MINISTRY OF HEALTH
SINGAPORE

Prescribing of Benzodiazepines

MOH CLINICAL PRACTICE GUIDELINES 2/2008

College of Family Physicians, Singapore

Academy of Medicine, Singapore

Singapore Sleep Society

Sept 2008

Levels of evidence and grades of recommendation

Levels of evidence

Level	Type of Evidence
1^{++}	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias.
1^{+}	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias.
1^{-}	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2^{++}	High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2^{+}	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2^{-}	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendation

Grade	Recommendation
A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1^{++} and directly applicable to the target population; or A body of evidence consisting principally of studies rated as 1^{+}, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2^{++}, directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1^{++} or 1^{+}
C	A body of evidence including studies rated as 2^{+}, directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2^{++}
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2^{+}
GPP (good practice points)	Recommended best practice based on the clinical experience of the guideline development group.

CLINICAL PRACTICE GUIDELINES

Prescribing of Benzodiazepines

MOH Clinical Practice Guidelines 2/2008

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Statement of Intent

These guidelines are not intended to serve as a standard of medical care. Standards of medical care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge advances and patterns of care evolve.

The contents of this publication are guidelines to clinical practice, based on the best available evidence at the time of development. Adherence to these guidelines may not ensure a successful outcome in every case. These guidelines should neither be construed as including all proper methods of care, nor exclude other acceptable methods of care. Each physician is ultimately responsible for the management of his/her unique patient, in the light of the clinical data presented by the patient and the diagnostic and treatment options available.

Contents

Foreword

Benzodiazepines are useful psychoactive drugs commonly prescribed for treating insomnia, anxiety and other psychiatric and medical conditions. These Clinical Practice Guidelines on 'Prescribing of Benzodiazepines' are a revised version of the previous 2002 'Guidelines for Prescribing Benzodiazepines'. The revised guidelines focus mainly on the prescribing of benzodiazepines in the primary healthcare context and include a wider range of clinical conditions and patient groups for which benzodiazepines may be prescribed. I am confident that these guidelines will help doctors prescribe benzodiazepines in an appropriate manner for the benefit of patients.

In Singapore, the prescribing of increasing quantities of benzodiazepines has become a cause for concern especially in the primary healthcare setting. It is well known that improper or long-term use of benzodiazepines can lead to tolerance as well as psychological and physical dependence. Withdrawal symptoms such as anxiety, perceptual disturbances and tremors may develop upon cessation of benzodiazepine use. Hence, proper prescribing of benzodiazepines is essential for preventing benzodiazepine addiction and withdrawal problems.

I thank the MOH CPG Workgroup for drafting these guidelines for use by all medical practitioners in their prescribing of benzodiazepines to patients.

PROFESSOR K SATKU
DIRECTOR OF MEDICAL SERVICES

Executive summary of recommendations

Details of recommendations can be found in the main text at the pages indicated.

Pharmacological considerations

D Appropriate facilities, equipment and drugs (including flumazenil) for respiratory or cardiovascular assistance should be readily available whenever benzodiazepines are administered intravenously. Close observation is required until the patient recovers fully from sedation (pg 12).

Grade D, Level 4

D Neither benzodiazepines nor zolpidem/zopiclone should be used in acute narrow angle glaucoma, acute pulmonary insufficiency, respiratory depression, sleep apnoea syndrome or marked neuromuscular respiratory weakness including unstable myasthenia gravis and in the presence of known hypersensitivity (to the drug or any excipents) (pg 12).

Grade D, Level 4

B Patients should be routinely warned that hypnotics/anxiolytics cause drowsiness and may impair ability to perform hazardous activities that require mental alertness or physical coordination (e.g. operating machinery or driving a motor vehicle). As such, the concomitant use of alcoholic drinks should also be avoided (pg 13).

Grade B, Level 2++

B Patients should be warned about possible effects on memory (e.g. amnesia) and report to their doctor any behavioural or mental changes (e.g. depression) that develop during treatment with benzodiazepines or zopiclone/zolpidem (pg 13).

Grade B, Level 1+

Psychiatric uses - insomnia, schizophrenia, depression and anxiety

A Prescription of zolpidem and zopiclone should be treated with the same cautions as benzodiazepines (pg 14).

Grade A, Level 1+

A Judicious use of hypnotic medications (e.g. benzodiazepines) may be indicated for short-term (up to 2-4 weeks) relief of insomnia symptoms after considering non-pharmacological treatments. Instructions are necessary concerning side effects (including tolerance and dependence), follow-up for efficacy and discontinuation (pg 15).

Grade A, Level 1+

A If treatment does not work with a shorter-acting benzodiazepine, zolpidem or zopiclone, the doctor should not prescribe one of another shorter-acting benzodiazepine, zolpidem or zopiclone (pg 15).

Grade A, Level 1+

D Patients with insomnia should be referred to an appropriate specialist if physical, psychological or benzodiazepine/substance abuse/dependence problems are suspected (pg 16).

Grade D, Level 4

A If acute insomnia (of less than 4 weeks) is severe, distressing and disabling, and is expected to resolve quickly, a short course of a benzodiazepine or a similar hypnotic drug (up to 2-4 weeks) may be considered (pg 16).

Grade A, Level 1+

D When a benzodiazepine is indicated as a hypnotic, the minimum effective dose should be used for the shortest duration so as to minimize side effects and risks of dependence (pg 16).

Grade D, Level 4

A For chronic insomnia (longer than 4 weeks), non-pharmacological therapies are the mainstay of management (pg 17).

Grade A, Level 1+

A Hypnotic drug use in patients with chronic insomnia (longer than 4 weeks) should be avoided as far as possible because efficacy is not clearly established (pg 17).

Grade A, Level 1+

A Benzodiazepines should not be used as monotherapy in the treatment of schizophrenia, schizophrenia-like psychoses and acute psychotic behaviour (pg 18).

Grade A, Level 1+

A A short-term trial of adjunctive benzodiazepines may be considered only in psychotic patients with persistent and clinically significant symptoms of anxiety, dangerous or assaultive behaviour (pg 18).

Grade A, Level 1+

A Benzodiazepines may be added (for less than 4 weeks) to an antidepressant in a depressed patient with anxiety and/or insomnia in the initial phase of treatment (pg 19).

Grade A, Level 1+

A Benzodiazepines should not be used as monotherapy for depression (pg 19).

Grade A, Level 1+

D Benzodiazepines are indicated for the short-term relief (2-4 weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness (pg 19).

Grade D, Level 4

D As an adjunct to antidepressant treatment in anxiety disorders, the use of benzodiazepines should be limited to 2-4 weeks in the lowest effective dose. The dose should be gradually tapered off. Benzodiazepine use should be closely monitored for adverse effects, abuse, tolerance, dependence and withdrawal symptoms (pg 19).

Grade D, Level 4

D Benzodiazepines prescribed for anxiety may be abused by some patients with co-morbid alcohol/substance abuse or dependence and are best avoided where possible in such patients (pg 20).

Grade D, Level 4

A Patients with panic disorder and co-morbid depression should not be treated with benzodiazepine monotherapy (pg 20).

Grade A, Level 1+

Medical uses

D Benzodiazepines such as clonazepam and clobazam may be used as add-on therapy in refractory focal and generalized epilepsy (pg 21).

Grade D, Level 3

A Intravenous lorazepam and diazepam are effective first-line treatments for prolonged seizures in adults (pg 21).

Grade A, Level 1+

D For treatment of prolonged seizures in adults, an initial dose of 5-10 mg diazepam is given either intravenously or rectally. If there is no response, the same dose can be repeated after 10 minutes. Respiratory or circulatory effects should be monitored for and usually occur with doses greater than 20 mg (pg 21).

Grade D, Level 4

A Benzodiazepines (e.g. chlordiazepoxide, diazepam, lorazepam) are the drugs of choice for treatment of acute alcohol withdrawal (including alcohol withdrawal delirium) (pg 23). (Refer to Annex A. Table A1 for suggested dosage ranges)

Grade A, Level 1+

GPP Patients with complicated alcohol withdrawal should be referred to general hospitals (pg 23).

GPP

Benzodiazepine abuse and dependence

A Long-term chronic use of benzodiazepines (e.g. for the treatment of insomnia or anxiety symptoms) is not recommended because efficacy is not clearly established. In view of this, for any continued or repeat benzodiazepine prescription, there must be appropriate clinical review, clear indications and adequate documentation (pg 24).

Grade A, Level 1+

D Benzodiazepine use should be limited to short-term relief (between 2-4 weeks), at the lowest dose and be taken intermittently (e.g. 1 night in 2 or 3 nights) (pg 24).

Grade D, Level 4

A Extended use of benzodiazepines (especially those with short half-lives) beyond 2-4 weeks is not recommended, even when prescribed at the therapeutic dosages (pg 25).

Grade A, Level 1+

A All patients receiving benzodiazepines should be routinely advised about the risk of developing dependence (pg 25).

Grade A, Level 1+

D Patients receiving prescription for benzodiazepines should be advised to obtain all such prescriptions from the same doctor wherever possible, so that risk of abuse and dependence may be monitored (pg 25).

Grade D, Level 4

D Avoid prescribing benzodiazepines to known polydrug users. In view of this, medical practitioners should examine for any signs of intravenous drug use before considering prescribing benzodiazepines (pg 25).

Grade D, Level 4

D Oral midazolam (e.g. Dormicum®) and nimetazepam (e.g. Erimin®) are not recommended for routine outpatient prescription as they are highly addictive and commonly abused by drug addicts in Singapore (pg 25).

Grade D, Level 3

A Benzodiazepines should be gradually tapered, monitored and titrated to minimize withdrawal symptoms (pg 26).

Grade A, Level 1+

A Propanolol, dothiepin, buspirone, progesterone or hydroxyzine should not be used in the primary management of benzodiazepine withdrawal (pg 26).

Grade A, Level 1+

A Patients may be switched to a long half-life benzodiazepine (e.g. diazepam), then tapered gradually to facilitate smoother withdrawal (pg 26).

Grade A, Level 1+

A Supervised gradual discontinuation of benzodiazepines with brief intervention strategies may be used. It has been shown to be more effective than discontinuation alone (pg 27).

Grade A, Level 1+

GPP For patients on less than 4 weeks of benzodiazepine therapy, the dose can be discontinued or reduced over 1-2 weeks (pg 27).

GPP

C Patients who have been on high dose for over four weeks or on regular doses for longer than 12 weeks may be switched from a short acting to a long-acting benzodiazepine (e.g. diazepam). The slower elimination of diazepam creates a smoother taper in blood level (pg 27). (See Table A3 in Annex A for approximate diazepam equivalent dose)

Grade C, Level 2++

GPP A suggested withdrawal protocol for patients with more than 4 weeks of benzodiazepine therapy is as follows:

1. Calculate the approximate equivalent daily dose of diazepam.
   (a) For those whose daily dose exceeds 30 mg/day, start reduction from half of this amount or 30 mg/day, whichever is lower.
   (b) For those on 30 mg/day or less, reduce from this dose.
2. Reduce diazepam dose every 1-2 weeks in steps of 2-5 mg.
3. If withdrawal symptoms are severe, reduce dose in smaller steps.
   If patients are unable to stop completely by 4-8 weeks, or if complications arise, consider referral to the appropriate specialist or general hospital (pg 27).

GPP

GPP Patients who are undergoing benzodiazepine discontinuation, especially those with concurrent medical or psychiatric conditions, should be closely monitored. Patients who develop complicated withdrawal symptoms (e.g. seizures, delirium) or serious psychiatric complications (e.g. psychotic symptoms, suicidal tendency) during benzodiazepine discontinuation should be referred to the specialist or general hospital (pg 28).

GPP

Special populations: elderly, child and adolescent, pregnancy and breast-feeding

A Non-pharmacological interventions, which have been shown to be effective for management of insomnia in older adults, should be initiated first before prescribing a benzodiazepine (pg 29). (See Annex B, Tables B1-3)

Grade A, Level 1++

A Benzodiazepines may be used with caution on a short-term basis in the elderly to improve sleep although the magnitude of improvement is modest compared to the risk of adverse events (pg 29).

Grade A, Level 1++

C Long-term use of benzodiazepines should be avoided in the elderly in view of the increased risk of cognitive impairment and fractures (pg 29).

Grade C, Level 2+

D The dose of benzodiazepines in the elderly should generally be only one-quarter to half of the normal adult dose (pg 30).

Grade D, Level 4

D Benzodiazepines with long half-lives (such as diazepam, flurazepam, clorazepate, chlordiazepoxide) should be avoided in the elderly (pg 30).

Grade D, Level 4

B Benzodiazepines should be gradually withdrawn in the elderly as this may produce improvement in cognitive functions (pg 30).

Grade B, Level 1+

D Children and adolescents are at increased risk of disinhibition with benzodiazepines; first-line treatment with benzodiazepines should be avoided (pg 31).

Grade D, Level 3

C Benzodiazepines should be avoided during pregnancy and breast-feeding (pg 31).

Grade C, Level 2+

1 Introduction

1.1 Background information

Benzodiazepines were first introduced in clinical practice in the 1960s and soon became the treatment of choice for anxiety and insomnia. They have replaced barbiturates because they were thought to be reliable, with few unwanted effects, less addictive and safer in overdose. During the 1970s and 80s, they were widely prescribed, although addiction problems were rapidly being recognized. Today, it has become clear that tolerance and physical dependence from prolonged use and from inappropriate use (e.g. intravenous use by the opioid users) of benzodiazepines are becoming widespread and problematic locally and in various parts of the world.

It is also now clear that while benzodiazepines are useful in conferring a positive therapeutic response in many psychiatric and medical conditions in the short term. Long-term usage carries the risk of dependence, which is very difficult to treat once established.

1.2 Objectives/target group

These guidelines have been formulated to assist medical practitioners in relation to appropriate prescribing of benzodiazepines. The guidelines are based on the evidence regarding the advantages, disadvantages and the risk of dependence associated with the use of benzodiazepines.

Guidance on the prescribing of benzodiazepines for drug-dependent patients is included, in response to concern over what is reasonable care for patients who use benzodiazepines in high doses on a regular basis.

These guidelines are not intended to be a list of do's and don'ts. Appropriate assessment and clinical judgement of each patient's condition is necessary for the best clinical outcome.

1.3 Development of guidelines

These guidelines have been produced by a multidisciplinary committee comprising psychiatrists in both hospital and private

practice who have special interests in sleep disorders, anxiety disorders and psychiatric problems in the elderly; addiction specialists; general practitioners; pharmacists; and a neurologist. The committee was appointed by the Ministry of Health.

Our committee attempted to cover the common uses, indications and prescribing concerns of benzodiazepines, but it is by no means exhaustive. The guidelines were developed based on the best evidence available and expert opinion.

The workgroup acknowledges that there is a paucity of high-level evidence for practices in this field. Nevertheless, it is important to provide guidance for the appropriate use of benzodiazepines given the potential for abuse.

1.4 Review of guidelines

Evidence-based clinical practice guidelines are only as current as the evidence that supports them. Users must keep in mind that new evidence could supersede recommendations in these guidelines. The workgroup advises that these guidelines be scheduled for review five years after publication, or if new evidence appears that requires substantive changes to the recommendations.

2 Pharmacological considerations

The benzodiazepines have similar major actions such as anxiolytic, hypnotic, muscle relaxant and anti-convulsant properties. Selection may depend on the pharmacodynamics and pharmacokinetics of a particular benzodiazepine.

2.1 Pharmacodynamics

The benzodiazepines have multiple sites of action but their effects on the limbic, thalamic and hypothalamic levels of the central nervous system (CNS) are particularly prominent to produce anxiolytic, sedative, hypnotic, skeletal muscle relaxant and anticonvulsant properties[1-3] (see Annex A. Table A1 – Benzodiazepine Indications and Dosages in Adults).

Benzodiazepines appear to potentiate the effects of gamma-aminobutyric acid (GABA), the major inhibitory neurotransmitter in the CNS, by attaching to the benzodiazepine-binding-site located on the $GABA_A$/Chloride receptor complex.[1-5] Unlike barbiturates, the availability of GABA limits the effects of benzodiazepines and this contributes to a relatively more favourable toxicity index of benzodiazepines compared to barbiturates.[1,3,6]

The $GABA_A$/Chloride receptor functions as a pentameric (5-subunit) ligand-gated chloride ion channel, formed from a mix and match of 19 possible subunits of which the major isoforms are the α, β and γ subunits.[5,7] The α_1-containing benzodiazepine-binding-sites were suggested to cause sedation.[7,8] The α_2 and/or α_3 subtypes were thought to mediate anxiolytic and myorelaxation effects while the α_5 subtype might be associated with cognitive processes.[7]

Benzodiazepines and non-benzodiazepine hypnotics (Z-drugs) vary in their selectivity for benzodiazepine-binding-sites.[9] Benzodiazepines bind non-selectively to all benzodiazepine-binding-sites containing the γ and α_1, α_2, α_3 or α_5 subunits while the Z-drugs (i.e. zolpidem, zopiclone) bind preferentially to benzodiazepine-binding-sites with γ and α_1 subunits.[9] This may account for the predominant hypnotic effects of the Z-drugs rather than anxiolytic or muscle relaxation actions.[9,10] As for the H_1-antihistamines, their sedative effects may be related to their blockade of the CNS histaminergic pathways involved

with regulation of the waking-sleep cycle but limited data is available to support their long-term use in the management of insomnia.[1,2,8,11]

Following sustained use of benzodiazepines, tolerance to their hypnotic effects develops within a few weeks while tolerance to their anxiolytic effects may occur over several months.[12] This is because regular use of benzodiazepines results in a progressive reduction in the number of $GABA_A$/Chloride receptors on the surface of brain cells.[12] Consequently, inhibition of excitation effects diminishes. This can lead to withdrawal symptoms when benzodiazepines are abruptly discontinued. The rate of withdrawal of benzodiazepine needs to allow time for $GABA_A$/Chloride receptors to regenerate if withdrawal symptoms are to be minimised.[12]

2.2 Pharmacokinetics

All benzodiazepines have similar major actions but pharmacokinetic differences between them can be important considerations in drug selection.[2,13-18]

Benzodiazepines are generally well absorbed from the gastrointestinal tract.[2] They (and their metabolites) are highly bound to plasma proteins and widely distributed into body tissues, human milk, the blood brain barrier and placenta.[2]

All benzodiazepines are metabolized in the liver through oxidation, glucuronidation or nitrogen reduction and all are eliminated by the kidneys.[2,3,13-15] Those that undergo oxidative metabolism (e.g. diazepam) should be used with additional caution in patients with hepatic impairment.[2,13-15] (see Annex A. Table A2 – Metabolism of Benzodiazepines).

2.3 Drug interactions

Benzodiazepines do not induce microsomal enzymes. Most of them (except possibly lorazepam) are metabolized by the hepatic cytochrome P450 3A4 (CYP3A4) isozyme.[2,13,16,17] This is similar for zolpidem and zopiclone. Inhibitors or inducers of CYP3A4 may respectively increase or reduce the effects of these drugs and should be used with caution.[2,13,16,17]

Additive CNS depression may occur when benzodiazepines (or other hypnotics/sedatives) are administered together with other CNS depressants (including alcohol).[1,2,13-18] Care should be exercised in such circumstances to avoid excessive sedation and overdose toxicity.[1,2,13-18]

2.4 Precautions and contraindications

D Appropriate facilities, equipment and drugs (including flumazenil) for respiratory or cardiovascular assistance should be readily available whenever benzodiazepines are administered intravenously.[1,2,19,20] Close observation is required until the patient recovers fully from sedation.[1,19,20]

Grade D, Level 4

D Neither benzodiazepines nor zolpidem/zopiclone should be used in acute narrow angle glaucoma, acute pulmonary insufficiency, respiratory depression, sleep apnoea syndrome or marked neuromuscular respiratory weakness including unstable myasthenia gravis and in the presence of known hypersensitivity (to the drug or any excipents).[1,2]

Grade D, Level 4

2.5 Side effects

Adverse effects common to benzodiazepines and zolpidem/zopiclone include CNS side effects (e.g. drowsiness, dizziness, fatigue, lethargy, amnesia, confusion and ataxia); dependence; disinhibition and paradoxical effects (e.g. increase in aggression); occasionally headache, vertigo; salivary changes, gastrointestinal disturbances; sleep problems (e.g. somnambulism, vivid dreams); perceptual or visual disturbances; tremors, palpitations; skin reactions.[1,2,4,13,21]

Paradoxical disinhibition with benzodiazepines may, in rare cases, result in attacks of rage or violence, or other indiscreet or antisocial behaviours.[1,2,18,22-26] Patient's personality type (e.g. history of poor impulse control or aggression) and age (especially extremes of age) can be risk factors for such reactions.[18,23-25]

Blood disorders, jaundice, muscle weakness, dysarthria, urinary retention or incontinence have been reported with

benzodiazepines.[1,2,13] Zopiclone may cause a bitter taste in the mouth.[1]

Hypnotics and anxiolytics may impair judgment, increase reaction time and increase the effects of alcohol.[1,10,11,13-16,27,28] The hangover effects of a night dose may impair driving the following day.[1] All sedative-hypnotics may also cause complex sleep-related behaviors (e.g. making phone calls, preparing food, sleep-driving etc) [21]

B Patients should be routinely warned that hypnotics/anxiolytics cause drowsiness and may impair ability to perform hazardous activities that require mental alertness or physical coordination (e.g. operating machinery or driving a motor vehicle).[1,2,27,28] As such, the concomitant use of alcoholic drinks should also be avoided.[1,2]

Grade B, Level 2++

B Patients should be warned about possible effects on memory (e.g. amnesia) and report to their doctor any behavioural or mental changes (e.g. depression) that develop during treatment with benzodiazepines or zopiclone/zolpidem. [2,21,26,29-33]

Grade B, Level 1+

3 Psychiatric uses - insomnia, schizophrenia, depression and anxiety

Benzodiazepines are widely used in primary care for a variety of indications, particularly for the symptomatic management of insomnia and anxiety.

3.1 Use of benzodiazepines in insomnia

Results from randomised controlled trials (RCTs) indicate that specific benzodiazepines (e.g. flurazepam) and non-benzodiazepine Z-drugs (e.g. zolpidem) are effective in the short-term management of insomnia.[34-36]

A UK National Institute for Health and Clinical Excellence (NICE) systematic review concluded that there was a lack of compelling evidence to distinguish the effectiveness, adverse effects (including next-day residual effects) and potential for dependency or abuse between the Z-drugs (zolpidem, zopiclone) and the shorter-acting benzodiazepines.[36]

Similar to benzodiazepines[37], the summaries of product characteristics of the Z-drugs (zolpidem and zopiclone)[38,39] warned of the possibility of physical and psychological dependence as well as withdrawal effects, and cautioned that tolerance can occur after repeated use for a few weeks.[38,39]

A Prescription of zolpidem and zopiclone should be treated with the same cautions as benzodiazepines.[36]

Grade A, Level 1+

The benefits of these hypnotic agents for long-term use (more than 4 weeks) have not been comprehensively studied using RCTs[34,35] and none of these drugs is licensed for treatment for longer than 4 weeks.[35,36,38,39] The available data does not support the long-term use of benzodiazepines.[40,41]

A Judicious use of hypnotic medications (e.g. benzodiazepines) may be indicated for short-term (up to 2-4 weeks) relief of insomnia symptoms after considering non-pharmacological treatments.[34-36,38,39] Instructions are necessary concerning side effects (including tolerance and dependence), follow-up for efficacy and discontinuation.[21,34-39]

Grade A, Level 1+

A If treatment does not work with a shorter-acting benzodiazepine, zolpidem or zopiclone, the doctor should not prescribe one of another shorter-acting benzodiazepine, zolpidem or zopiclone.[36]

Grade A, Level 1+

3.1.1 Approach to the patient with insomnia

Insomnia refers to the difficulty in falling or staying asleep, leading to impairment of daytime functioning.

Categorising insomnia according to the duration of symptoms can be helpful in determining its management:

- Acute insomnia[42]:
  - Periods of sleeping difficulty lasting between 1 night and a few weeks (less than 1 month).
- Chronic insomnia[42]:
  - Sleep difficulties at least 3 nights per week for 1 month or more.

Management of insomnia involves identifying and managing its possible underlying causes, such as a physical or psychological condition, drugs or excessive alcohol use, problems of sleep environment, irregularity of sleep or negative conditioning to sleep.[43]

Non-pharmacological interventions such as sleep hygiene education, relaxation training and cognitive-behavioural therapy have been found to be efficacious in the management of insomnia.[44-48] (See Tables B1-3 in Annex B). Non-pharmacological interventions are first-line treatments for management of insomnia and these may include[43,44]:

- Sleep diary for about 14 days to identify the correctable causes and their extent. This should contain information about: time of going to bed; time taken to get to sleep; number of episodes of waking through the night; time of getting up; episodes of daytime tiredness

and naps; times of meals, alcohol consumption, and significant events during the day such as exercise or stress.

- Sleep hygiene and stimulus control measures if the person's behaviour and sleep environment are correctable causes.
- Additional non-drug therapies such as relaxation techniques, exercise, or sleep restriction advice if insomnia does not improve.
- Cognitive-behavioural therapy as guided by clinical judgement, patient preference and availability of such a service. Some limitations for the use of cognitive-behavioural therapy in Singapore may include language barriers for many patients, poor adherence secondary to impatience to the slower onset of treatment effects and insufficient mental health professionals adequately trained to administer the therapy.

D Patients with insomnia should be referred to an appropriate specialist if physical, psychological or benzodiazepine/substance abuse/dependence problems are suspected.[43,48]

Grade D, Level 4

3.1.2 Management of insomnia of less than 4 weeks duration

A If acute insomnia (of less than 4 weeks) is severe, distressing and disabling, and is expected to resolve quickly, a short course of a benzodiazepine or a similar hypnotic drug (up to 2-4 weeks) may be considered.[36,40,41,49,50]

Grade A, Level 1+

An important consideration in the prescription of benzodiazepines is the potential for dependence, even when used at therapeutic doses for relatively short periods of time.[49-51] Withdrawal reactions have been noted after use of lorazepam for as short as one week.[52]

D When a benzodiazepine is indicated as a hypnotic, the minimum effective dose should be used for the shortest duration so as to minimize side effects and risks of dependence.[48,49]

Grade D, Level 4

3.1.3 Management of insomnia of longer than 4 weeks duration

In a patient with insomnia longer than 4 weeks, there is a need to identify and manage the cause.

Some causes of chronic insomnia could be:

- Dysfunctional beliefs about the amount of sleep a person needs.
- Physical and psychological conditions or drugs causing insomnia
- Correctable causes of primary insomnia: e.g. too much physical or intellectual activity prior to going to bed; day time napping; eating large meals close to bedtime, taking caffeinated drinks and excessive alcohol in the evening.

A For chronic insomnia (longer than 4 weeks), non-pharmacological therapies are the mainstay of management.[43,44,53-55]

Grade A, Level 1+

In a person with long-term insomnia, there will be considerable pressure on the doctor to continue prescription. However, there is a need to explain that long-term benzodiazepines use leads to tolerance, dependence, and rebound insomnia on attempted cessation of treatment.[43,54]

A Hypnotic drug use in patients with chronic insomnia (longer than 4 weeks) should be avoided as far as possible because efficacy is not clearly established.[43,54,56]

Grade A, Level 1+

3.2 Use of benzodiazepines in schizophrenia and related psychoses

Benzodiazepines have been used in the management of acute catatonia and acute behaviour disturbances in the context of schizophrenia but this particular patient population can be more vulnerable to both the abuse of these agents and the addiction to them.[57]

Rapid tranquillisation protocols require that resuscitation equipment and drugs (including flumazenil) must be available for appropriately trained staff to employ either oral or intramuscular lorazepam (with or without an antipsychotic) for prompt short-term behavioural control of

extreme agitation, aggression and potentially violent behaviour.[19,20,57-60] The effectiveness of benzodiazepines in such situations is limited to the acute phase and may not be sustained.[57,58]

Benzodiazepines offer only short-tem sedation effects at best and there is currently insufficient and inconclusive clinical evidence to suggest them as a superior monotherapy or an effective adjunctive agent in the treatment of schizophrenia and related psychoses.[58,59]

A Benzodiazepines should not be used as monotherapy in the treatment of schizophrenia, schizophrenia-like psychoses and acute psychotic behaviour.[46,47]

Grade A, Level 1+

A A short-term trial of adjunctive benzodiazepines may be considered only in psychotic patients with persistent and clinically significant symptoms of anxiety, dangerous or assaultive behaviour.[20,57,58,60,61]

Grade A, Level 1+

For further guidance on the management of schizophrenia, please refer to the MOH Clinical Practice Guidelines for Schizophrenia (2003).[61]

3.3 Use of benzodiazepines in depression

A literature review[62] of double-blinded randomized controlled trials shows that benzodiazepines have little or no antidepressant effect and they have even been suggested to cause depression.[63]

However, anxiety frequently coexists with depression and benzodiazepines have been added to antidepressants to treat anxiety and insomnia symptoms. Benzodiazepines may lose their efficacy in the long-term and their use carries the risk of dependence and proneness to accidents.

Systematic reviews[64-66] show that in the initial phase of treatment, combination of benzodiazepines with antidepressants leads to fewer dropouts and lesser depression severity at four weeks compared to antidepressants alone. However, this has to be balanced against possible harm from adverse effects and dependency.

A Benzodiazepines may be added (for less than 4 weeks) to an antidepressant in a depressed patient with anxiety and/or insomnia in the initial phase of treatment.[64-66]

Grade A, Level 1+

A Benzodiazepines should not be used as monotherapy for depression.[62,63]

Grade A, Level 1+

For further guidance on the management of depression, please refer to the MOH Clinical Practice Guidelines for Depression (2004).[67]

3.4 Use of benzodiazepines in anxiety disorders

Antidepressants are recommended as effective agents for the treatment of panic disorders, social phobia, obsessive-compulsive disorders, generalized anxiety disorder and post-traumatic stress disorder.[68]

Benzodiazepines provide rapid and effective relief of anxiety, but their use is associated with problems of dependence, rebound anxiety and withdrawal symptoms on cessation, as well as psychomotor/cognitive adverse effects. Benzodiazepines may be especially indicated where rapid control of anxiety symptoms is crucial. Benzodiazepines are also useful for the early control of anxiety symptoms while awaiting response to the benefits from antidepressant treatment or cognitive-behavioural therapy.

D Benzodiazepines are indicated for the short-term relief (2-4 weeks only) of anxiety that is severe, disabling or subjecting the individual to unacceptable distress, occurring alone or in association with insomnia or short-term psychosomatic, organic, or psychotic illness.[1]

Grade D, Level 4

D As an adjunct to antidepressant treatment in anxiety disorders, the use of benzodiazepines should be limited to 2-4 weeks in the lowest effective dose.[1] The dose should be gradually tapered off. Benzodiazepine use should be closely monitored for adverse effects, abuse, tolerance, dependence and withdrawal symptoms.[1]

Grade D, Level 4

D Benzodiazepines prescribed for anxiety may be abused by some patients with co-morbid alcohol/substance abuse or dependence and are best avoided where possible in such patients.[68]

Grade D, Level 4

Treating patients with panic disorder and co-morbid depression with benzodiazepines alone would result in poorer outcomes than patients taking antidepressants.[69,70]

A Patients with panic disorder and co-morbid depression should not be treated with benzodiazepine monotherapy.[60-70]

Grade A, Level 1+

Cognitive-behavioural therapy has been demonstrated to be useful in the primary care management of anxiety.[71-73]

For guidance on the management of anxiety disorders, please refer to the MOH Clinical Practice Guidelines for Anxiety Disorders (2003).[68]

4 Medical uses

Benzodiazepines have a place in the medical treatment of the following conditions:

- Epilepsy
- Sleep Disorders:
  - Restless Legs Syndrome (RLS)
  - Rapid Eye Movement Sleep Behaviour Disorder (REMBD)
- Alcohol Withdrawal Syndrome
- Dystonia and Spasticity

4.1 Epilepsy

Benzodiazepines are effective in both focal and generalized epilepsy.[74-80] They can be used orally, and given intravenously or rectally for prolonged seizures.[74,75,79-83] The use of benzodiazepines is, however, limited by sedation and dependence.

Among the most commonly prescribed benzodiazepines for epilepsy are clonazepam and clobazam. Clonazepam has been used as add-on therapy in resistant primary and secondary generalized seizures, as well as difficult-to-control absence and myoclonic seizures.[74] Clobazam is a broad-spectrum antiepileptic agent with a high therapeutic index and has been used as adjunctive therapy in refractory epilepsy.[83]

D Benzodiazepines such as clonazepam and clobazam may be used as add-on therapy in refractory focal and generalized epilepsy.[74,83]

Grade D, Level 3

A Intravenous lorazepam and diazepam are effective first-line treatments for prolonged seizures in adults.[74,80-82]

Grade A, Level 1+

D For treatment of prolonged seizures in adults, an initial dose of 5-10 mg diazepam is given either intravenously or rectally. If there is no response, the same dose can be repeated after 10 minutes. Respiratory or circulatory effects should be monitored for and usually occur with doses greater than 20 mg.[74,75]

Grade D, Level 4

For further guidance on the management of epilepsy, please refer to the MOH Clinical Practice Guidelines for Diagnosis and Management of Epilepsy in Adults (2007).[74]

4.2 Sleep disorders: Restless Legs Syndrome (RLS), Rapid Eye Movement Sleep Behaviour Disorder (REMBD)

Benzodiazepines have been shown to improve the quality of sleep and reduce periodic limb movements in sleep (PLMS) or PLMS associated with arousals in patients with restless legs syndrome (RLS).[84] Benzodiazepines may be useful in mild cases of RLS and as adjunct therapy for associated residual insomnia.[84] Clonazepam is effective and may be useful in the treatment of Rapid Eye Movement Sleep Behaviour Disorder (REMBD).[85] Patients with restless legs syndrome or rapid eye movement sleep behaviour disorder should be diagnosed and managed by a sleep specialist or neurologist.

4.3. Alcohol withdrawal syndrome

Detoxification, an important step in the management of patients with alcohol dependence, involves managing the alcohol withdrawal syndrome and monitoring abstinence.

Supportive care for patients undergoing detoxification is also needed. This includes providing treatment for nutritional and electrolyte deficiencies, monitoring withdrawal severity, monitoring abstinence, and providing referrals for further alcoholism treatment and self-help meetings (e.g. 12-Step groups, Alcoholics' Anonymous).

Benzodiazepines are effective in the treatment of alcohol withdrawal symptoms, in particular seizures, when compared to placebo. Benzodiazepines reduce withdrawal severity, as well as incidence of delirium and seizures.[86-89]

Different benzodiazepines (e.g. chlordiazepoxide, diazepam, lorazepam) appear to have similar efficacy in ameliorating signs and symptoms of alcohol withdrawal.[86-89] The longer-acting benzodiazepines may be more effective in preventing seizures.[86-88] Alcohol detoxification can usually be completed within 1 week.

A Benzodiazepines (e.g. chlordiazepoxide, diazepam, lorazepam) are the drugs of choice for treatment of acute alcohol withdrawal (including alcohol withdrawal delirium).[86-89] (Refer to Annex A. Table A1 for suggested dosage ranges)

Grade A, Level 1+

Facilities and clinical services (including specialist services) are available in general hospitals for the treatment of medical emergencies (e.g. generalized seizures, delirium tremens) associated with severe and complicated alcohol withdrawal.

GPP Patients with complicated alcohol withdrawal should be referred to general hospitals.

GPP

4.4 Dystonia and spasticity

Benzodiazepines have been anecdotally reported to be helpful in dystonia, and may be of additional benefit in patients with inadequate response to anticholinergics. Clonazepam and diazepam have been used by specialists to treat dystonia, with neither agent being shown to be superior.[79]

Benzodiazepines have been employed by specialists to treat spasticity related to upper motor neurone disorders such as multiple sclerosis and cerebral palsy.[90-92]

5 Benzodiazepine abuse and dependence

5.1 Benzodiazepine abuse and dependence

The potential of benzodiazepines to produce physical and/or psychological dependence is widely recognized.[93] Long-term benzodiazepine use leads to the development of dependence.[94] A small but important sector of the population abuses benzodiazepines, as part of a wider drug and alcohol problem.

A Long-term chronic use of benzodiazepines (e.g. for the treatment of insomnia or anxiety symptoms) is not recommended because efficacy is not clearly established.[40,41,43,49,54] In view of this, for any continued or repeat benzodiazepine prescription, there must be appropriate clinical review, clear indications and adequate documentation.

Grade A, Level 1+

5.1.1 Benzodiazepine dependence

Dependence on benzodiazepine is mainly manifested by withdrawal symptoms on its discontinuation, as well as evidence of tolerance, strong desire to take the drugs and difficulties controlling the drug-taking behaviour.[94] (Refer to DSM-IV-TR[94] for detailed criteria for substance abuse and dependence)

Benzodiazepines with shorter half-lives are associated with higher risks of dependence based on more severe withdrawal and rebound syndrome.[93]

The risk factors for benzodiazepine dependence are the use of more potent and short-acting benzodiazepines,[95] use of high doses,[95,96] longer duration of use, the interaction of higher dose with longer duration of use, younger age and lower level of education.[96]

D Benzodiazepine use should be limited to short-term relief (between 2-4 weeks), at the lowest dose and be taken intermittently (e.g. 1 night in 2 or 3 nights).[1,4,49,97,98]

Grade D, Level 4

A Extended use of benzodiazepines (especially those with short half-lives) beyond 2-4 weeks is not recommended, even when prescribed at the therapeutic dosages.[49,93,99,100]

Grade A, Level 1+

A All patients receiving benzodiazepines should be routinely advised about the risk of developing dependence.[93]

Grade A, Level 1+

5.1.2 Benzodiazepine abuse

Intravenous injection of benzodiazepines, especially midazolam, in polydrug users may result in emboli and subsequent gangrene and amputation, as well as increase the risk of blood-borne infections such as hepatitis C and HIV.[48,97,101] Medical practitioners should be vigilant that benzodiazepine prescriptions (especially midazolam) are not diverted for illicit use.

D Patients receiving prescription for benzodiazepines should be advised to obtain all such prescriptions from the same doctor wherever possible, so that risk of abuse and dependence may be monitored.[48]

Grade D, Level 4

D Avoid prescribing benzodiazepines to known polydrug users.[48] In view of this, medical practitioners should examine for any signs of intravenous drug use before considering prescribing benzodiazepines.

Grade D, Level 4

D Oral midazolam (e.g. Dormicum®) and nimetazepam (e.g. Erimin®) are not recommended for routine outpatient prescription as they are highly addictive and commonly abused by drug addicts in Singapore.[101-104]

Grade D, Level 3

5.2 Benzodiazepine withdrawal and discontinuation

For the long-term user who is clearly dependent, there is a need to educate the patient and schedule a benzodiazepine discontinuation plan. These should be clearly documented.

The benzodiazepine withdrawal syndrome may develop at any time up to 3 weeks of stopping a long-acting benzodiazepine, but may occur within a day in the case of a short-acting one.[1,36]

Common benzodiazepine withdrawal reactions include sweating, increased heart rate, tremors, insomnia, agitation, hallucinations, rebound anxiety, and gastrointestinal symptoms such as nausea or vomiting. Tonic-clonic seizures are possible in cases of abrupt discontinuation from high doses.[4]

5.2.1 Benzodiazepine withdrawal strategies

Successful benzodiazepine withdrawal strategies include gradual dosage reduction and management of withdrawal symptoms.

A Benzodiazepines should be gradually tapered, monitored and titrated to minimize withdrawal symptoms.[105-107]

Grade A, Level 1+

Direct withdrawal from short-acting benzodiazepines is more likely to cause withdrawal symptoms because rapid elimination of these drugs causes their blood concentrations to fall between two doses.

There is some evidence for switching from a short-acting benzodiazepine to a longer-acting benzodiazepine before gradual discontinuation.[105] There are no benefits of propanolol, dothiepin, buspirone, progesterone or hydroxyzine in managing benzodiazepine withdrawal or improving abstinence.[105] However, anti-histamines like hydroxyzine may be added for symptomatic use during withdrawal when tapering off long-acting benzodiazepines.

A Propanolol, dothiepin, buspirone, progesterone or hydroxyzine should not be used in the primary management of benzodiazepine withdrawal.[105]

Grade A, Level 1+

A Patients may be switched to a long half-life benzodiazepine (e.g. diazepam), then tapered gradually to facilitate smoother withdrawal.[105]

Grade A, Level 1+

A Supervised gradual discontinuation of benzodiazepines with brief intervention strategies may be used. It has been shown to be more effective than discontinuation alone.[106]

Grade A, Level 1+

Brief intervention strategies may include documenting advice to discontinue, explaining the process and non-pharmacological measures to aid relaxation.[106,108]

5.2.2 Benzodiazepine discontinuation schedules (suggested guides)

GPP For patients on less than 4 weeks of benzodiazepine therapy, the dose can be discontinued or reduced over 1-2 weeks.

GPP

C Patients who have been on high dose for over four weeks or on regular doses for longer than 12 weeks may be switched from a short acting to a long-acting benzodiazepine (e.g. diazepam). The slower elimination of diazepam creates a smoother taper in blood level.[109] (See Table A3 in Annex A for approximate diazepam equivalent dose)

Grade C, Level 2++

There are various protocols for benzodiazepine withdrawal for patients with established benzodiazepine dependence.[109] The exact weaning rate should be individualised.

GPP A suggested withdrawal protocol for patients with more than 4 weeks of benzodiazepine therapy is as follows:

4. Calculate the approximate equivalent daily dose of diazepam.
   (a) For those whose daily dose exceeds 30 mg/day, start reduction from half of this amount or 30 mg/day, whichever is lower.
   (b) For those on 30 mg/day or less, reduce from this dose.
5. Reduce diazepam dose every 1-2 weeks in steps of 2-5 mg.
6. If withdrawal symptoms are severe, reduce dose in smaller steps.

If patients are unable to stop completely by 4-8 weeks, or if complications arise, consider referral to the appropriate specialist or general hospital.

GPP

GPP Patients who are undergoing benzodiazepine discontinuation, especially those with concurrent medical or psychiatric conditions, should be closely monitored. Patients who develop complicated withdrawal symptoms (e.g. seizures, delirium) or serious psychiatric complications (e.g. psychotic symptoms, suicidal tendency) during benzodiazepine discontinuation should be referred to the specialist or general hospital.

GPP

6 Special populations: elderly, child and adolescent, pregnancy and breast-feeding

6.1 Use of benzodiazepines in the elderly (aged 65 years or more)

Chronic insomnia is common among the elderly. Between 5% and 33% of elderly people in North America and the United Kingdom are prescribed a benzodiazepine or a benzodiazepine receptor agonist (zolpidem, zopiclone) for sleep problems. Older adults are more susceptible to the effects of benzodiazepines and other psychotropics because of age-related changes in pharmacokinetic processes (particularly distribution, metabolism and clearance), which can greatly prolong the effects of these drugs. Older people often take a combination of drugs, including centrally-acting ones, which can compound side effects.

A Non-pharmacological interventions, which have been shown to be effective for management of insomnia in older adults, should be initiated first before prescribing a benzodiazepine.[45,47,110] (See Annex B, Tables B1-3)

Grade A, Level 1++

A Benzodiazepines may be used with caution on a short-term basis in the elderly to improve sleep although the magnitude of improvement is modest compared to the risk of adverse events.[111]

Grade A, Level 1++

Prolonged use of benzodiazepines in the elderly is associated with cognitive impairment.[112] A recent meta-analysis showed that users of benzodiazepines have a moderate but significant increase in the risk of fractures.[113] Prolonged use of more than 1 month has been shown to be associated with increased risk of fractures.[114]

C Long-term use of benzodiazepines should be avoided in the elderly in view of the increased risk of cognitive impairment and fractures.[112-114]

Grade C, Level 2+

D The dose of benzodiazepines in the elderly should generally be only one-quarter to half of the normal adult dose.[18,115]

Grade D, Level 4

Epidemiological studies show that the risks of an accident increase with increasing half-life of the hypnotic, but that the use of hypnotics with a short half-life can also be associated with increased risks of adverse events.[114]

D Benzodiazepines with long half-lives (such as diazepam, flurazepam, clorazepate, chlordiazepoxide) should be avoided in the elderly.[114,116]

Grade D, Level 4

Older adults are significantly less likely to stop benzodiazepines than younger patients. Gradual withdrawal of benzodiazepines, together with psychological support, in the elderly who are long-term users may produce some subtle cognitive advantages, yet with little withdrawal symptoms or emergent sleep difficulties.[117]

B Benzodiazepines should be gradually withdrawn in the elderly as this may produce improvement in cognitive functions.[117]

Grade B, Level 1+

6.2 Use of benzodiazepines in children and adolescents

In general, benzodiazepines are not as commonly used in children and adolescents as in adults.[118] Most reported investigations of benzodiazepine use in children and adolescents have been open trials or conducted in patient populations that are not well characterized, making it difficult to determine whether these medications would be effective and safe.[118-121]

To date, the available data inconsistently suggests the efficacy of some benzodiazepines (e.g. alprazolam, clonazepam and lorazepam) employed by specialists for the short-term management of anticipatory and situation-related anxiety symptoms, severe school phobia, panic disorders, generalized anxiety disorder and avoidant personality disorder in children.[118-121] Specialists have also used benzodiazepines pre-operatively and for controlling various types of seizures in children.[118]

Benzodiazepines are sometimes used by specialists for short-term treatment of unusually frequent and severe sleep terror and sleepwalking.[118,120,121]

Benzodiazepines can increase activity and produce or aggravate behavioural disorders, particularly in children with attention deficit hyperactive disorders.[18,118-123] Disinhibition, cognitive impairment, depression and physiological dependence may be problematic.[18,118-123]

D Children and adolescents are at increased risk of disinhibition with benzodiazepines; first-line treatment with benzodiazepines should be avoided.[18,118-123]

Grade D, Level 3

6.3 Use of benzodiazepines in pregnancy and lactation

The maternal use of benzodiazpeines may increase the risk for preterm birth and low birth weight and cause neonatal symptoms, but does not appear to have a strong teratogenic potential.[124]

The effects of benzodiazepines on the human embryo and foetus are still controversial.[124-126] Some studies have reported an association with various types of congenital defects, while other studies have not found such association.[124-126] Benzodiazepines may lead to the development of dependence and consequent withdrawal symptoms in the foetus.[127] They are distributed into breast milk and thus the potential for adverse reactions from the drugs in nursing infants should be considered.[1,2,128] The safety of benzodiazepine use in pregnancy and nursing infant is not established.[1,2,124-128]

C Benzodiazepines should be avoided during pregnancy and breast-feeding.[1,2,124-128]

Grade C, Level 2+

7 Cost-effectiveness issues

There are currently no local data on cost-effectiveness of pharmacological agents, non-pharmacological methods and complex caregiver intervention programmes in the treatment of psychiatric and medical problems involving the use of benzodiazepines.

Due to the different healthcare funding mechanisms in other countries, we are unable to extrapolate from cost-effectiveness studies from overseas countries.

8 Clinical assurance of benzodiazepines prescribing

Clinical assurance of benzodiazepine prescribing involves the monitoring of relevant clinical indicators of prescribing benzodiazepines.[129] These indicators are generally based on the recommended benzodiazepine prescribing practices stipulated in these guidelines and may be monitored by the medical practitioner himself, his professional peers or health authorities. In conjunction with these guidelines, the results obtained from monitoring these indicators can be used by the practitioner to improve his prescribing practices.

Based on these guidelines, the following are some suggested clinical indicators of benzodiazepine prescribing that can be monitored for the purpose of clinical assurance:

General indicators

A = Number of patient visits where benzodiazepines are prescribed
B = Number of patients prescribed with benzodiazepines

- Proportion of (A) prescribed benzodiazepines for a cumulative duration longer than 4 weeks[129] (pg 24,25)
- Proportion of (A) advised on non-pharmacological therapies[129] (pg 15,16,17,29)
- Proportion of (A) given appropriate advice on the risks of taking benzodiazepines, including the potential for dependence[129] (pg 25)
- Proportion of (B) with indications adequately documented[129] (pg 24)
- Proportion of total visits where benzodiazepines are prescribed.

Annex A Use of benzodiazepines

Table A1 Benzodiazepine indications and dosages in adults

Indications	Benzodiazepine	Dosage in Adults	Remarks
Alcohol withdrawal syndrome	Chlordiazepoxide*†	Initially p.o. 50- 100 mg in 3-4 divided doses. Max 300 mg/day.[2,13]	Adverse Reactions[1,2,13] - Dependence and withdrawal symptoms can occur especially in patients with history of drug dependence. - Central Nervous System effects (e.g. sedation, drowsiness, muscle weakness, ataxia, and amnesia. Less commonly, slurred speech, vertigo, headache, confusion) - Paradoxical excitement or sleep-related behaviours may occur. General Precautions[1,2,13] - Muscle weakness - Respiratory disease - Renal or hepatic impairment (avoid if severe) - Children, elderly and the debilitated - Pregnancy and breastfeeding (avoid use unless potential benefits clearly outweighs risks) - History of drug/alcohol abuse or psychiatric disorders (e.g. marked personality disorder, depression, psychosis). - Prolonged medication usage (and abrupt discontinuation thereafter) should be avoided.
	Clorazepate*†	Initially p.o. 30 mg, followed by 30-60 mg in divided doses in first 24 hours; 45-90 mg in divided doses in second 24 hours; 22.5-45 mg in divided doses in third 24 hours; 15-30 mg in divided doses in fourth 24 hours; thereafter gradually reduce dose to 7.5-15 mg/day and discontinue.[2,13,130]	
	Diazepam*†	Initially p.o. 10 mg TDS-QDS for first 24 hours, then reduce to 5 mg TDS-QDS as needed.[1,2,13]	
	Lorazepam	p.o. 2 mg q6hr for four doses, then 1 mg q6hr for eight doses.[13]	
Anxiety	Alprazolam*†	Initially p.o. 0.25-0.5 mg BD-TDS. Max. 4-6 mg/day.[1,2,13]	
	Bromazepam*	p.o. 1.5-3 mg up to TDS.[131]	
	Chlordiazepoxide*†	p.o. 5-10 mg TDS or QDS. Max. 60-100 mg/day.[1,2,13]	
	Clobazam*	p.o. 20-30 mg/day.[132]	
	Clorazepate*†	p.o. up to 30 mg in divided doses. Max. 60-90 mg/day.[2,130]	
	Diazepam*†	p.o. 2-10 mg BD-QDS.[2,13]	
	Lorazepam*†	p.o. 1-3 mg/day (in 2-3 divided doses). Max. 6 mg/day.[1,2,13]	
	Nordazepam*	p.o. 7.5-15 mg at bedtime.[133]	
	Pinazepam*	p.o. 5-10 mg BD.[134]	
Insomnia	Flurazepam*	p.o. 15-30 mg at bedtime.[1,2,13]	
	Lorazepam*†	p.o. 1-2 mg at bedtime.[1]	
	Nitrazepam*†	p.o. 5-10 mg at bedtime.[1]	
Panic Disorder	Alprazolam*†	Initially p.o. 0.25-0.5 mg BD-TDS. Max. 4-6 mg/day.[1,2,13]	
	Clonazepam†	Initially p.o. 0.5 mg BD. Max 4 mg/day.[13]	
Seizure	Clobazam*	Initially p.o.5-15 mg/day. Max. 80 mg/day.[132]	
	Clonazepam*†	Initially not more than p.o. 1.5 mg/day (in 3 divided doses). Max. 20 mg/day.[13]	
	Clorazepate†	Partial Seizure: Initially up to p.o. 7.5 mg TDS. Max. 90 mg/day.[2,13]	
	Diazepam*†	*Seizure*: p.o. 2-10 mg BD-QDS.[2,13] *Refractory Seizure*: Rectal enema 0.25-0.5 mg/kg when rapid effect required and IV administration is impractical.[1,2] *Severe recurrent convulsive seizure*: Initially slow IV (or IM if impossible for IV) 5-10 mg, may be repeated at 10-15 minutes intervals, until max. total of 30 mg has been given.[2]	
Skeletal muscle spasm	Diazepam*†	p.o. 2-10 mg TDS-QDS.[2,13]	

* HSA approved uses
† FDA labelled indications
Please refer to the BNF[1], AHFS[2] and the respective manufacturer's package inserts for complete drug information.

Table A2 Metabolism of benzodiazepines

Drug	Duration of Action*[2,13,135]	Primary Hepatic Metabolism[13-15,135]	Elimination Half-life (hours)† [2,4,13-15,135]	
			Parent compound	Active metabolites
Alprazolam	Short	Oxidation	11.2 (6-20)	No active metabolites
Bromazepam	Short	Oxidation	8-20	No active metabolites
Chlordiazepoxide	Long	Oxidation	5-48	14-95 (36-200)
Clobazam	Long	Oxidation	18-24 (9-77)	36-46 (73)
Clonazepam	Long	Oxidation/ Nitroreduction	18-40	46-48
Clorazepate	Long	Oxidation	2.29	36-200
Diazepam	Long	Oxidation	20-54	40-533
Flurazepam	Long	Oxidation	2.3	16-100
Lorazepam	Short	Glucuronidation	12 (8-25)	No active metabolites
Midazolam	Very short	Oxidation	1.8-6.4	1
Nimetazepam	Insufficient data	Insufficient data	Insufficient data	Insufficient data
Nitrazepam	Long	Nitroreduction	24-29	N.A.
Nordazepam	Long	No data	36-200	No data
Pinazepam	Long	Demethylation	12 (10-15)	70

*Approximate duration of action (in healthy adults):
Very Short: about 2 hour or less Short: about 6 hours Long: more than 10 hours

† Elimination $T_{½}$ (in healthy adults): Reported usual range in parentheses.

Please refer to the respective manufacturer's package insert or reference texts for complete drug information.

Table A3 Benzodiazepine oral dose equivalence

Benzodiazepine	Approximate Oral Dose Equivalence (reported range in parentheses)
Alprazolam[4]	0.5 mg
Bromazepam[4,16]	6 mg (5-6 mg)
Chlordiazepoxide[1,16,18]	25 mg (25-30 mg)
Clobazam[16]	20 mg
Clonazepam[1,4,18]	1 mg (0.5-2 mg)
Clorazepate[4,16]	15 mg (15-20 mg)
Diazepam[1,16,18]	10 mg
Flurazepam[16]	15-30 mg
Lorazepam[1,4,16,18]	1 mg (1-2 mg)
Midazolam[13]	2.5-3.3 mg
Nimetazepam	Insufficient data at present
Nitrazepam[1,4,16,18]	10 mg
Nordazepam[4]	10 mg
Pinazepam[13]	5 mg

Annex B Non-pharmacological measures for insomnia

Table B1 Sleep hygiene[44]

1. Avoid the use of caffeine-containing products, nicotine and alcohol especially later in the day.
2. Avoid heavy meals within 2 hours of bedtime.
3. Avoid drinking fluids after dinner to prevent frequent nighttime urination.
4. Avoid environments that will make you really active after 5 pm (i.e. avoid noisy environments).
5. Only use your bed for sleep. Sit in your chair when you just want to relax.
6. Avoid watching television in bed.
7. Establish a routine for getting ready to go to bed.
8. Set time aside to relax before bed, and utilise relaxation techniques.
9. Create an atmosphere conducive to sleep:
   Keep yourself at a comfortable temperature by modifying the number of blankets you use.
   Use earplugs if it is too noisy.
   Make the room darker if there is too much light (e.g. close the door).
   Put an extra mattress on your bed if is uncomfortable.
10. When in bed, relax and think pleasant thoughts to help you fall asleep.
11. Get up at the same time every day, including weekends. Use an alarm clock if it will help.
12. Avoid taking daytime naps. If you have to take them, make sure you do so before 3.00 pm and that the total napping time does not exceed one hour.
13. Pursue regular physical activities like walking or gardening but avoid vigorous exercise too close to bedtime.

Adapted from Petit L et al 2003.

Table B2 Stimulus control[44]

1. Go to bed only when you feel tired.
2. Use the bed and bedroom for sleep and sex. For example, do not read books or magazines, watch TV, eat or worry while in bed.
3. Leave the room if you do not fall asleep within 15-20 min. Remain in the other room for as long as you wish or need. Return to bed only when you feel sleepy again.
4. If you still cannot sleep, repeat step 3. Do this as often as necessary throughout the night.
5. Get up at the same time every morning regardless of how much sleep you obtained the night before (use an alarm clock if necessary).
6. Avoid napping.

Adapted from Petit L et al 2003.

Table B3 Sleep restriction[44]

1. Determine the average estimated total sleep time. The data used to do this can be obtained from a sleep diary that has been filled out for at least 2 weeks.
2. Restrict the time in bed to the average estimated total sleep time.
3. Each week, determine the patient's weekly sleep efficiency (total sleep/time in bed x 100%) from the data obtained from the sleep diary.
4. Increase total time in bed by 15-20 min when sleep efficiency exceeds 90%. Decrease it by 15-20 min when sleep efficiency is below 80%. Keep total time in bed the same when sleep efficiency is between 80–90%.
5. Each week, adjust the total time in bed until the ideal sleep duration is obtained.
6. Do not reduce time in bed to below 5 hours.
7. Brief midday naps may be permissible, especially in the early phase of treatment.
8. When applying this protocol to the elderly, some recommend reducing the time in bed only when sleep efficiency is below 75%.

Adapted from Petit L et al 2003.

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Self-assessment (MCQs)

After reading the Clinical Practice Guidelines, you can claim one CME point under Category III (Self-Study) of the SMC Online CME System. Before you login to claim the CME point, we encourage you to evaluate whether you have mastered the key points in the Guidelines by completing this set of MCQs. This is an extension of the learning process and is not intended to "judge" your knowledge and is not compulsory. The answers can be found at the end of the questionnaire.

Instruction: Choose "True" or "False.

		True	False
1.	Pharmacological considerations		
	A) Benzodiazepines that undergo oxidative metabolism should be used with caution in hepatic impairment.	☐	☐
	B) Paradoxical excitement or sleep-related behaviours may occur with benzodiazepines.	☐	☐
	C) Prolonged usage (and abrupt discontinuation thereafter) of benzodiazepines should be avoided.	☐	☐
	D) Zolpidem and zopiclone should be treated with the same cautions as benzodiazepines	☐	☐
	E) Zolpidem or zopiclone should be substituted for a short-acting benzodiazepine that is ineffective.	☐	☐
2.	Psychiatric uses of benzodiazepines		
	A) Pharmacotherapy in anxiety disorders is indicated only when symptoms are severe with significant functional impairment.	☐	☐
	B) Benzodiazepine use should be limited to 2-4 weeks, at the lowest dose and taken intermittently (e.g. once in 2 or 3 nights).	☐	☐
	C) Benzodiazepine monotherapy is as effective as antipsychotics in the treatment of schizophrenia.	☐	☐
	D) Benzodiazepine monotherapy is as effective as antidepressants in the long-term treatment of depression and anxiety disorders.	☐	☐
	E) Patients on a short course of benzodiazepine can be discontinued from the drug over 1-2 weeks.	☐	☐

	True	False
3. General and medical uses of benzodiazepines		
A) Patients with complicated alcohol or benzodiazepine withdrawal should be referred to general hospitals.	☐	☐
B) For the treatment of epilepsy, dystonia and spasticity, patients should be referred to the appropriate specialist.	☐	☐
C) Benzodiazepines can routinely be given to patients with co-morbid substance abuse or dependence problems by providing instructions on safe use.	☐	☐
D) Gradually withdrawing benzodiazepines in the elderly may improve cognitive functions.	☐	☐
E) Benzodiazepines are safe treatment options of choice for children and adolescents, as well as female patients who are pregnant or breast-feeding.	☐	☐
4. Regarding benzodiazepine dependence		
A) The longer-acting benzodiazepines are associated with higher risks of dependence compared to those with shorter half lives.	☐	☐
B) Benzodiazepine prescriptions such as midazolam are sometimes diverted to intravenous use by polydrug users.	☐	☐
C) Patients may become dependent on benzodiazepines only with longer prescriptions of more than a year.	☐	☐
D) The use of a more potent benzodiazepine is an identified risk factor for the development of dependence syndrome.	☐	☐
E) Long-term chronic use of benzodiazepines is not recommended	☐	☐
5. Regarding benzodiazepine discontinuation		
A) Shorter-acting preparations are used to withdraw patients	☐	☐
B) The withdrawal symptoms may manifest within 24 hours of discontinuing short-acting benzodiazepines.	☐	☐
C) The withdrawal of long-acting benzodiazepines can continue up to 3 weeks.	☐	☐
D) Gradual and slow discontinuation of benzodiazepines is associated with high dropout rates.	☐	☐
E) Propanolol, dothiepin or hydroxyzine can be used in the primary management of benzodiazepine withdrawal.	☐	☐

		True	False
6.	When prescribing benzodiazepines as a hypnotic:		
	A) It should only be prescribed for insomnia that is severe, disabling or causing extreme distress.	☐	☐
	B) For those whose insomnia is likely to recur or persist, benzodiazepine prescription should be avoided.	☐	☐
	C) Pharmacological therapy is the mainstay of treatment for any form of insomnia.	☐	☐
	D) Prescription within therapeutic dosage will not lead to dependence syndrome.	☐	☐
	E) Assess for any underlying physical or psychological conditions, or drugs causing insomnia	☐	☐
7.	When prescribing benzodiazepines, it is recommended that:		
	A) All patients must be warned about the risk of dependence and the side effects of benzodiazepines.	☐	☐
	B) The use of benzodiazepines (especially long-acting ones) in the elderly should be avoided.	☐	☐
	C) There should be clear indications and they must be documented for the continued or repeat prescription of benzodiazepines.	☐	☐
	D) Patients should be examined for signs of substance misuse such as the presence of needle tracks.	☐	☐
	E) Benzodiazepines with high risk of misuse such as midazolam (Dormicum®) and nimetazepam (Erimin®) should be avoided.	☐	☐

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Answer

1 A)	T	(pg 11)
1 B)	T	(pg 12)
1 C)	T	(pg 14)
1 D)	T	(pg 14)
1 E)	F	(pg 15)

2 A)	T	(pg 19)
2 B)	T	(pg 19)
2 C)	F	(pg 18)
2 D)	F	(pg 19)
2 E)	T	(pg 27)

3 A)	T	(pg 23)
3 B)	T	(pg 23)
3 C)	F	(pg 25)
3 D)	T	(pg 30)
3 E)	F	(pg 31)

4 A)	F	(pg 24)
4 B)	T	(pg 25)
4 C)	F	(pg 24)
4 D)	T	(pg 24)
4 E)	T	(pg 25)

5 A)	F	(pg 26)
5 B)	T	(pg 26)
5 C)	T	(pg 27)
5 D)	F	(pg 27)
5 E)	F	(pg 26)

6 A)	T	(pg 16)
6 B)	T	(pg 17)
6 C)	F	(pg 15)
6 D)	F	(pg 16)
6 E)	T	(pg 16)

7 A)	T	(pg 15)
7 B)	T	(pg 30)
7 C)	T	(pg 24)
7 D)	T	(pg 25)
7 E)	T	(pg 25)

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