more common. Such reactions are similar to those sometimes provoked by alcohol. They most frequently occur in anxious and aggressive individuals, children and the elderly, and following high doses of benzodiazepines. This is probably due to release of inhibited behavioural tendencies that are normally suppressed by self-control and social restraints. Suicidality and self-harm may also occur. Cases of non-accidental injuries in children and the elderly, as well as incidents of domestic violence, have also been attributed to benzodiazepines.

Users of high-dose benzodiazepines may also feel euphoric and disinhibited, and engage in extremely disinhibited or uncharacteristic behaviour. They may perpetrate assaults or other criminal activity (e.g. shoplifting) in full view of witnesses. This occurs when the users feel invulnerable, invincible and indeed invisible - in what has been described as the ‘Rambo syndrome’. The user is often unable to recall any events related to the offence, because of the amnesic effects of high benzodiazepine doses. In people who inject drugs there is a higher rate of risk-taking behaviour, with regard to HIV (Darke, Hall et al. 1992).

Physical health problems

Use of benzodiazepine and Z-drug hypnotics is associated with an increased risk of many physical health conditions and death (Kripke, Langer et al. 2012). Increased deaths also

occur because of poisoning by overdose, increased deaths in illicit drug users and possibly by driver-responsible fatalities (Charlson, Degenhardt et al. 2009).

Dependence

Dependence occurs when the user of the drug becomes less able to control the intake of a substance. It encompasses a range of features initially described in connection with alcohol misuse, now recognised as a syndrome associated with a range of substances.

It has two components: psychological dependence, which is the subjective feeling of loss of control, cravings and preoccupation with obtaining the substance; and physiological dependence, which is tolerance and the physical consequences of withdrawal and is specific to each drug. For benzodiazepines both psychological and physiological dependence occur and when unobtainable, the user suffers from withdrawal symptoms.

The criteria for dependence can be divided into three pairs of symptoms (Table 2). A diagnosis of dependence is made if 3 of the 6 criteria have been met in the last 12 months:

Table 2 ICD-10 Criteria for diagnosing benzodiazepine dependence

2 drug-related criteria: • Compulsion/cravings to take benzodiazepines • Difficulties in controlling benzodiazepine use
2 consequences of use criteria: • Progressive neglect of alternative pleasures / interests due to benzodiazepine use • Persistent benzodiazepines use despite harmful consequences
2 physiological criteria: • Characteristic benzodiazepines withdrawal state • Evidence of tolerance to benzodiazepines

These criteria make no mention of the frequency, amount or chronicity of benzodiazepine use; thus frequent long-term, high-dose users are not necessarily dependent, although they are, of course, more likely to be so (National Treatment Agency for Substance Misuse 2011). http://www.nta.nhs.uk/uploads/addictiontomedicinesmay2011a.pdf

Long-term use of benzodiazepines and other drugs produces chronic changes in receptor functioning in the central nervous system and benzodiazepine receptors are not thought to return fully to their pre-addiction state following detoxification and abstinence. As with all addictions, psychologically conditioned effects may be extinguished during a period of abstinence, but may be reactivated in response to re-exposure to the drug for the rest of their lives.

Once dependence has become established, it can in some cases be extremely difficult to treat, may result in persistent withdrawal symptoms and may become a long-term or even permanent state (Royal College of Psychiatrists 1997). In these people it may be that continuation of the benzodiazepine prescription is felt to be appropriate for the foreseeable future.

Dependence and withdrawal symptoms

Physical dependence on benzodiazepines is manifested by the presence of a characteristic withdrawal syndrome when the benzodiazepine is reduced or stopped. Long-term use can cause withdrawal symptoms in many people – between 30 and 45% (Ashton 1987; Lader and Russell 1993). Withdrawal reactions develop relatively slowly in therapeutic-dose users on long-acting benzodiazepines in non-addiction populations, but it is much less clear how quickly these reactions develop with the shorter-acting benzodiazepines (Lader, Ron et al. 1984).

Withdrawal symptoms can take almost any psychological and / or somatic form, but can be considered as falling into three main groups (Table 3).

Table 3 Acute withdrawal symptoms from benzodiazepines

Anxiety symptoms (can mimic symptoms the drug was first taken for and also appear on rebound as drug stopped)		**Distorted perceptions** (usually a sign of drug withdrawal, rather than anxiety)	**Major incidents** (occurs especially when high doses are stopped abruptly)
Psychological	**Physical**		
• Anxiety • Panic attacks • Insomnia • Poor memory • Depression • Paranoia • Intrusive memories • Cravings • Nightmares • Excitability • Agoraphobia • Social phobia • Obsessions • Rage, aggression • Irritability	• Agitation • Tremor • Headache • Weakness • Dizziness • Nausea • Vomiting • Diarrhoea • Constipation • Palpitations • Rashes • Tingling, numbness, altered sensation • Fatigue, • Flu-like symptoms	• Hypersensitivity to sound, light, touch, taste, etc. • Abnormal body sensation, e.g. itching, widespread pain & stiffness, blurred vision, paraesthesia, muscle twitching, tinnitus, burning sensations, etc. • Feeling self or world to be abnormal • Depersonalisation •	• Fits (1–2% of patients, esp. if stopping high dose abruptly) • Delirium (rare) • Transient hallucinations (visual, tactile, auditory) or illusions (rare) • Psychosis (very rare)

Predicting the risk of withdrawal symptoms

The risk of withdrawal symptoms increases with longer use and higher doses (Rickels, Schweizer et al. 1990) and use of high-potency benzodiazepines with a short / intermediate half-life (e.g. lorazepam).

Also they are more likely if a patient has chronic psychiatric and personality problems (Rickels, Schweizer et al. 1990; Murphy and Tyrer 1991), those with chronic physical health problems, especially the elderly and those in pain or with chronic sleep difficulties. A history of current or past alcohol or other sedative-hypnotic dependence, or a family history of these is also significant.

Protracted withdrawal syndrome

The protracted withdrawal syndrome occurs in a minority (up to 15%) of patients who develop a post-withdrawal syndrome on detoxifying from benzodiazepines. Most have taken benzodiazepines for many years, often 20 or more and may have already had a bad withdrawal experience (Ashton 2002). It can also be made worse by stress or life events but people can be supported through these rather than increasing benzodiazepines or using another drug. Symptoms typically last for 6 months to 1 year or more before gradually improving. The most common features are anxiety, depression, tinnitus, paraesthesia, muscle jerking and irritable bowel (Ashton 1984; Higgitt, Fonagy et al. 1988; Higgitt, Fonagy et al. 1990). A whole range of other symptoms, including neurological ones, may also occur, and may on occasion last for several years (Table 4).

Table 4 Some protracted benzodiazepine withdrawal symptoms (Ashton 2002)

Symptom	Usual course
• Anxiety	• Gradually diminishes over 1 year
• Insomnia	• Gradually diminishes over 6–12 months
• Depression	• May last a few months. May respond to antidepressants
• Cognitive impairment	• Gradually improves but may last for >1 year
• Perceptual symptoms: tinnitus, paraesthesia, pain (usually in limbs)	• Gradually recede but may last for at least 1 year
• Motor symptoms: muscle pain, weakness, tension, painful tremor, jerks	• Gradually recede but may last for at least 1 year and rarely persist for longer
• Gastrointestinal symptoms	• Gradually recede

Patient and user groups talk in terms of the 'month per year rule': namely, that there will be one month of protracted symptoms for every year of benzodiazepine use. This is a helpful model to prepare patients psychologically, but is not currently supported by research.

4.2 Withdrawal from long-term use

Withdrawal is possible in most patients who are dependent on benzodiazepines once problems related to prolonged use of benzodiazepines and other drugs are explained and discussed. Reports demonstrate that patients provided with information (e.g. letter from GP) explaining the disadvantages of regular use of these medicines will voluntarily reduce their usage (Ashton 2005).

Patients currently taking hypnotics or anxiolytics will fall into broadly three different categories, although there is overlap:

1. Patients suitable for managed withdrawal: who may have been appropriately initiated on treatment, but inadvertently continued long-term use. This group tend to take therapeutic doses and are described as "therapeutic users" (BAP 2012)
2. Patients who are dependent often on high-doses and / or use illicit drugs and / or alcohol: who may be on opioid substitution therapy. This group will be dealt with in more detail under special groups in section 6.4.
3. Patients who may need to remain on treatment: who may have serious physical illness, be terminally ill or have severe mental health problems and their psychiatrist is managing their drugs.

Detoxification for a benzodiazepine-dependent individual

Managed withdrawal from benzodiazepines is possible in most people. Consideration needs to be given as to when and how to detoxify and extra help and services may be needed (Hallstrom 1990). An assessment should be made as to whether the patient is emotionally ready to withdraw and understands the advantages of stopping. Remember to ask about alcohol, as some patients may simply substitute alcohol for the benzodiazepine (NICE July 2013).

Preparation for detoxification

Before starting give the patient information about the problems of long-term benzodiazepine use and explain the process of withdrawal and possible effects. The offer

of support, information and advice may trigger independent reductions and withdrawal from benzodiazepine in some patients (Cormack, Sweeney et al. 1994). Patient information leaflets may be useful and are available from a number of sources (www.patient.co.uk/health/Benzodiazepines-and-Z-Drugs-Stopping-After-Long-Term-Use.htm).

Before starting on a reduction always tackle the underlying problem causing the insomnia or anxiety, if there is one. Ensure that they have good treatment of physical health problems including pain, anaemia, asthma, oesophagitis and cardiovascular disease; treat any psychiatric symptoms, such as depression, mania and / or anxiety, as continuing symptoms are the strongest predictor of failure at detoxification and are on a good diet. Check they aren't doing activities such as late night eating or exercise, daytime napping that would worsen the situation and that stress or grief are being addressed through psychological support. If the patient has not thought about coping strategies, then consider doing some work on them before commencing the withdrawal (Home Office Advisory Committee on the Misuse of Drugs 2000).

Consider the use of anxiety management, relaxation and other non-pharmacological treatments, mentioned previously and advise the patient about specific and generic support groups (if available). CBT improves numbers able to detoxify and maintain abstinence following detoxification (Baillargeon, Landreville et al. 2003).

Useful advice about withdrawal based on that provided by The Welsh Medicines Partnership 2011 (www.awmsg.org) and BAP updated guidelines in 2012 is below:

1. **Dose reduction:** This should be tailored to the individual and tapered. The rate of reduction should be individualised according to the drug, dose, and duration of treatment. Patient factors such as personality, lifestyle, previous experience and specific vulnerabilities should also be taken into account. Gradual reduction is better than abrupt discontinuation (Denis, Fatseas et al. 2006). It may take weeks, months or even years but there should be no hurry, as the person needs to learn how to manage without drugs.

2. **Speed and rate of reduction:** Going too fast can cause the patient enormous difficulties with multiple withdrawal symptoms and often leads to failure. It is best to allow the patient control. If there are problems, reduce speed but try not to go backwards.The BNF recommends reducing diazepam dose by first trying 5–10% of the patient's usual daily dose every 2–3 weeks e.g. reduce by 1mg (5%) of 20mg dose every 2-3 weeks (Joint National Formulary Committee 2011) and then maintaining this dose until any symptoms improve. Plan to reduce over a minimum of 6 weeks and advise the patient to take the divide the dose into 3 and take 3 times / day. Different withdrawal plans below are given for guidance only. Start from the most relevant point of the schedule depending on the patient's current dose. See appendix for further help.
3. **Gradual reduction and additional therapies:** Some patients will manage with minimal interventions, such as advice and standard letters. Graded reduction, achieved a 66% short-term cessation rate. Others will need additional psychological therapies and these seemed particularly beneficial for insomnia and panic disorder. Additional pharmacotherapy has been shown to have no benefit (Parr, Kavanagh et al. 2009).

4. **Problematic withdrawal symptoms:** If patients experience difficulties with a dose reduction, encourage them to persevere and suggest delaying the next step down. Do not revert to a higher dosage.

5. **Monitoring the patient:** Review frequently and at each stage enquire about general progress and withdrawal and rebound symptoms. Reassure patients that if

they are experiencing any difficulty with the withdrawal schedule, they can contact the surgery or their prescriber service for advice. Ask the patient about their particular problems and it is always best to agree changes with the patient by negotiation, rather than imposing them. Psychotic symptoms, confusion and convulsions are rare and usually only occur on rapid withdrawal of high doses. Offer advice on good sleep hygiene and reduction of anxiety throughout.

6. **Regime agreement**: Agree a regime tailoring the pace of withdrawal to the patient's needs, goals for reduction and a provisional time frame for reduction. If the patient persistently uses up the prescribed drugs before the next instalment is due, then the withdrawal needs to be renegotiated (Home Office Advisory Committee on the Misuse of Drugs 2000).

7. **Substitution of one benzodiazepine for another:** If withdrawal symptoms are a problem, consider substitution of short- or medium-acting benzodiazepines by long-acting compounds to reduce the risk of withdrawal symptoms with shorter-acting compounds but there if little support for this (Denis 2006 and Murphy & Tyrer 1991, both which you have but don't know how to add link). There is some evidence that using longer-acting benzodiazepines for withdrawal reduces the number of dropouts from withdrawal programmes (Voshaar, Gorgels et al. 2006). Reassure patients that any initial sedation or other changes after converting to diazepam will usually wear off. Substitution can be immediate or gradual, i.e. the whole amount is substituted at once, or the original benzodiazepine is gradually replaced with diazepam. It is suggested that a gap of at least 1 week should separate each partial substitution.

8. **Additional psychosocial support:** a counselor or practice nurse at the surgery, mental health services or local and national specific projects, if available should always offer ongoing support.

9. **Support from family and friends**: Identify family or friends who will support cessation of drug use and avoid friends who still use benzodiazepines (Home Office Advisory Committee on the Misuse of Drugs 2000).

10. **Self-help:** Introduce self-monitoring procedures (e.g. diary of drug use) and methods of reduction (e.g. waiting before taking the next tablet). Consider use of self-help advice and groups (Battle Against Tranquillisers (BAT), www.bataid.org; Ashton self-help manual for benzodiazepine withdrawal, www.benzo.org.uk/manual/index.htm; Council for Information on Tranquillisers and Antidepressants (CITA), www.citawithdrawal.org.uk). NB See fuller list in Resources - appendix 1.

11. **Record keeping:** A copy of the protocol should be given to the patient and the patient's pharmacy. A copy should also be kept in the practice's records.

NB: See appendix 2, table 2: Ten steps to reducing long-term benzodiazepine use in patients who are physically dependent on them (based on (Mant and Walsh 1997) for further help

Detoxification contract: Some practitioners like to formulate a written 'contract' with patients when entering into a detoxification regime, to explain exactly what will happen and what the result of particular actions will be (e.g. sourcing own benzodiazepines on top of planned doses, missing doses, alcohol misuse and so on). Acceptable 'pauses' in the rate of reduction may also be planned in case reduction proves particularly difficult. The patient and the prescriber have jointly agreed the terms.

Examples of withdrawal schedules shown below and see further in Welsh Medicines Partnership 2011 educational pack (www.awmsg.org) and British National Formulary.

Table 5 Examples of hypnotic and anxiolytic withdrawal schedules

Examples of Hypnotic Reduction Protocols to Support Withdrawal number of tablets per day(mg)					
Each stage can be 1-2 weeks	**Nitrazepam**	**Temazepam**	**Lormetazepam**	**Zopiclone**	**Zolpidem & Zaleplon**
Tablet size	5mg	10mg	0.5mg	3.75mg	5mg
Stage of detox					
1	4 (20mg)	4(40mg)	6(3mg)	7 (26.25mg)	3½(17.5mg)
2	3 (15mg)	3(30mg)	5(2.5mg)	6(22.5mg)	3(15mg)
3	2½ (12.5mg)	2½(25mg)	4(2mg)	5(18.75mg)	2½(12.5mg)
4	2 (10mg)	2(20mg)	3(1.5mg)	4(15mg)	2(10mg)
5	1½(7.5mg	1½(15mg)	2(1mg)	3(10.25mg)	1½(7.5mg)
6	1(5mg)	1(10mg)	1(0.5mg)	2(7.5mg)	1(5mg)
7	½(2.5mg)	½(5mg)	½(250ug)	1(3.75mg)	½(2.5mg)
8	½ alt nights	½ alt nights	½ alt nights	1 alt nights	½ alt nights
9	stop	stop	stop	stop	stop

Examples of Anxiolytic Reduction Protocols to Support Withdrawal number of tablets per day (mg) where D = diazepam						
	Diazepam Slow Detox (Lader, Tylee et al 2009	**Diazepam Rapid Detox**	**Diazepam Standard Detox**	**Chlordiaze -poxide**	**Oxazepam**	**Lorazepam**
Tablet size	2mg	5mg	5mg, then 2mg D	5mg	15mg, then 5mg D, then 2mg D	1mg, then 5mg D, then 2mg D
Stage of detox						
1						6 (6mg)
2						5½ (5½mg)
3			14 (70mg)			5 (5mg)
4			13 (65mg)			4½ (4½mg)
5			12 (60mg)		8 (120mg)	4 (4mg)
6			11 (55mg)		7 (105mg)	3½ (3½mg)
7			10 (50mg)		6 (90mg)	3 (3mg)
8			9 (45mg)		5 (75mg)	2½ (2½mg)
9			8 (40mg)		4 (60mg)	2 (2mg)
10			7 (35mg)		3 + 1 D (45mg+5mg)	1½ + 1 D (1½mg+5mg)
11			6 (30mg)	18 (90mg)	2 + 2 D (30mg+10mg)	1 + 2 D (1mg+10mg)
12	7½ (15mg)		5 (25mg)	15 (75mg)	1 + 3 D (15mg+15mg)	½ + 3 D (½mg+15mg)
13	5½ (11 mg)		10 (20mg)	12 (60mg)	0 + 4 D (0mg+20mg)	0 + 4 D (0mg+20mg)
14	4¼ (8½mg)		9 (18mg)	11 (55mg)	9 D (18mg)	9 D (20mg)
15	3 (6mg)		8 (16mg)	10 (50mg)	8 D (16mg)	8 D (16mg)
16	2⅜ (4¾mg)		7 (14mg)	9 (45mg)	7 D (14mg)	7 D (14mg)
17	1¾ (3½mg)		6 (12mg)	8 (40mg)	6 D (12mg)	6 D (12mg)
18	1¼ (2½mg)		5 (10mg)	7 (35mg)	5 D (10mg)	5 D (10mg)
19	1 (2mg)	3 (15 mg)	4 (8mg)	6 (30mg)	4 D (8mg)	4 D (8mg)

20	¾ (1½mg)	2½12½mg)	3 (6mg)	5 (25mg)	3 D (6mg)	3 D (6mg)
21	½ (1mg)	2 (10mg)	2 (4mg)	4 (20mg)	2 D (4mg)	2 D (4mg)
22	⅜ (¾mg)	2 (10mg)	1½ (3mg)	3 (15mg)	1½ D (3mg)	1½ D (3mg)
23	¼ (½mg)	1 (5mg)	1 (2mg)	2 (10mg)	1 D (2mg)	1 D (2mg)
24	⅛ (¼mg)	½ (2½mg)	½ (1mg)	1 (5mg)	½ D (1mg)	½ D (1mg)
25	stop	stop	stop	stop	stop	stop

4.3 Other pharmacological treatments that may sometimes be useful

There are no drugs that can act as a substitute for benzodiazepines and are generally best avoided. Rarely the drugs below can be used to help a particular symptom.

Antidepressants

There is limited evidence that antidepressants help benzodiazepine withdrawal (Denis, Fatseas et al. 2006; Voshaar, Couvee et al. 2006; Parr, Kavanagh et al. 2009) if depression is present or emerges during withdrawal, then antidepressants are indicated. It may be beneficial to consider a more sedating antidepressant, such as trazodone or mirtazapine. If this is prescribed for a patient who also uses alcohol or stimulants and the doses are high, the antidepressant effect may be undermined. Also antidepressants have disadvantages: they can on starting increase anxiety, can take 2-3 weeks to reach maximum effect and can cause withdrawal problems in their own right when stopped.

Beta-blockers

These may be useful for short-term management of physical symptoms of anxiety e.g. palpitations, tremor, panic attacks but do not help the psychological symptoms.

Anti-epileptics / mood stabilizers

There is some evidence that carbamazepine or oxcarbazepine may be helpful in reducing withdrawal symptoms, especially to reduce the risk of seizures, especially in patients taking more than 20 mg / day (Denis, Fatseas et al. 2006). It may be used instead of benzodiazepines for withdrawal from high doses, based on descriptive studies (Ries, Roy-Byrne et al. 1989; Schweizer, Rickels et al. 1990), most commonly in an inpatient setting.

Melatonin

A retrospective longitudinal study by Kunz et al indicated that MR-melatonin may facilitate the reduction and discontinuation of long term benzodiazepine/Z-drug drug use especially in older insomniacs (Kunz, Bineau et al. 2012).

NB: Flumazenil is a benzodiazepine antagonist which has been used for rapid and relatively painless benzodiazepine detoxification but much more evidence is needed before this treatment is accepted, and giving flumanezil to a benzodiazepine-dependent patient can precipitate withdrawal.

Table 6 Responding to problems withdrawing from benzodiazepines

Problem	Potential response
▪ Difficulty coping with BZ withdrawal symptoms	• Use a BZ with a longer half-life (e.g. diazepam) • Reduce rate of BZ reduction or hold dose temporarily at current level • Increase psychosocial support
▪ Liking benzodiazepine too much to reduce it	• Use slow-onset BZ, e.g. oxazepam
▪ Continuing anxiety or depression	• Treat psychiatric problems more effectively
▪ Difficulty coping with stress	• Increase psychosocial support, e.g. counselling or BZ user group

▪ Difficulty sleeping: ○ Short-term ○ Long-term	• For short-term problems, reassure patient • For longer-term problems, use sleep hygiene and other psychological strategies
▪ Using different amounts each day, bingeing, etc.	• Increase frequency of pickup, even to daily on interval prescriptions • Increase level of supervision by relatives (or pharmacists if willing)
▪ Protracted withdrawal symptoms	• Increase psychosocial support and reassure patient that these will resolve over time

Inpatient versus community detoxification

If the patient is taking large doses and feels unable to reduce in the community, then in some areas withdrawal can be started in an inpatient setting. A switch to long-acting medication usually takes place over 2–3 weeks and may reduce the severity of the withdrawal symptoms, but does not prevent the ongoing withdrawal syndrome. If the use has been long-term it can rarely be completed as an in-patient because of the time that would be needed.

4.4 Longer-term prescribing

The decision to prescribe longer-term benzodiazepines should be rare and made with care. If patients are prescribed long-term benzodiazepines, they are inevitably put at risk of all the negative effects including cognitive impairment etc.

Unfortunately, most often, long-term benzodiazepine use results from inadvertent continuation of short-term prescriptions and started many years ago before all problems of their long-term use were fully known, or from inappropriate and poor prescribing. Many of these problems can be reduced by strong clinical management and an assessment of the likely risks and benefits in an individual.

Conditions under which longer-term prescription may be considered

The Royal College of Psychiatrists Guidance from 1997 (Royal College of Psychiatrists 1997), states that for benzodiazepines in psychiatric disorders 'the decision to allow dependence to develop is sometimes defensible but it must be appreciated, that once dependence has become established, it is *often* extremely difficult to treat and may become a long-term or even permanent state.' It goes on to say that 'there are circumstances in which longer-term prescription of benzodiazepine may be considered desirable because the alternatives to benzodiazepine are considered worse than the use of benzodiazepine.…". In rare instances long-term prescriptions of benzodiazepine may be seen as maintenance treatment or harm reduction in patients who would otherwise consume illicit benzodiazepines.' But BAP state that "Maintenance prescribing in illicit drug users cannot be recommended on the basis of existing evidence, although it may reduce illicit benzodiazepine use in some patients (Lingford-Hughes, Welch et al. 2012).

There are three types of clinical situation in which long-term prescribing of benzodiazepines may be considered defensible, on the understanding that dependency may develop (Department of Health 2007):

1. In psychiatric illness, for the treatment of resistant, persistent severe anxiety or insomnia, panic disorder, generalised anxiety disorder, social phobia, dysphoric disorder, and anxiety due to medical illness
2. In benzodiazepine users, where there are withdrawal symptoms that are persistent, debilitating or intolerable and have tried everything with support and are unable to stop
3. As part of a harm reduction treatment, in those who have an inability to stay off alcohol or illicit benzodiazepines but in whom the harm reduces significantly when on a benzodiazepine prescription. In this case continuing to prescribe (e.g.

diazepam) may cause less harm than stopping the prescription, especially if the patient has chronic active hepatitis C. The benzodiazepine script should be stopped immediately if the patient relapses to alcohol or illicit benzodiazepines.

Such prescribing must, however, meet the following criteria:

1. Treatment must be for a recognised illness or disorder, with which alternative treatments with non-addictive drugs have failed, i.e. treatment resistance exists.
2. The benefits of treatment must outweigh the risks, i.e. the alternatives are worse or the benefits are better.
3. The decision is taken in conjunction with patient, who must accept increased risks, such as memory problems, emotional suppression and dependency etc.
4. The treatment is strictly individualized and treatment is reviewed periodically.
5. The clinician must be able to justify the clinical decision to prescribe and demonstrate an appropriate discussion with the patient, with details noted in the clinical records.

PART 2 SECTION 5 SPECIAL GROUPS

Introduction
People of all ages and both genders use and misuse benzodiazepines or similar drugs, for many different reasons and so far we have discussed the vast commonality of use and treatment for long-term use. In this section there is more detail about specific groups and their specific problems.

People who use these drugs are on a spectrum but tend to fall into three main groups. The first group are patients with a mental health problem and these are discussed below in 5.1. The second group, the “therapeutic dose” users are patients who use therapeutic doses and although covered in part 1, more detail is given here in 5.2. The third group are people who tend to use high-doses, may use illicit benzodiazepines and other illicit drugs and / or alcohol are seeking pleasure. They are discussed in detail in 5.3 and 5.4.

There is overlap between all these groups but it is important to distinguish between the as the clinical approach may have to differ. The therapeutic group are more likely to be over 40 years old, female and never or rarely use other drugs, including alcohol. They were most likely to have had them started by a doctor, in the beginning for the relief of debilitating symptoms such as anxiety and or insomnia. They rarely misuse benzodiazepines and rarely increase their dose. The people who use high-dose benzodiazepines are more likely to be male, under 30 years old and often are using other illicit drugs and / or alcohol. Their use tends to increase and they may use in binges. For further characteristics of these groups see table below:

Table 7 Classification of benzodiazepine users by dose used and tolerance effects (Smith and Wesson 1983; Smith and Landry 1990)

	Therapeutic-dose benzodiazepine users	**High-dose benzodiazepine users**
Person variables	▪ Female>Male	▪ Male>Female
	▪ Age >40 yrs	▪ Age <30 yrs
	▪ Never or rarely use other drugs	▪ Often use other illicit drugs (⅔ use opiates) regularly or in binges
	▪ Seek relief from unpleasant (negative) symptoms, e.g.	▪ Seek positive effects that give fun or pleasure/high

	insomnia, anxiety	▪ Seek mind numbing effects or memory / thought suppression
Drug variables	▪ Low doses are sufficient, over an extended period of time	▪ Lower doses are not sufficient, once started
	▪ Continuing efficacy reported, so happy on current dose	▪ Efficacy wears off rapidly, so seek higher doses
	▪ Seek hypnotic effects to which tolerance may develop ▪ Seek anxiolytic or anti-panic effects	▪ Seek sedation, 'high', euphoria to which rapid tolerance develops ▪ Seeking mind-numbing effects to escape, achieve oblivion, control anger or other feelings to which tolerance develops rapidly
	▪ Dose escalation uncommon, even over long-term follow-up, as little tolerance develops to desired effects ▪ If escalation occurs, it is to treat the problem more effectively (rather than for fun or pleasure), so illicit use is rare	▪ Dose escalation common, as tolerance develops rapidly to desired effects ▪ Often binge, use with other drugs to potentiate the effects ▪ Prefer rapid onset / potent BZ ▪ Use techniques to increase the speed of onset of effects
	▪ Stable daily dose which is constant or decreasing over time ▪ On a legal script or self-medicators, who do not typically misuse BZ	▪ Often obtain BZ illicitly from other users or via internet ▪ May supplement prescribed dose ▪ May try more than one prescriber
	• For anxiety typically take BZ 3–4 times a day, in order to maximize reduction in anxiety • For insomnia, typically taken once daily at night time for night sedation	▪ Typically take BZ as single dose in day, in order to maximize euphoria/buzz ▪ Typically taken at a similar time to other sedative drugs (e.g. opiates) to enhance the buzz
Treatment variables	▪ Easier to treat, esp. in primary care	▪ More difficult to treat; may need secondary care treatment
	▪ Low control / monitoring over treatment required	▪ High control / monitoring needed
	▪ Engage well in treatment and are happy to take most alternative treatments suggested ▪ Relapse risk low following cessation	▪ Typically difficult to engage in treatment and often do not follow agreed treatment plans ▪ Relapse risk high following cessation

Populations at risk of misusing benzodiazepines

About half of the population do not find the effects of benzodiazepines either positive or reinforcing (Johanson and Uhlenhuth 1980; De Wit, Johanson et al. 1984), meaning that they do not want to continue taking them, whereas the other half find benzodiazepines reinforcing and are therefore at risk from misuse.

5.1 People with mental illness

Benzodiazepines are used much less in the treatment of mental illness than they used to be but are still prescribed extensively, particularly at the time of acute admission. They have proven efficacy in the treatment of generalised anxiety disorder, panic disorder and social phobia, but because of risks of sedation and dependency they are now

recommended as third line treatments after a selective serotonin reuptake inhibitor (SSRI) antidepressant and psychological treatment (Wilson, Nutt et al. 2010); www.bap.org.uk/pdfs/BAP_Sleep_Guidelines.pdf). Counselling alone may have similar or greater efficacy in anxiety management (Catalan, Gath et al. 1984). Benzodiazepines nevertheless remain useful in a small number of patients with these conditions. Dose escalation does not usually occur and concerns about potential problems in long-term use should not prevent their use in patients with persistent, severe, distressing and impairing anxiety symptoms' (Nutt 2005).

But studies have shown that hypnotics and anxiolytics are still likely to be used in psychotic conditions, all anxiety disorders, especially for panic disorder, phobias and obsessive-compulsive disorder, a depressive episode and generalised anxiety disorder, but much less commonly for neurotic disorders in general. However NICE clinical guidance now states that benzodiazepines should not be used in the treatment of panic disorder with or without agoraphobia, and should not be used in the treatment of generalized anxiety disorder except in acute crises (NICE 2011). Use during depressive episodes is thought to be largely inappropriate, and there is a risk of disinhibition and increased suicidality (Singleton, Bumpstead et al. 2001; Barbui, Cipriani et al. 2011). They should never be prescribed in dementia.

Depression is definitely not a primary indication for benzodiazepines but may be prescribed for symptomatic relief for a few days, giving antidepressants time to act, or cover an initial increase in anxiety when some antidepressants are prescribed (Royal College of Psychiatrists 1997).

In an acute emotional crisis such as bereavement or psychological adjustment the cognitive impairment from benzodiazepines may not allow patients to make an optimum response to the situation they are facing. On the other hand, short-term symptomatic relief may restore sleep and aid the natural healing process.

There is some evidence to support the short-term use of benzodiazepines in the prevention of relapse in schizophrenia, when premonitory symptoms are present. In this case, they would be employed in addition to prophylactic neuroleptics.

Benzodiazepines and similar drugs in personality disorders are best avoided, as there is a high risk of dependency and dose escalation. The disinhibiting effects may increase the incidence of aggression and suicidal behaviour, particularly when combined with alcohol. They can be used in the treatment of acute agitation or behavioural disturbance, whether due to psychosis, delirium or other causes. High doses may be required, e.g. lorazepam 1–4 mg stat, orally or parenterally, or chlordiazepoxide 40–60 mg q.d.s. Doses may need to be raised until sedation is achieved (NICE guidance on bipolar disorder 2006 Bipolar disorder
The management of bipolar disorder in adults, children and adolescents, in primary and secondary care)

5.2 People who have become dependent on prescribed benzodiazepines, sometimes referred to as "involuntary, therapeutic or iatrogenic users"

This group have been discussed previously in part 1 but are often the forgotten group. They were most likely to be started and continued prescribing by a doctor, rarely misuse them and rarely increase their dose. Although the risk of dependency of benzodiazepines was known early, many people were prescribed benzodiazepines long-term, often for years, as they appeared to work. Many of these people then realised they were dependent on them and the result was worse than the original problem. Sadly this poor long-term prescribing of benzodiazepines is still continuing, although z-drugs and analgesic prescribing have replaced some of it, bringing their own problems.

Some people knowing the problems want to come off and many succeed with the right help but others are not able due to the over-whelming withdrawal symptoms on any attempt. Or they want to continue knowing the risks and prescribers - after ensuring informed consent - need to support the patient's decision. Many want to come off and detoxification is undertaken as described earlier. The reduction in dose should always be flexible and controlled by the patient, not the doctor. The decision to reduce should not be forced by the doctor.

How best to support this decision, sample reduction regimes and additional support suggestions can all be found in section 4.2.

5.3 People who use alcohol

Benzodiazepines have proven value in alcohol detoxification (Sellers, Naranjo et al. 1983; Mayo-Smith 1997; Kosten and O'Connor 2003). The regime may be fixed, led by the patient or dictated by the severity of the symptoms.

According to the 2007 Clinical "Orange" Guidelines (Department of Health 2007), patients are deemed suitable for home alcohol detoxification if they have no history of fits or delirium tremens, do not pose a suicide risk, have social support, show no significant poly-drug misuse, and are not dependent on benzodiazepines. If these criteria are not met, inpatient detoxification is recommended.

Chlordiazepoxide is commonly the benzodiazepine of choice in alcohol detoxification, although sometimes diazepam is used as an alternative. Both reduce seizures during alcohol withdrawal. The role of anticonvulsants such as carbamazepine in alcohol withdrawal remains unclear but is equally efficacious to chlordiazepoxide in treatment regime and seizure prevention but they have no advantage when combined (Lingford-Hughes, Welch et al. 2012)

The use of benzodiazepines in alcohol problems outside of the detoxification context is less clear, with no satisfactory evidence either for or against. Anecdotally, there appears to be widespread use of benzodiazepines in primary care for patients wishing to reduce their alcohol consumption and for those who have stopped drinking – apparently substituting benzodiazepine dependence effectively for alcohol dependence but there is no evidence to support this and should not be done. The combination of benzodiazepines and alcohol enhances the 'buzz' experienced, but also increases the risk of central nervous system and respiratory depression. Chronic (but not acute) consumption of alcohol results in enhanced benzodiazepine metabolism, thereby reducing the length of action of its effects. Hence benzodiazepines should not be used outside of detoxification in people who drink.

GP prescription of benzodiazepines to people who are dependent on alcohol before referring them to another service for a community detoxification and should be avoided, as should prescribing 'a small dose of diazepam' to help alcohol-dependent patients who claim to 'have stopped' or 'cut down'. Benzodiazepines can increase relapse rate and alcohol consumption and increase cravings in people who have been previously dependent (Kushner, Abrams et al. 2000; Poulos and Zack 2004; Gitlow 2006).

We also know that people who drink moderately or harmfully but not light drinkers (average 4 units a week), have an increased liking for the effects of benzodiazepines hence care needs to be taken in all people who use about 4 units / week (Ciraulo, Sands et al. 1988; De Wit, Pierri et al. 1989; de Wit and Doty 1994; Evans, Griffiths et al. 1996).

5.4 People who use illicit drugs or are in drug dependence treatment

Benzodiazepine misuse is a serious problem in people who use drugs, especially for polydrug users (Royal College of General Practitioners 2004) and there is little evidence to guide practitioners (Lingford-Hughes, Welch et al. 2012). As well as taken orally, they can be snorted and / or injected (Seivewright 1998). Up to 90% of attendees at drug treatment services reported their use in a 1-year period (Gossop, Marsden et al. 2003). In another study 54% of those entering treatment had used illicit benzodiazepines in the last 3 months, 34% were using them weekly or more frequently and 4% were injecting them. Use of benzodiazepines was higher in those who also had an alcohol problem (Gossop, Marsden et al. 2001). Hence many people presenting to drug and alcohol dependency services have a problem with long-term dependence on benzodiazepines.

People who use them, along with other illicit drugs and / or alcohol generally are using them for a different reason as they tend to increase rather than dampen activity in the brain reward centres. They are also used to alleviate withdrawal symptoms from other drugs, especially crack and / or heroin and are more likely to be taken in binges.

But people who use drugs may also use benzodiazepines and similar drugs as self-medication to improve their mood or their coping skills (Seivewright 2000), but these are not clinically appropriate reasons to use benzodiazepines; psychological therapy is the treatment of choice.

There is also evidence of the various harms associated with benzodiazepine use:

1. Use of benzodiazepines, whether prescribed or not, amongst heroin users and those on opioid substitution therapy, appears to lead to higher rates of risk behaviour and social dysfunction, and problems may lead to fatal overdose (Darke 1994; Strang, Griffiths et al. 1994; Bleich, Gelkopf et al. 1999; McCowan, Kidd et al. 2009), and poorer clinical outcomes (Darke, Ross et al. 2010)
2. HIV and other infections are more common in people using opioids plus non-prescribed benzodiazepines, and there is little evidence that these risks reduce if all the drugs being used are prescribed (Darke 1994). This risk is increased where preparations not meant for injecting are be injected.
3. Use of opioids in combination with benzodiazepines is associated with increased opioid toxicity and performance deficits (Lintzeris, Mitchell et al. 2006)
4. Dependence and tolerance are significant problems with these drugs and probably worse in dependent populations.
5. Withdrawal symptoms are worse with longer use (Seivewright and Dougal 1993).
6. There is a real risk of diversion on to the illicit market.

But there are some indications for prescribing benzodiazepines in patients who use drugs:
a) Short-term:

- Detoxification from alcohol or other sedative or hypnotic withdrawal but not for relapse prevention. Naltrexone, disulfiram and acamprosate are better used for preventing relapse
- Persistent debilitating or intolerable benzodiazepine withdrawal symptoms on reduction programme when all else has been tried.
- Adjunct to detoxification from high use cannabis or skunk if irritability and restlessness are marked (Winstock, Ford et al. 2010)
- Detoxification from solvents and other alcohol-like substances, GHB (gamma-hydroxybutyrate) and its prodrugs GBL (gamma-butyrolactone) and 1,4-CB (1,4-butanediol) (McDonough, Kennedy et al. 2004; Snead and Gibson 2005; Wojtowicz, Yarema et al. 2008; van Noorden, van Dongen et al. 2009)
- Opioid withdrawal particularly where acute and or nearing the end to reduce anxiety and distress.
- Ketamine withdrawal to reduce anxiety or distress (Winstock AR, Mitcheson L. 2012)
- Treatment of choice in cocaine-induced delirium, where neuroleptics may react with cocaine to produce dyskinesia or hyperthermia.

b) Longer-term

- To terminate illicit benzodiazepine or contact with illicit drug markets
- Anecdotal evidence suggests using in chronic hepatitis C to help to reduce or stop drinking but need to be stopped if drinking continues.

Prescribing for people who are using high doses and those who use illicit drugs

Using high doses tolerance can develop quickly and people need to often escalate their dose and use as a single dose in the day, in order to maximize the effect.

Before benzodiazepines are prescribed to illicit users, it is important to undertake the usual assessment covering the amount and pattern of their use, other drug use, any side-effects, withdrawal symptoms including fits and a physical and mental health history. Also there needs to be at least two consecutive recent urine screens, which are positive for benzodiazepines, no negative urine screens for benzodiazepines in the last 4 months in and evidence from the history and symptoms that the patient is dependent on benzodiazepines. In addition the benefits of treatment will outweigh the risks (diversion, overdose, etc) and be happy to prescribe.

It is important to use psychological interventions and not prescribing in patients who binge-use benzodiazepines. An algorithm to assist in deciding whether or not to prescribe benzodiazepines to high-dose users is shown in Appendix 3, Figure 2.

The 2007 Drug Misuse and Dependence Guidelines on Clinical Management (Department of Health 2007) and the BNF (Joint National Formulary Committee 2011) both recommend that all benzodiazepines are converted to diazepam, although this has now been questioned in the BAP guidance for the treatment of benzodiazepine dependence for the following reasons:

- Diazepam has a long half-life (1–3 days, and an active metabolite 2–5 days), which allows a smooth and gradual withdrawal.
- Diazepam comes in three different strengths (2 mg, 5 mg and 10 mg) and in an oral solution (2 mg / 5 ml), which allows flexibility when planning dose reductions for individual patients.
- Doses of benzodiazepine approximately equivalent to 10 mg diazepam can be used when calculating a conversion (Table 1).
- Diazepam can be issued on an FP10MDA interval prescription, allowing for daily pickup (or supervised consumption where local arrangements exist).
- A single benzodiazepine should be prescribed at a time. Only if there are definite problems caused by the rapid onset of diazepam (e.g. benzodiazepine-seeking behaviour, difficulty reducing) should an alternative slow-onset benzodiazepine such as oxazepam be used, and this may require daily prescriptions initially.

The disadvantages of converting all patients to diazepam are as follows:

- Changing to another medication may upset a patient's stability, especially if diazepam does not seem to suit them.
- It has a rapid onset of effect, giving patients a drug 'high', and therefore is psychologically reinforcing and strengthens the desire to take it again.
- Diazepam has a high street value and 10mg diazepam tablets have a greater street value than other sizes so consider issuing 5 mg or even 2 mg tablets

- It is widely available on the black market and the Internet, for anyone who wishes to buy it illicitly. This is not illegal if for personal use.

It is rarely appropriate to start a dose of more than 30 mg diazepam daily, and indeed a lower starting dose may be adequate. In almost all cases, 30 mg is sufficient to protect

against withdrawal fits, even in patients who have been taking much above this dose. In patients with difficulty sleeping, they should be encouraged to split the dose and keep back at least a third of the total dose for night-time use to assist with sleep (Ford, Roberts et al. 2005)

As with new opioid substitute prescribing, daily dispensing on FP10MDA (or supervised consumption if appropriate) should be stipulated at first; progress to less frequent dispensing (e.g. 3 times a week) should only be made if and when the prescriber is satisfied that the patient is able to manage this appropriately and safely. The frequency of dispensing of all drugs may be reduced concurrently or consecutively, according to the clinical priorities.
Always ensure safe storage of medication in a locked receptacle out of reach of children.

All patients should be offered detoxification in the same way as other patients. Trials show that high-dose users are equally successful as others, over half were able to reduce their dose and there was no significant difference in discontinuation rates (Vorma, Naukkarinen et al. 2002). Also these reductions were maintained (Vorma, Naukkarinen et al. 2003).

Prescribing for patients who use both opiates and benzodiazepines

Benzodiazepines are commonly used in combination with opioids, such as heroin and methadone to try and enhance the 'buzz' experienced. Such combined use increases the risk of central nervous system and respiratory depression. Concurrent benzodiazepine and methadone use increases methadone blood levels but not benzodiazepine blood levels.

A strategy for prescribing benzodiazepines for these patients is shown in table 8 below:

Table 8 Strategy for prescribing benzodiazepines to opioid-dependent patients

1. Treat the opioid dependence first; this has a good evidence base, whereas benzodiazepine maintenance treatment does not.
2. Discuss with patients how they will control and reduce their benzodiazepine use themselves (without the need for a benzodiazepine prescription). Many are able to reduce their illicit supply themselves.
3. Reassess patients' benzodiazepine use once they are stable on their opioid prescription and it has been optimised. Clinical experience shows that benzodiazepine use (even what clinically appears to be dependence) often ceases once on a stable opioid substitution.
4. If use of benzodiazepines is continuing, reassess the reasons. Is it for sedation, the 'buzz', anxiety or the comedown from crack or other drugs? Does it enhance the opioid 'buzz'? Do not prescribe benzodiazepines if use is for pleasure or in binges.
5. If dependence on benzodiazepines is present, consider a short-term (6 weeks to 6 months) reducing prescription of benzodiazepines on daily pickup (a minimum of 6 days a week).
6. Stop the benzodiazepine prescription if persistent illegal benzodiazepine use or alcohol dependence present.
7. Consider similar staged detoxification as with other patients dependent on benzodiazepines.

Patients on opioid substitution therapy who might benefit from longer-term prescribing

A few people have a long-term opioid and benzodiazepine problem and do not stabilize on opioid substitution medication alone. One study, which looked at benzodiazepine prescribing in methadone maintenance treatment, showed that 79% on maintenance benzodiazepines stopped illicit use, compared to 27% when benzodiazepines tailed off (Weizman, Gelkopf et al. 2003). A study of opiate overdoses showed two risk factors

associated with respiratory arrest: prior abstinence from opiates and prior abstinence from benzodiazepines. A study undertaken in Edinburgh showed reduced injecting when benzodiazepine was prescribed (Rosenberg, Melville et al. 2002). However, controlled studies of benzodiazepine prescription in addition to other substitute medication are lacking and the guidance is limited (Department of Health 1999; Home Office Advisory Committee on the Misuse of Drugs 2000).

When considering longer-term prescribing this must always be balanced against the risks, especially the negative effects on memory and cognitive skills.

5.5 Women

Benzodiazepines and similar drugs are prescribed more often to women than to men and are often over-prescribed. They are used to help sleep disturbances, which are associated with other poor health issues and depression. Benzodiazepine metabolism doesn't seem to be altered by the menstrual cycle. Women are more likely than men to be living in poverty, to be single parents, and to be the main child and home carer, and so need community support. Many women and their GPs fail to recognize the symptoms of benzodiazepine overuse as well as women may feel ashamed of their dependence and often do not seek help.

Women may be given benzodiazepines without their knowledge; in particular for the sedative and amnesic effects of benzodiazepines. Flunitrazepam (Rohypnol) may be used for date rape but it is only available illicitly in UK. Victims of domestic violence or women who work in the sex industry, commonly use benzodiazepines (or other drugs or alcohol) to cope.

5.6 Pregnant women, neonates and breast-feeding mothers

Clinicians are cautious about prescribing drugs during pregnancy or when a mother is breast feeding because of possible risks to the foetus and infant. During breast feeding many drugs are excreted in the milk and ingested by the infant, with consequent concerns about short-term toxicity and longer-term neurodevelopment (Yoshida, Smith et al. 1999).

In some women benzodiazepines are used with other drugs, so the risks of poly-drug use (opiates, amphetamines, cocaine and crack, cannabis, nicotine, alcohol) for the foetus and neonate need to be recognized, along with the accompanying social and behavioural issues.

There may also be other problems associated with the pregnancy, such as poor social circumstances, poor nutrition, domestic violence, injecting risks (including infections, especially hepatitis B and C and HIV, deep vein thrombosis) and childcare issues. Of course, all the usual issues surrounding pregnancy, including good antenatal and postnatal care, need to be taken into account.

Pregnancy

As benzodiazepines are highly fat-soluble, they rapidly cross the placental barrier, as well as rapidly entering the central nervous system. Their use should therefore be avoided in pregnancy, particularly in the first trimester, and where it is at all feasible they should be stopped. If the woman is already taking benzodiazepines when she becomes pregnant, then a planned detoxification is best. If benzodiazepine use is considered essential during pregnancy, then it should be maintained at the minimum effective dose for as short a time as possible. Consideration should be given to dose reduction or discontinuation 2–4 weeks prior to delivery. Short-term use can be stopped quickly, while longer-term use must be reduced slowly in order to prevent withdrawal symptoms.

There seems to be no evidence to suggest that withdrawal, as long as it is done properly, causes any additional problems to the pregnancy or increases the risk of miscarriage or premature labour. It is not known how many benzodiazepines could cause foetal abnormalities. If benzodiazepine dependence from illicit or prescribed use is established, then the advice remains the same. Withdrawal always has to be balanced against the importance of retaining the patient in treatment.

If there is long-term in utero exposure to benzodiazepines, then a foetal benzodiazepine withdrawal syndrome is likely to follow birth and neonatal monitoring will be necessary. The withdrawal syndrome is worse when other drugs such as opioids are involved.

In early pregnancy the risk of teratogenesis is a concern but evidence linking benzodiazepines to congenital malformations is controversial. Pooled data from cohort studies showed no apparent association between foetal exposure to benzodiazepines and the risk for major malformations or oral cleft (Dolovich, Addis et al. 1998). But data from case-control studies showed that the risk of major malformations or oral cleft alone was increased (Laegreid, Olegard et al. 1990).

Until further studies are available, it is prudent to perform level 2 ultrasonography, if this is available, to rule out visible forms of cleft lip (Dolovich, Addis et al. 1998).

Third trimester and labour

The main risks associated with benzodiazepines in later pregnancy are neonatal toxicity or benzodiazepine withdrawal syndrome following delivery, as well as a possible long-term impact on neurodevelopment (Altshuler, Cohen et al. 1996). Neonates who are exposed to regular benzodiazepines during the third trimester of pregnancy and labour should be monitored for neonatal drowsiness, respiratory depression, benzodiazepine withdrawal syndrome and floppy infant syndrome (hypotonicity) following delivery. The latter may need treatment and can occur up to 1 month post-delivery.

Postnatal period and breast feeding

As a rule, benzodiazepines are not ideal during breast feeding and new prescriptions should be avoided in breast-feeding mothers. If an infant is exposed to benzodiazepines, monitoring for central nervous system depression and apnoea is advised. Drowsiness and a reduced sucking reflex have been reported in infants exposed through breast milk.

If babies have been exposed in utero then breast feeding may be beneficial to reduce neonatal withdrawal (Pons, Rey et al. 1994; Yoshida, Smith et al. 1999). In some social circumstances, it may be of greater benefit to both mother and child if breast feeding is continued, in order to facilitate the establishment of a good materno-foetal bond.

If the mother uses a number of drugs, then the risk of neonatal abstinence syndrome relating to any other drugs that she is using (e.g. opiates) also needs to be taken into consideration.

5.7 Parents and carers

The following groups of parents / carers need special consideration:

- Parents / carers of children who take benzodiazepines for their medical conditions, such as chronic anxiety, epilepsy.
- Parents / carers of children who use illicit benzodiazepines and/or other illicit drugs
- Parents / carers who may misuse their children's medication, and also may abuse their children by wrongly dispensing the medication to the child.

All the above issues are explored further in *Hidden Harm*, a report by the Advisory Council on the Misuse of Drugs (Advisory Council on the Misuse of Drugs 2003).

5.8 Children and young people

Benzodiazepines are generally not recommended for use in children. They should only be prescribed in exceptional circumstances, such as in febrile or epileptic seizures. In general, if benzodiazepines are to be prescribed to children, then they should be given in lower doses than in adults and only for very short periods of time.

Other issues to be considered include the following:

- Children may take prescribed benzodiazepines for epilepsy and treatment of febrile convulsions.
- Children may use non-prescribed benzodiazepines themselves.
- Children may use benzodiazepines and other drugs and may be injecting.
- Children's parents may misuse benzodiazepines and other drugs or may be on prescribed benzodiazepines. The child may, in fact, be acting as a carer while the parent is under the influence or withdrawing (Advisory Council on the Misuse of Drugs 2003).
- Children may be in risky situations, being used in the sex industry or involved in other forms of child abuse.
- The cognitive and emotional development of the child needs to be taken into account, as do relationships with siblings.

Benzodiazepines may paradoxically make young people and people with developmental disabilities more aggressive, anxious, nervous and less tolerant, more unfriendly, more impulsive and less inhibited, hence should not be used. Young people may take benzodiazepines to try to relax, reduce withdrawal symptoms involved with other drugs, or enhance the effects of another drug or substance. They may also self-medicate for internal pain and distress. They may see their parents taking medication and think this is the way to solve their own problems. The Internet is an easily accessible source of illegal benzodiazepines for the young.

If dependence in a young person has been established, then (as in adults) rapid withdrawal should *not* be attempted, as an acute withdrawal syndrome can occur. Withdrawal should be gradual and Fraser Guidelines and the rules of confidentiality should be observed.

Rates of prescribed use and non-prescribed use of sedatives and tranquillizers have fallen markedly in the UK in young people.

5.9 Older people

Prevalence and risks

The long-term use of benzodiazepine and similar drugs is significantly higher in older adults than in younger people throughout North America, Australia and Europe (Egan, Moride et al. 2000). In the UK, it has been estimated that around 15% of people aged over 65 years regularly take sleeping pills and older adults receive 80% of all prescriptions written for benzodiazepine hypnotics (Jorm, Grayson et al. 2000) and are commonly given to patients over 65 years in repeat prescriptions. Additional evidence based guidance on the use of hypnotics in older people has been published recently (Wilson, Nutt et al. 2010).

In the residential care setting, the use of benzodiazepines is lower where staff has received education in elderly care and where the organizational culture is supportive of low levels of use (Roberts, King et al. 1998). Successful reduction in benzodiazepine use

has been shown to increase mobility, improve alertness, reduce incontinence and promote wellbeing (Gilbert, Owen et al. 1993).

Adverse effects

Older people are more sensitive to the central nervous system depressant effects of benzodiazepines, which can cause confusion, night wandering, amnesia, ataxia (loss of balance), hangover effects and 'pseudo-dementia' (sometimes wrongly attributed to Alzheimer's disease). In the older patient with liver disease there is also a risk of benzodiazepines precipitating or contributing to a worsening of hepatic encephalopathy, even in those who have been maintained on a relatively low dose for some years (Madhusoodanan and Bogunovic 2004). Older people can be supported to come off long-term benzodiazepines, and have some benefit even when doses were small.

Their use should therefore be avoided wherever possible and when they are used the dosage should be half that recommended for other adults, and short-term. In addition, benzodiazepines without active metabolites (e.g. oxazepam, temazepam, lorazepam) are tolerated better than those with slowly eliminated metabolites (e.g. diazepam, chlordiazepoxide, nitrazepam). Equivalent potencies of different benzodiazepines are approximately the same in older and younger people.

Falls and fractures

There is evidence of an increased risk of falls and fractures in older people who take benzodiazepines (Leipzig, Cumming et al. 1999). The incidence of hip fracture appears to be associated with rates of benzodiazepine use, risk being highest during the first 2 weeks after starting a benzodiazepine and declining thereafter. It is unclear whether short-acting benzodiazepines are safer than long-acting types. In some studies, a slightly lower risk of falls was shown (Mendelson 1992), whereas in others the opposite was true.

Road accidents

Studies in older people suggest that this increased risk is related to dose and compounded when alcohol has also been used (Barbone, McMahon et al. 1998).

Insomnia and anxiety

Benzodiazepines are often ineffective as treatments for insomnia and higher cumulative intake is associated with increased sleep problems. There is some evidence that insomnia itself can be a major risk factor for injurious falls (Koski, Luukinen et al. 1998), and also that night sedation can actually reduce the incidence of falls (Avidan, Fries et al. 2005). Older people who wanted to stay on their benzodiazepine dose had elevated anxiety ratings when given the opportunity to withdraw compared with people who were willing to withdraw (Curran, Collins et al. 2003).

Cognitive changes

A trial of benzodiazepine withdrawal in general practice demonstrated subtle cognitive advantages and negligible costs in terms of discomfort to patients (Curran, Collins et al. 2003). Improvements in performance occurred in map searching, information processing, reaction time and digit span tests, which tap into real-life cognitive demands, e.g. to retain and manipulate numbers mentally. Improved accuracy and speed of information processing enhances performance in many daily activities, as do faster reaction times generally. In particular, enhanced information processing, reaction time and visuo-spatial abilities contribute positively to driving performance.

Benefits of benzodiazepine withdrawal

As well as individual benefits, there are also potential savings to health services in terms of reduced drug costs, and possibly through fewer road traffic accidents, falls and fractures. Rates of success are higher in the elderly population compared to other adults.

Success rates can be maximized if patients are provided with a tapered dose regime, information about sleep, and psychological support (see section 3).

Although professionals fear the consequences of benzodiazepine withdrawal in older people (Iliffe, Curran et al. 2004), particularly the unmasking of depression, there was no evidence from the Curran trial of emergent depression / anxiety that this occurred.

5.10 People with physical health problems

Benzodiazepines and other hypnotics and anxiolytics can occasionally be helpful when a person has an underlying physical health problem. If secondary insomnia is a result of underlying medical conditions, these should be identified and treated. They may also be helpful after a serious diagnosis, in an acute illness where there is agitation, acute anxiety or insomnia, as a pre-medication, as a muscle relaxant or as an anticonvulsant, either for status epilepticus or as an adjunct to other medication in treatment resistant epilepsy (Brodie 1990).

5.11 Hospital populations

Benzodiazepines are used frequently in hospital on a short-term basis, as they help patients sleep and reduce anxiety in an unusual environment. Some patients will, of course, be admitted to hospital who are already dependent on benzodiazepines and they may be concerned and anxious about their supplies.

Patients in hospital may be observed to have episodes of sedation or 'nodding', which are typical signs of intoxication and over-medication. On admission, signs may be minimal but may include 'drunken' behaviour, agitation, nervousness, drowsiness, stupor and sleep / unconsciousness. These effects may be exaggerated if a patient is taking other drugs, particularly an opioid or alcohol.

If the on patient is prescribed benzodiazepines in the community then their usual dose should be confirmed with their GP or drug treatment agency, and a drug screening test performed.

If the patient's prescriber cannot be contacted and there are signs of withdrawal, diazepam should be prescribed, in divided doses up to the usual maximum of 30 mg in 24 hours. Symptoms may occur 3–10 days following discontinuation of treatment with a long-acting benzodiazepine, and within 24 hours following abrupt withdrawal of a benzodiazepine with a short half-life.

5.12 Prison populations (Singleton, Farrell et al. 1999; Lader, Singleton et al. 2000)

Prison is a place where many people who use illicit drugs seek to address their drug problems, but is also where large numbers of them are housed in a confined space without access to the volume of illicit drugs available in the community. This presents a particular challenge to prison-based prescribers, who can find themselves a target for requests for benzodiazepines that prisoners intend to take and / or divert. Models of best practice for benzodiazepine prescribing in prisons will make provision for thorough assessment first and for ensuring that benzodiazepines are prescribed in liquid form.

Prescribing a reducing regime of benzodiazepines on first-night reception is a critical part of safe prescribing practice in remand prisons, where many users are received from the courts or police custody displaying marked symptoms of withdrawal. However, some inmates subsequently present with requests for repeat prescriptions and it can be very difficult to assess appropriateness in a brief consultation. It is important to be aware that many people who use illicit drugs will take a benzodiazepine or other drug prior to their

court appearance, so that if they are sent to prison their urine screen will be positive and they will be able to claim they are dependent. Having a benzodiazepine prescription in prison, even a reducing one, is highly valued as it helps pass the time in prison and can be used on the internal prison free market economy. Faced with such requests, many prison-based GPs refer the prisoner for psychosocial support prior to writing a script.

For further information, see Safer Prescribing in Prisons: a guide for clinicians (Royal College of General Practitioners Secure Environments Group 2011)

SECTION 6: OTHER ISSUES

6.1 Patient education

Patients and prescribers alike commonly understand benzodiazepines poorly. Generally, patients find them helpful and would like doctors to prescribe them but patients need to be made fully aware of the problems they cause, particularly long-term use. Just because benzodiazepines are effective and reduce suffering quickly, does not mean that they are the best treatment to give. The length of time a prescription will be provided for should be clear at the outset, as should the reasons why only short-term treatment will be given. If patients have been on long-term they must be made aware of the long-term problems and given information and support to detoxify off them.

They must also be explained the risks including the risk of overdose when combined with other sedative substances such as alcohol and opioids, as well as with psychiatric medications such as antipsychotics and antidepressants.

Advice on safe storage should be provided, particularly if children are around. Warning should also be given about potential sensory impairment that may affect safety when using machinery or driving, and the patient's responsibilities vis-à-vis the Driver and Vehicle Licensing Agency should be fully explained (Appendix 5).

Good written as well as verbal information may be appropriate. Patient information booklets do exist and there are some useful websites (see Resources appendix 1).

6.2 Referral to secondary care services

The decision to refer on from primary to secondary care needs to be when the complexity of the patient is beyond our expertise or the patient requests it. It may also been when inpatient stabilization or detoxification is being considered, especially as part of a polydrug and alcohol problem.

It may also involve the following factors:

Who to refer (for assessment +/- treatment)

- Patients with a dual diagnosis.
- Patients with complex needs – chaotic users.
- Patients with alcohol dependence syndrome.
- Patients with high-dose polydrug use.
- Patients with long-term therapeutic dependency who aren't managing with detoxification.

Where to refer to can also be a problem as there are few specialist benzodiazepine services. There are some voluntary agencies and a few areas have specific services that run individual and group support and work closely with primary care (see resources). There are sub-national and local variations in the level of prescribing and have access to

the information but most local areas offer treatment for people who develop problems but some provide very little.

Many community drug and alcohol teams will only address benzodiazepine problems in the context of polydrug use and some won't at all. Some regional alcohol units and drug centres may help. Those who do not have concurrent problems with illegal drug use are a distinct population within drug treatment services but may be under representative of the treatment need (National Treatment Agency for Substance Misuse 2011)

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APPENDICES

Appendix 1 Resources

Information

- www.appgita.com – All Party Parliamentary Group for Involuntary Tranquilliser Addiction.
- *Benzodiazepines: How they work and how to withdraw* – Professor C Heather Ashton DM, FRCP; revised August 2002. Download at http://www.theashtonmanual.com and http://www.benzo.org.uk/ashsupp11.htm

Support

Online

- BenzoBuddies – benzodiazepine withdrawal support.
- The Benzo Group Support Site.
- The Minor Tranquilliser Project (Benzodiazepine Support from Camden Mind).
- The T.R.A.P – The Tranquilliser Recovery and Awareness Place.

Local services

- BAT - Battle Against Tranquillisers, PO Box 658, Bristol, BS99 1XP. Tel: 0117 966 3629/965 3463. Mondays to Sundays 9am–8pm. Support for carers. Aims to help people who wish to withdraw from tranquillisers or sleeping pills. Provides individual counselling and local support groups.
- The Bridge Project / Bradford Benzodiazepine Withdrawal Service. Contact Jon Royle, Services for Drug Users, 35 Salem Street, Bradford BD1 4QH. Email: Jon.Royle@bradford.nhs.uk. Open to any adult residing in Bradford who requires help and support to reduce or cease their use of benzodiazepines.
- Bristol and District Tranquilliser Project, 88 Henleaze Road, Henleaze, Bristol BS9 4JY. Tel/Fax: 0117 962 2509 (Office); 0117 962 8874 (Helpline). Mondays to Thursdays 10am–4pm.
- Council for Involuntary Tranquilliser Addiction (CITA), JDI Centre, 3–11 Mersey View, Waterloo, Liverpool L22 6QA. Tel: 0151 474 9626. Fax: 0151 284 8324. Helpline: 0151 932 0102 (Mondays to Fridays 10am–1pm). Advice and support for people addicted to tranquillisers and sleeping tablets. Information, advice and leaflets available on anxiety, tranquillisers and antidepressants. Training offered for professionals.
- MIND – The Mental Health Charity, Granta House, 15–19 Broadway, London E15 4BQ. Tel: 0208 522 1728 (in London); 08457 660 163 (outside London). Email: contact@mind.org.uk. Mental health charity covering England and Wales. Works towards a better life for everyone with experience of mental distress. Has a network of over 200 local associations. Also produces a range of publications: see the website for

further details. (MIND publishes a booklet called *Making Sense of Treatments and Drugs: Minor Tranquillisers*).

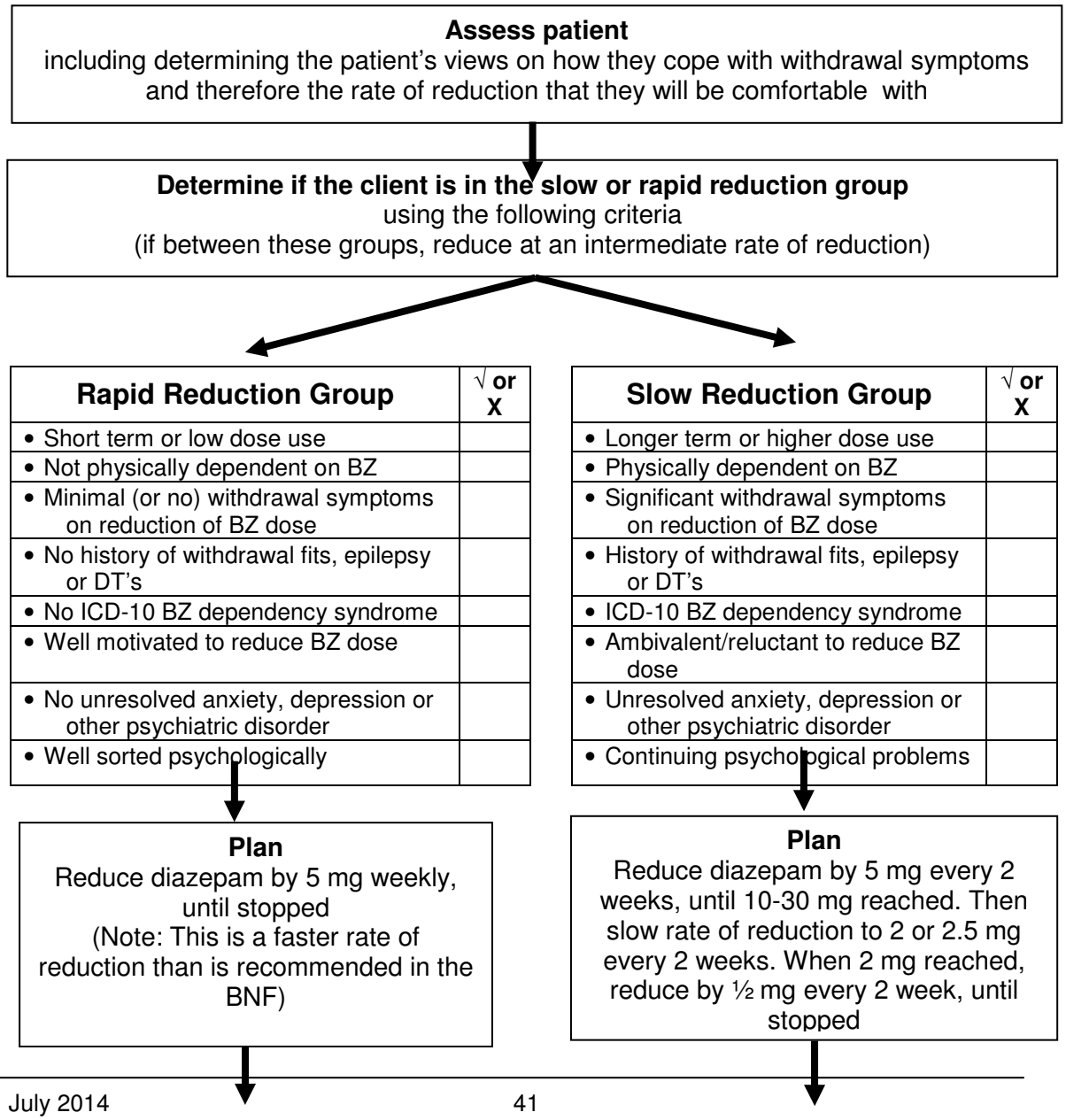
- Minor Tranquilliser Service, Mind in Camden. Tel: 0207 241 8980. Contact Melanie Davis. On Facebook.
- NECA (North East Council for Addiction), Bridge View House, 15–23 City Road, Newcastle Upon Tyne NE1 2AF. Tel: 0191 222 1262. Fax: 0191 263 9908. Email: newcastlebvh@neca.co.uk. Professor Heather Ashton is a member of the NECA Executive Committee.
- Recovery Road. Recovery Road Wellness Project is a charity which supports those affected by tranquilliser and antidepressant dependence. Visit website for contact details and helpline number.
- TRANX (Oldham), The Link Centre for Independent Living, 140 Union Street, Oldham OL1 1DZ; meets on Mondays 11am–1pm. Phone Barry Haslam on 01457 876355.

Appendix 2 Withdrawal from benzodiazepines

BAP guidelines suggest evidence on what is the optimal speed of withdrawal is lacking and this may help

A2: 1.Determining Rates of Reduction During Detoxification

NB: see BNF for further recommendations



If problems develop e.g. withdrawal symptoms, life stress: Reduce rate of reduction to weekly, or size of each reduction to 2 or 2.5 mg	If problems develop e.g. withdrawal symptoms, life stress Reduce rate of reduction to monthly, or size of each reduction (e.g. from 5mg to 2 or 2.5 mg, or from 2 mg to ½ mg

Note: Very high dose users (>50mg diazepam per day), may be reduced more rapidly (10mg per week), until 40mg is reached. In high dose users, it may be appropriate to aim for a therapeutic dose of 30mg diazepam daily, and allow a period of stability at this level, before reducing further (in order to reduce the risk of relapse during detoxification).

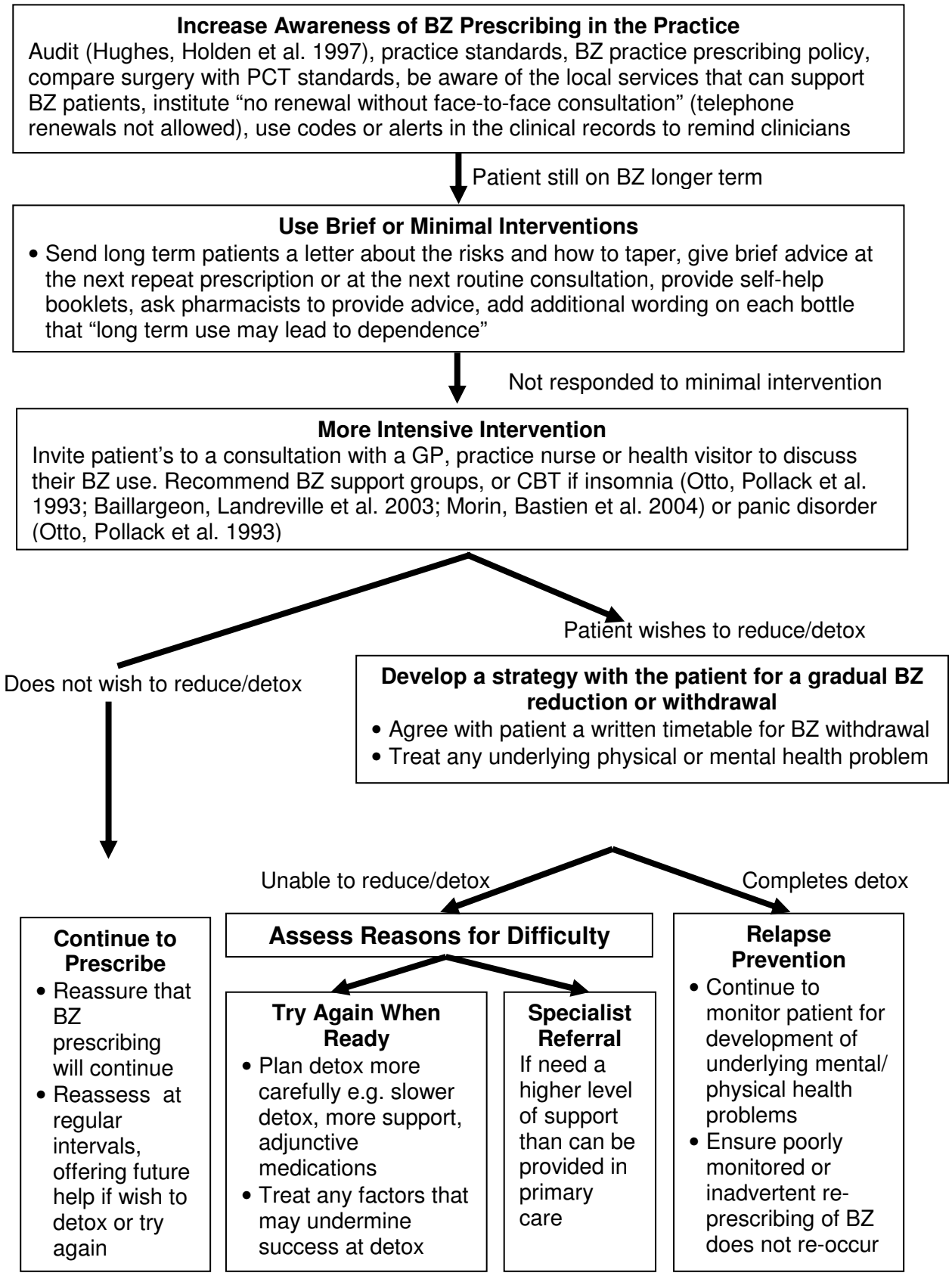
A2 Table 1 Ten steps to reducing long-term benzodiazepine use in patients who are physically dependent on them based on (Mant and Walsh 1997)

Step 1	Advise the patient that you wish to review their BZ medication with them.
Step 2	Assess dosage and pattern of BZ use over time, why it was first prescribed and when. Look for evidence of tolerance or dose escalation. Consider taking a urine sample to ascertain that BZ is being taken and no other drugs are being taken.
Step 3	Assess use of other psychotropic drugs, including opiates, alcohol and caffeine.
Step 4	Assess BZ withdrawal symptoms that the patient experiences, including fits, delirium and hypersensitivity to light and noise.
Step 5	Assess BZ side effects reported by the patient and / or observed by others, e.g. forgetfulness, ↓concentration, ↓energy, ↓motivation, ↓alertness, sedation, vagueness, being 'knocked off', ↓intellectual functioning, emotional blunting, poor coping, emotional suppression.
Step 6	Assess history of depression and anxiety. This may be due to long-term BZ use, BZ withdrawal or another cause. If depression or anxiety is severe or pre-dated BZ use, consider antidepressant treatment or psychological treatment.
Step 7	Assess other medical or psychiatric problems and how these are managed. Ensure treatment is optimized.
Step 8	Discuss the risks of long-term BZ use, tailoring the advice to the individual patient, and covering any BZ side effects identified espescially memory problems, emotional suppression, reduced coping and dependence.
Step 9	Discuss issues identified by the patient around withdrawing from BZ, e.g. fear of withdrawal, sleep problems, managing stress-related anxiety, while offering your help and support.
Step 10	Finalize the management plan by helping the patient to make an informed decision about whether they wish to attempt a reduction. If the patient agrees to the reduction: • Identify psychosocial supports amongst friends, relatives and self-help groups, as well as professionals. • Consider converting all diazepam tablets to 2 mg, or ask the patient to obtain a tablet cutter from the pharmacist in order to cut 5 mg tablets in half. • Negotiate an individualized withdrawal or reduction plan with the patient, involving them in key decisions about the design of the reduction regime, as patients invest more in a collaborative treatment approach. Agree the dose reductions and amounts, an agreed start date, flexibility built into the plan if it proves more difficult than expected, and a specified time for follow-up (usually in 1 week); ideally, write this down. • At review, positively reinforce any progress, and continue to see the patient weekly – a typical reduction will take 6–8 weeks to 6 months or sometimes

	longer. If patient distress threatens compliance or increases risk of relapse to illicit BZ, hold or slow the rate of reduction. • If the patient is unable to withdraw completely, congratulate them on progress made, and provide a stable dose (or intermittent use) for the time being, until the next big review. • Reassess the need for BZ periodically (e.g. every 3–6 months) and taper BZ if the patient agrees.

Appendix 3 Minimizing inappropriate prescribing

A3 Figure 1: A stepped care approach to reducing the prescribing of benzodiazepines in primary care based on (Lader and Russell 1993; Lader, Tylee et al. 2009)

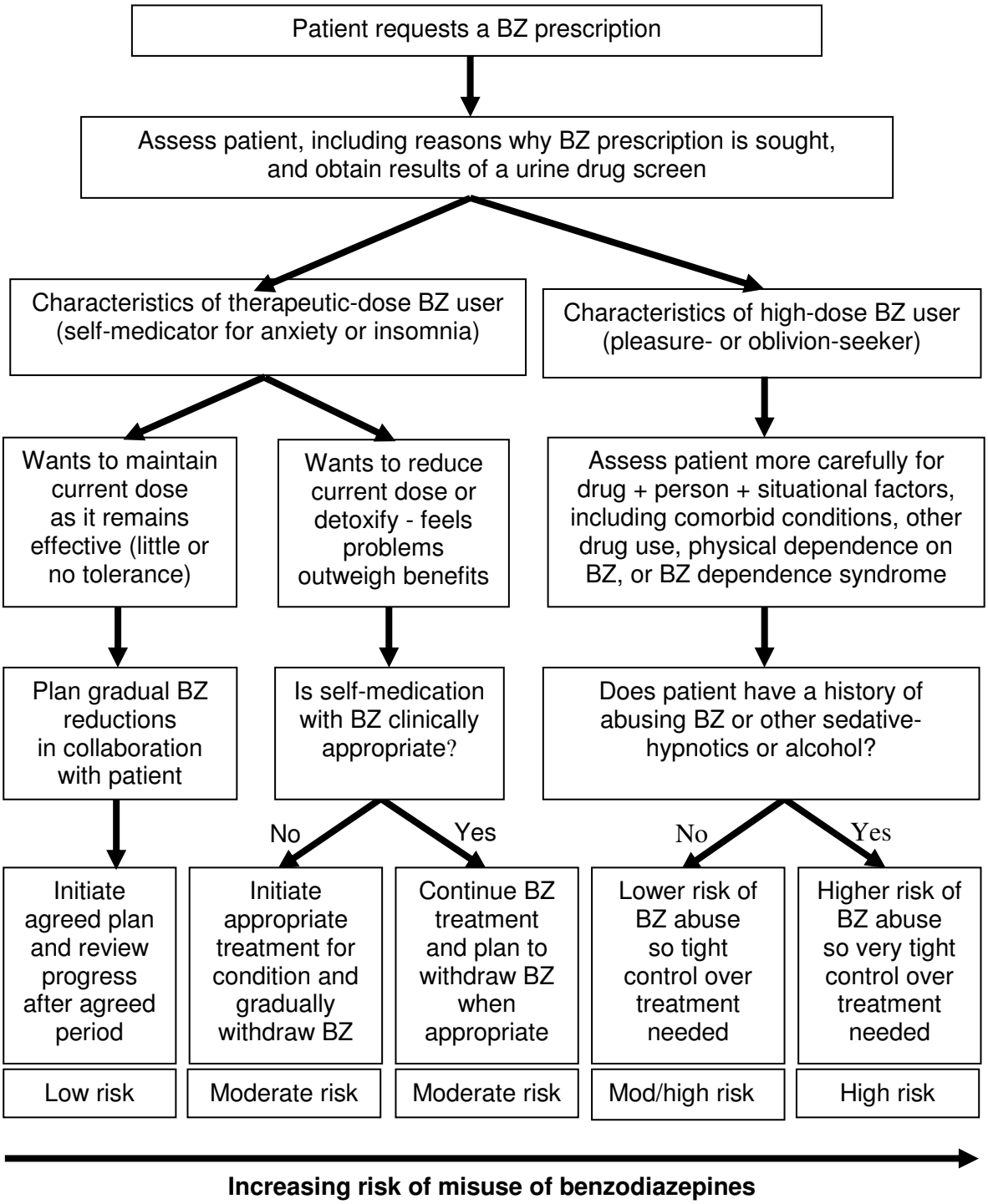


A3 Table.1 The 12 principles of benzodiazepine prescribing

Do's	
1.	Follow up-to-date evidence-based BZ guidelines.
2.	Help and support long-term BZ users in making an informed decision about whether they wish to attempt to reduce or stop BZ use.
3.	Be aware that BZ may work merely by suppressing symptoms, may cause many adverse effects, especially on cognitive functioning, and may appear to be clinically effective simply by preventing rebound insomnia / anxiety or withdrawal, rather than promoting genuine sleep or truly reducing anxiety.
4.	Optimize treatment of underlying conditions (5 Ps: physical, physiological, pharmacological, psychiatric and psychological) before considering treatment with a BZ.
5.	Remember that most insomnia and anxiety should be treated non-pharmacologically. Only prescribe BZ where the following five criteria have *all* been met: • A clear indication or diagnosis has been confirmed in which BZ use is appropriate. Do not prescribe for 'general stress' or 'poor coping'. • Underlying conditions causing the anxiety or insomnia have been treated. • The short-term goals of BZ treatment have been clearly defined and agreed with the patient. They must be clear enough for you to determine whether the BZ treatment is proving effective or not. • The risks and benefits of initiating or not initiating BZ treatment in a particular patient have been weighed up and discussed with the patient; this includes cognitive effects, driving, rebound and dependence (Posternak and Mueller 2001). If you are unsure whether the benefits outweigh the risks, do not prescribe. • The symptoms are severe, acute and self-limiting (*all* three must be present or anticipated), or BZ are being used as an adjunct for treatment-resistant anxiety or insomnia or they have been recommended by specialists.
6.	If you are initiating a BZ prescription, actively pursue best practice (as you would with other addictive drugs): • Specify to the patient the maximum length of time for which you are prepared to prescribe BZ for their condition at the outset, with an agreed time frame for review, explaining the risks of BZ use and why long-term use is not justified. • Issue short-term prescriptions only, use the lowest effective dose (building up if necessary), and prescribe for the briefest possible time. • Promote intermittent use as standard, in order to reduce tolerance and prolong the period of clinical effectiveness. With hypnotics, encourage the patient to take the hypnotic after being unable to initiate sleep at bedtime, or being unable to return to sleep after awakening in the night. • Review the patient regularly during the period of the prescription, assessing progress against the agreed goals of treatment (e.g. every 1–2 weeks). Terminate the prescription if it is ineffective, if tolerance develops, if there is BZ misuse (overuse, variable use, diversion), or if alcohol or another sedative-hypnotic is used simultaneously by the patient. • Set up mechanisms to prevent patients from obtaining continuation prescriptions from other partners in your practice, e.g. place an alert on the computer screen.
Don'ts	
1.	Do not add to the population of long-term BZ users via your prescription practices.
2.	Do not prescribe BZ for conditions in which there is a limited evidence base that they are effective (e.g. chronic insomnia) or where they may cause further

	deterioration (e.g. depression).
3.	Do not commence BZ for conditions in which they are contraindicated (e.g. sleep apnoea); take extra care in patients who have a high risk of misuse (e.g. moderate or high alcohol drinkers, opiate users, sedative-hypnotic abusers).
4.	Do not provide BZ prescriptions to patients who are not known to you, unless you check with the normal prescriber and you complete any other checks that you would normally perform for drugs of abuse (e.g. opiate users).
5.	Do not prescribe BZ precipitously or against your better judgement in response to pressure from the patient.
6.	Do not prescribe BZ without considering the pharmacokinetic differences between the different types, and their effect on different patient groups: • Avoid long-acting BZ and those with active metabolites in the elderly (e.g. diazepam). • Avoid rapid-onset BZ in people with cognitive compromise (e.g. risk of falls) or who are prone to abuse them (unless carefully monitored).

A3 Figure 2 Assessing a patient's risk of abusing benzodiazepines if provided with a prescription



Reducing diversion and illicit use

General practice-generated scripts were previously the largest source of diverted benzodiazepines but this has now been superseded by supply from abroad and via the Internet.

Recommendations on how to reduce benzodiazepine diversion from a report looking at Bolton, Salford and Trafford (Honor, Kearney et al. 2002) include:

- Tighter controls on the prescribing of benzodiazepines by GPs, hospitals and drugs services

- Development of PCT-led strategies utilizing techniques proven to work, such as sending letters to all those in receipt of long-term scripts, review by GPs, and employment of benzodiazepine nurses to work with long-term dependent users in a time-limited way
- Better support for GPs to inform their practice and protect them from intimidation
- Encouragement of GPs to join shared care programmes and attachment of more drug liaison workers to GP practices
- Piloting of a benzodiazepine service and / or harm reduction programme for dependent polydrug users
- Development of a police-coordinated strategy focusing on diverted benzodiazepines and especially the development of organized bulk supply from abroad. Without a police strategy, there is a real potential for the trafficking market to replace any drought created by tighter prescribing.

Appendix 4 Alternative medications to benzodiazepines in the treatment of anxiety and insomnia

NB: Mainly used in specialist settings and some out of license

Drug class	Hypnotic	Anxiolytic
Antidepressants		
• First choice	• **Trazodone** (Molipaxin) • **Mirtazapine** (Zispin) • Non-sedative drugs (e.g. **SSRIs** (selective serotonin reuptake inhibitor)) effective if reduce anxiety or depression, e.g. paroxetine	• **SSRIs** effective for all anxiety disorders but start at half normal dose to minimize increased anxiety • **MAOIs (**monoamine oxidase inhibitor); effective for social anxiety disorder • Others: **trazodone duloxetine, venlafaxine**
Antipsychotics		
• First choice	• **Quetiapine** (Seroquel) in low dose (25–50 mg ON) is least likely to cause problems.	• Only recommended when they would already be clinically indicated in a patient, e.g. for treatment of psychosis
• Not recommended	• Typical antipsychotics no longer recommended due to extra-pyramidal side effects and tardive dyskinesia, e.g. chlorpromazine • Atypical antipsychotics no longer recommended due to metabolic side effects, e.g. olanzapine (Zyprexa)	• No longer recommended due to risk of extra-pyramidal side effects and tardive dyskinesia. Licensed for adjunctive management of severe anxiety and psychomotor agitation. May be used for control of agitation or disturbed behaviour in schizophrenia or mania
Other drugs that have a role		
• Antihistamines	• Sedative antihistamines, e.g. **promethazine** hydrochloridine (Phenergan, Avomine), **diphenhydramine** (Nytol)	• **Promethazine** hydrochloride (Phenergan, Avomine) has a long half-life but may cause agitation • **Beta-blockers** effective against somatic symptoms of anxiety (e.g. tachycardia, palpitations, tremor, sweating), e.g. propranolol (Inderal), oxprenolol (Trasicor)
• Others	• **Melatonin** (Circadin) licensed for insomnia in adults over 55 years	• **Pregabalin** (Lyrica) and **gabapentin** (Neurontin) • Licensed for generalized anxiety disorder • Care needed as there is major misuse in prison and suspected sudden deaths have occurred with buprenorphine or methadone • **Buspirone** (Buspar) is non-sedative and non-addictive; licensed for anxiety

Appendix 5 Legal and practical aspects of benzodiazepine prescription

Writing prescriptions

The majority of the benzodiazepine subgroup of drugs are classified as Schedule 4 (CD Benz) drugs under the Misuse of Drugs Regulations 2001. This effectively means that restrictions only apply to their import and export.

The only exceptions are temazepam, midazolam and flunitrazepam, which are Schedule 3 (CD no reg) drugs. This places restrictions on who can be in possession of them and on invoice retention, and details the requirement for safekeeping (although this class of drugs is generally exempt from safekeeping requirements). Prescription requirements for Schedule 3 drugs also apply to flunitrazepam *but not* temazepam, i.e. a flunitrazepam prescription would need to stipulate dose, form and quantity in words and figures, but temazepam would not. Flunitrazepam is *not* available on the National Health Service (NHS) and must be given as a private prescription only.

Following the Shipman Inquiry, changes were introduced that affect prescribing . These are all legal requirements unless otherwise stated:

- The validity of prescriptions will be reduced to 28 days. If an interval prescription (e.g. FP10MDA in England) is issued, this is 28 days from the last day the medication is issued on the prescription. Where the start date of the prescription is different from the date on the prescription (e.g. FP10MDAs), then the prescriber should state this and initial the entry.
- Prescriptions for Schedule 3 drugs must contain a prescriber identifier (six-figure NHS number or new six-figure identifier for private prescriptions).
- A standard private prescription form is required for schedule 2 or 3 drugs issued privately (FP10PCD).
- It is good practice for the quantity of schedule 2, 3 or 4 drugs not to exceed 30 days.
- It is good practice for prescribers not to prescribe or administer controlled drugs for themselves, or for close family or friends, except in exceptional circumstances.

The reader is referred to the following website for full guidance on these rules. (Royal Pharmaceutical Society of Great Britain 2006)
http://www.npc.nhs.uk/controlled_drugs/resources/controlled_drugs_third_edition.pdf

The majority of prescriptions for benzodiazepines in general practice substance misuse work are for diazepam, classified as a Schedule 4 (CD Benz) drug. It may be prescribed in instalments on the FP10MDA prescription form for a period of up to 14 days, allowing for daily pickup by the patient. Local arrangements mean that daily supervised consumption (DSC) can sometimes be used. Although prescription requirements do not apply to this class of controlled drugs, good practice would dictate that the following information is provided:

- Name, strength and form of the tablet, e.g. ‘Diazepam 5 mg tablets’.
- Dose stated clearly, e.g. ‘four tablets to be taken each day’.
- Any reducing schedule, written in a non-ambiguous manner, e.g. ‘four tablets to be taken each day in week one, then reduce to three tablets each day in week two’.
- Collection schedule, with instructions for Sundays and bank holidays, e.g. ‘collect daily with Sunday dose on Saturday and bank holiday doses on previous pickup days’.
- Quantity, e.g. 56. This does not have to be given in words and figures but prescribers may want to do so in order to reduce the risk of forgeries.

The cost of a diazepam prescription is small compared to other treatments for substance misuse patients. A 30 mg a day prescription using 10 mg tablets will cost £2.61 for 28 days or £33.93 a year (NHS Electronic Drug Tariff 2011).
http://www.ppa.org.uk/edt/July_2011/mindex.htm.

Benzodiazepines and driving

The Driver and Vehicle Licensing Agency (DVLA) have a unique view of benzodiazepines compared to other drugs of misuse and dependence. For licensing purposes, the DVLA finds it acceptable if the prescribed benzodiazepine use is within BNF limits, even if benzodiazepine dependence syndrome or benzodiazepine physical dependence exists, provided none of the following three criteria is met:

- There is no non-prescribed use of benzodiazepines.
- There is no prescribed use above BNF limits, e.g. >30 mg diazepam.
- There is no prescribed use within BNF limits associated with impairment.

For group 1 entitlement (cars and motorcycles), the presence of any of these three criteria will lead to licence refusal or revocation until the applicant has spent a minimum of 1 year free of such use. For group 2 entitlement (large goods vehicles, passenger-carrying vehicles) the period is 3 years (Driver and Vehicle Licensing Agency 2011).
www.dvla.gov.uk/dvla/medical/ataglance.aspx.

The literature on benzodiazepines and driving is extensive. Briefly summarized, it indicates that the risk of accident increases proportionately to dose, but that there is no dose without increased risk. Risk is highest soon after initiation of the medication, and when benzodiazepines are taken with other sedatives, particularly alcohol. Sleeping tablets can impair driving skills for up to 16 hours after ingestion. Tolerance to this effect occurs, but is slow and often incomplete. Longer-acting medications carry greater risk. It could be argued, therefore, that all patients who have been prescribed benzodiazepines are impaired to some extent, so we should warn all patients taking benzodiazepines that:

- Both illness and medication can result in driver impairment
- The risk of car accidents is increased, particularly if there is also use of alcohol or other sedatives
- The risk of car accidents is often reduced when drivers with psychiatric illnesses are well than when they are ill, and are on regular psychotropic medication, rather than on inadequate treatment or with irregular compliance
- They should avoid driving during the first month of treatment
- They should avoid driving while undertaking rapid withdrawal

If they are using illicit benzodiazepines or are on a prescribed dose higher than 30 mg/day, they should be advised:

- Not to drive until they have informed the DVLA and received permission to do so. The DVLA will, however, wish to revoke the licence or refuse to issue it, until the patient has been free of such use for 12 months (3 years for group 2 users)
- That it is the patient's responsibility to inform the DVLA, and the doctor's responsibility to inform the patient of this
- That the doctor will note in the clinical records that this advice has been given to the patient.

Sometimes patients will continue to drive after being warned not to do so, even when they are clearly impaired. Both the DVLA and General Medical Council state that, if doctors are aware that patients continue to drive in a dangerous way, their first response should be to press them more forcefully not to do so. If patients continue, doctors should break confidentiality and inform the DVLA, ideally after having informed the patient that they are going to do so. The doctor need not inform the patient first, if unable to communicate with the patient within a brief timescale or if this would put himself / herself at risk. This is a

very difficult area of practice. Doctors may not want to endanger their relationship with patients, but it would certainly be tragic, as well as highly problematic for any doctor, if patient's hurt or killed people while driving in a manner already known to be unsafe.

Appendix 6 Benzodiazepines and other drug interactions

Most drug interactions with benzodiazepines and other similar drugs involve enhanced central nervous system, respiratory and cardiovascular depressant effects and decrease motor coordination, when benzodiazepines are used in conjunction with other central nervous system depressants and sedatives which include:

Alcohol

- Combination of benzodiazepines with alcohol produces respiratory depression, heavy sedation, coma and death, an effect occurring with all sedative drugs.

Opioids

- Deaths have been associated with the concomitant use of benzodiazepines and methadone (Home Office Advisory Committee on the Misuse of Drugs 2000) or buprenorphine (Royal College of General Practitioners 2004), although these appear to be fewer with buprenorphine (Lintzeris, Mitchell et al. 2006; Lintzeris, Mitchell et al. 2007; Lintzeris and Nielsen 2010). It is therefore important to have a thorough assessment and review procedure with appropriately trained staff in place when prescribing benzodiazepines in conjunction with methadone or buprenorphine.
- In France, benzodiazepines are by far the most common drug found in the blood on post-mortem in those who have died while taking buprenorphine, with 80% having benzodiazepines, 50% cannabis, 50% psychotropics, 30% alcohol, 20% narcotics and 4% cocaine detected (Kintz 2002). Most patients used the benzodiazepines by injection, but oral benzodiazepine use may also result in death (Gaulier, Marquet et al. 2000).
- There is preclinical evidence that the combination of benzodiazepines and methadone may have an enhanced effect on the QTc, increasing the risk of torsades de pointes. Benzodiazepines, while having no effect on its own of prolonging the QTc, removes the protective effect of sodium channel blocking, especially at higher methadone dose levels. In contrast buprenorphine has little effect on the QTc (Kuryshev, Bruening-Wright et al. 2010).

Other clinically significant interactions (Martindale 2002)

- *Quinolone antibiotics:* (e.g. nalidixic acid, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin) can precipitate acute withdrawal in people dependent or withdrawing from benzodiazepines, presumably by displacing benzodiazepines from their binding sites on the GABA-receptors (McConnell 2008). The risk may be increased by using NSAIDs which probably cause an inhibition of GABA uptake, but which in combination with quinolone antibiotics may increase benzodiazepine withdrawal, seizures and other symptoms of quinolone toxicity (Unseld, Ziegler et al. 1990; Wong 1993).
- *Rifampicin:* may increase the metabolism of benzodiazepines by inducing cytochrome P450 enzymes resulting in a decreased effect.
- *Disulfiram:* inhibits the metabolism of benzodiazepines leading to a prolonged half-life, reduced clearance and increased sedative effect.
- *Buproprion*: There is an increased risk of seizures during benzodiazepine withdrawal as both the drug and withdrawal state lower the seizure threshold.
- *St John's Wort*: a herbal antidepressant may increase the metabolism of benzodiazepines by inducing cytochrome P450 enzymes resulting in a decreased effect.
- *Antiepileptics:* Carbamazepine, phenobarbital and phenytoin may all increase the metabolism of benzodiazepines by inducing cytochrome P450 enzymes resulting

in a decreased effect. Some studies have suggested that benzodiazepines may also decrease or increase phenytoin levels.
- *Theophylline:* may reduce the effects of benzodiazepines
- *Antivirals / HIV medication:* The HIV protease inhibitors indinavir, nelfinavir, ritonavir and saquinavir should *not* be used concomitantly with alprazolam, diazepam, flurazepam and midazolam because of the increased risk of prolonged sedation and respiratory depression; this is due to inhibition of the hepatic microsomal systems involved in the metabolism of these benzodiazepines.
- *Antifungal agents:* which also inhibit cytochrome P450 enzymes will reduce the rate of elimination of the benzodiazepines leading to increased effects including side-effects.
- *Antacids anticholinergics:* Absorption of benzodiazepines is decreased, resulting in delayed onset of clinical effects. Antacids may slow down absorption of some benzodiazepines; however, this effect is marginal and inconsistent.

Diazepam

The metabolism of diazepam and related benzodiazepines by hepatic microsomal oxidation makes it more susceptible to pharmacokinetic interactions (affecting absorption, distribution, metabolism or excretion) than some of the other benzodiazepines. These are subject to individual variance and may have limited clinical significance, but are specified due to the primary use of diazepam as a maintenance and withdrawal agent.

A few additions include:

- *Esomeprazole, omeprazole and cimetidine:* which inhibit the metabolism of diazepam, resulting in an increased plasma concentration and possibly increased toxic effects.
- *Isoniazid, oral contraceptives:* Metabolism of diazepam is inhibited, resulting in increased plasma concentration and a prolonged elimination half-life.
- *Rifampicin:* Metabolism of diazepam is accelerated, resulting in reduced plasma concentration and a shortened elimination half-life.
- *Digoxin:* Protein binding of diazepam is altered, leading to increased digoxin levels.
- *L-Dopa:* Parkinsonian symptoms are exacerbated (mechanism unknown).

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