BENZODIAZEPINES Z-DRUGS AND DEPENDENCE

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Benzodiazepines and z-drugs are some of the most widely prescribed medication. They work as anxiolytics, sleep inducers, and in various other capacities, such as muscle relaxants and against epileptic seizures. For people with anxiety and panic attack, they can normalize life, while long-term treatment options are explored, and they can be used as emergency standby medication. However, they also carry risks, such as cognitive impairment and sedation in the short-run and tolerance and dependence in the long-run. Fortunately, there are alternatives to the benzodiazepines and z-drugs, which can be used in many cases.

Keywords: benzodiazepine, z-drug, medication, psychiatry

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Introduction

Benzodiazepines and z-drugs are important components of the psychiatric repertoire. They reduce anxiety fast and facilitate sleep. Besides anxiolytics and hypnotics, they are also anticonvulsants, muscle-relaxants and induce anesthesia. They play very important roles in many areas of medicines and are relatively safe if used once of or sporadically on an as needed basis. If used regularly, however, they can induce tolerance and dependency in the long-run. (Haverkampf, 2017, 2018b, 2018a). Adverse effects can also include sedation as well as cognitive and psychomotor impairment.

The Short Term

In the short term, they are important components in treating anxiety, agitation several other acute psychiatric symptoms. They can lead to significant relief for the time until the pharmacological and non-pharmacological long-term therapies work. As such, they can bring about a large increase in the quality of life temporarily. Particularly in patients who suffer from pronounced anxiety and panic attacks, the relief of having the option of a quick relief available can break the vicious cycle of anxiety leading to even greater anxiety or anxiousness about becoming anxious. Caring a benzodiazepine in the pocket can have the effect, which often means not actually having to take it because the anxiety about losing control in an anxiety or panic attack is significantly reduced. The fact that most tablets require at least half an hour to work usually does not reduce this psychological effect.

The Long Term

In the long term, there are the risks of tolerance, dependence and withdrawal symptoms. However, some patients, who cannot be switched to another sleep-inducing medication, for example, do not seem to develop tolerance even in the long-run. There is no good explanation yet why some individuals do not seem to develop tolerance, while many others do. In any case, the regular use of benzodiazepines and z-

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drugs in the long-run should only be a choice if safer medication does not work or causes unacceptable side effects. One potential side effect among the alternatives, which may require switching to another alternative, is weight gain in the case of sedating antidepressants and second-generation antipsychotics. Particularly among the second-generation antipsychotics there are also potentially more severe, but usually relatively rare, side effects, including changes in liver enzymes or tardive dyskinesia.

'Withdrawal'

A sizable fraction of patients medicated with benzodiazepines and z-drugs experience symptoms and signs on attempting to withdraw – anxiety, insomnia, muscle spasms and tension and perceptual hypersensitivity. There can also be mood instability and in rare cases psychosis-like symptoms. How long it takes for a patient to build tolerance and become physically dependent on a benzodiazepine or z-drug can be very different from individual to individual. Some do not show physical withdrawal symptoms even after years of regular administration. A psychological dependency should, however, be the basic assumption in a case of regular long-term use.

With respect to hypnotics, numerous studies have compared a long list of benzodiazepines and Z-drugs with placebo and with each other [33, 34]. Another meta-analysis identified 24 studies in the elderly where the bulk of the prescribing is concentrated [35]. Sleep quality was found to have improved, total sleep time increased, and the number of night time awakenings decreased with hypnotic use as compared with placebo. However, adverse effects were nearly five times as common. The authors concluded that improvements in sleep did occur but the size of the effects was 'small'. Their use in the over 60-year-olds was attended by increased risk.

Benzodiazepines

Benzodiazepines are useful in treating anxiety, insomnia, agitation, seizures, muscle spasms, alcohol withdrawal and as a premedication for medical or dental procedures. [55] In psychiatry, they are often used in the short-run to alleviate anxiety, panic attacks or agitation before the longer-term medication works. They have been on the market since the 1960s and are one of the most widely prescribed group of medications there is in the world. Some general practitioners use them as the general psychiatric medication for most abnormal mental health states, while others avoid them as much as they can. Under- and over-prescription are probably the largest problems associated with the benzodiazepines, and to a lesser extent with the z-drugs. In between, there is a third way, however, to make them available as much

as necessary. 'Necessary' should mean using them as long as there is no better alternative which keeps the patient largely symptom free. In a case of generalized anxiety, for example, this may imply using them until the antidepressant, most commonly a selective serotonin reuptake inhibitors (SSRI), works at an adequate dose.

Mechanism

The active site of the GABA-A receptor is the binding site for GABA and several drugs such as muscimol, gaboxadol, and bicuculline. The protein also contains a number of different allosteric binding sites which modulate the activity of the receptor indirectly. These allosteric sites are the targets of various other drugs, including the benzodiazepines, nonbenzodiazepines, neuroactive steroids, barbiturates, alcohol (ethanol), inhaled anesthetics, and picrotoxin, among others. Activation of GABA-A receptors tends to stabilize or hyperpolarize the resting potential and can make it more difficult for excitatory neurotransmitters to depolarize the neuron and generate an action potential. The effect is thus largely inhibitory. Since benzodiazepines enhance the effect of the neurotransmitter gamma-aminobutyric acid (GABA) at the GABA-A receptor, they have sedative, hypnotic (sleep-inducing), anxiolytic (anti-anxiety), anticonvulsant, and muscle relaxant properties.

Pharmacokinetics

The pharmacokinetic properties of benzodiazepines vary substantially from ultra-short acting to very long acting. Therefore, their efficacy is dependent on numerous considerations. Benzodiazepines are categorized as either short-, intermediate-, or long-acting. Short- and intermediate-acting benzodiazepines are preferred for the treatment of insomnia; longer-acting benzodiazepines are recommended for the treatment of anxiety. [56] High doses of many shorter-acting benzodiazepines may also cause anterograde amnesia and dissociation. [54] An important factor with respect to long term use is whether tolerance is a major complicating factor.

Side Effects

Benzodiazepines are generally viewed as safe and effective for short-term use, although cognitive impairment and paradoxical effects such as aggression or behavioral disinhibition occasionally occur. A minority of people can have paradoxical reactions such as worsened agitation or panic. [57]

Benzodiazepines are also associated with increased risk of suicide. [58] Long-term use is controversial because of concerns about adverse psychological and physical effects, decreasing effectiveness, and physical dependence and withdrawal. [59][60] As a result of adverse effects associated with the long-term use of benzodiazepines, withdrawal from benzodiazepines often leads to improved physical and mental health. [61][62] The elderly are at an increased risk of suffering from both short- and long-term adverse effects, [61][63] and as a result, all benzodiazepines are listed in the Beers List of inappropriate medications for older adults. [64]

There is controversy concerning the safety of benzodiazepines in pregnancy. While they are not major teratogens, uncertainty remains as to whether they cause cleft palate in a small number of babies and whether neurobehavioral effects occur because of prenatal exposure; [65] they are known to cause withdrawal symptoms in the newborn. Benzodiazepines can be taken in overdoses and can cause dangerous deep unconsciousness. However, they are less toxic than their predecessors, the barbiturates, and death rarely results when a benzodiazepine is the only drug taken. When combined with other central nervous system (CNS) depressants such as alcoholic drinks and opioids, the potential for toxicity and fatal overdose increases. [66][67] Benzodiazepines are commonly misused and taken in combination with other drugs of abuse. [68][69][70]

Z-Drugs

Z-drugs are a group of nonbenzodiazepine drugs with effects similar to the benzodiazepines, which are used in the treatment of insomnia, and most of whose names start with the letter "Z". Some Z-drugs may have advantages over benzodiazepines. Benzodiazepines can worsen sleep architecture, whereas the Z-drug zaleplon (Sonata) may have less or no disruption of sleep architecture.

Therapeutic Benefits

Traditionally, there has been a division of the benzodiazepines into anxiolytics and hypnotics, although some drugs such as diazepam, oxazepam and lorazepam may be listed under both headings. [1]

The beneficial effects of benzodiazepines include

- the reduction of
- anxiety

- the induction and maintenance of sleep
- muscle relaxation and
- the treatment and prevention of epileptic seizures.

These properties are shared by most currently approved benzodiazepines but to varying degrees, depending on their potency and pharmacokinetic properties.

Treatment of anxiety disorders

Randomized controlled trials have provided evidence for the efficacy of some benzodiazepines in certain anxiety disorders, usually in acute treatment for the reduction of anxiety symptoms, but sometimes in longer-term treatment, designed to prevent a relapse of symptoms in someone who has made a good response to acute treatment. There is good evidence for efficacy in acute treatment of generalized anxiety disorder, social anxiety disorder and panic disorder, but limited evidence for efficacy in obsessive-compulsive disorder. Benzodiazepines have not been found to be efficacious in randomized controlled trials in post-traumatic stress disorder, and may indeed be unhelpful in preventing the emergence of posttraumatic symptoms after traumatic events.

Benzodiazepines are indicated for the short-term relief (2 to 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. The use of benzodiazepines to treat short term ‘mild’ anxiety is inappropriate and unsuitable.

A meta-analysis systematically reviewed 27 randomized controlled trials of drug treatments for generalized anxiety disorder (GAD) [32]. The only benzodiazepine included was lorazepam, presumably reflecting the advent of BZDs antedating the establishment of GAD as a diagnostic category. Fluoxetine was ranked first for response and remission and pregabalin for tolerability. Lorazepam showed up poorly but data for it were limited and the authors did not comment further.

Numerous guidelines are extant for the management of anxiety disorders and insomnia. The most quoted are those issued by the National Institute for Health and Clinical Excellence (NICE) [36]. With respect to anxiolytic use, selective serotonin re-uptake inhibitors (SSRIs) are favored as drugs of first choice, pregabalin is regarded as a stand-by for patients who cannot tolerate SSRI or serotonin-norepinephrine re-uptake inhibitor (SNRI) antidepressants. BZDs are relegated for the treatment of GAD in primary and secondary care for use only as a short term measure during crises.

Benzodiazepines vs Antidepressants

The common approach is to use an SSRI or SNRI for long-term anxiolysis and a benzodiazepine to help the patient remain largely anxiety free until the antidepressant starts to fulfill this function. Benzodiazepine anxiolytics should be prescribed primarily either for the short-term relief of severe anxiety symptoms, or where anxiety disorders are disabling and severe and causing both significant personal distress and substantial impairment of daily activities. Where the rationale for treating anxiety symptoms does not meet either of these criteria, psychological or pharmacological treatments with an evidence base for long-term use are more suitable.

'As required'

To reduce the risk of dependence on benzodiazepines they should generally not be prescribed as a regularly administered medication for longer than four weeks. Ideally, they should be given on an 'as required' basis and intermittently every few days during this period.

Long-term medication

There are clinical circumstances in which longer-term prescription of benzodiazepines might be considered desirable because the alternatives are probably worse than the continued use of benzodiazepines.

This may be the case in conditions such as

- chronic treatment-resistant anxiety disorders or
- established dependence (with unsuccessful attempts to stop treatment).

In rare instances, longer-term prescriptions of benzodiazepines may be seen as a form of harm reduction in patients who would otherwise consume illicit benzodiazepines or abuse alcohol to 'cope' with anxiety.

There are other situations where anxiety is complicated by other medical conditions, or where the risk of dependence with benzodiazepine use may be considered acceptable because of the severity of illness and potential hazards associated with other treatment approaches.

Induction of sleep

Adequate treatment of insomnia is often difficult, and depends on many factors such as age, presence of physical illness, pain, use of concomitant medication, and history of drug or alcohol misuse.

Benzodiazepines should be used to treat insomnia only when it is severe, disabling or subjecting the individual to extreme distress. However, benzodiazepines and Z-drugs are the most effective drugs for the short-term treatment of insomnia that is disabling and causing distress, after 'sleep hygiene' techniques have been tried unsuccessfully and/or there had to be a fast solution to the sleep disturbance. If at all possible, however, preference should be given to the z-drugs, which may be less likely to cause tolerance and psychological dependence in the short-run than some benzodiazepines.

Treatment of underlying conditions

Care should be taken to exclude or manage associated conditions such as mood disorders or substance misuse. Some conditions such as sleep apnea may be aggravated by the use of benzodiazepines.

Other pharmacological approaches

The only alternative to hypnotic BZDs is the melatonin prolonged release formulation (Circadin) [38], and then only for insomniacs aged over 55 years. Off-label alternatives include sedative antidepressants such as mirtazapine [39], and sedative antihistamines. This paucity of choice may alter soon as non-BZD hypnotics become increasingly available, such as orexin antagonists.

Initiating and maintaining sleep

They can reduce the time taken to fall asleep, increase the duration and efficiency of sleep, and reduce periods of wakefulness after the onset of sleep. Drugs with a relatively short half-life can facilitate falling asleep with a lower risk of residual daytime drowsiness ("hangover") than is seen with drugs that have longer half-lives. As for the z-drugs, zolpidem is often used to help initiate sleep, while zopiclone is used for both, initiating and maintain sleep. Zopiclone, however, is more likely to cause hangover the next day and can leave a metallic taste in the morning, which is for some patients very irritating.

Four weeks

The continuous treatment with benzodiazepines and, probably to a lesser extent, z-drugs should be limited to a maximum of four weeks. Prescriptions for longer terms should preferably be at the lowest effective dose and given intermittently. However, otherwise treatment-resistant patients should not become anxious and deprived of sleep, because they fear they will not get their sleep medication.

Chronic Insomnia

In patients with chronic insomnia, benzodiazepines should be used only in the short term while more appropriate longer-term treatments are started. Elderly individuals are more vulnerable to the adverse effects of prescribed medication, but consume the majority of sleeping tablets. They often have co-existing physical disease, and a pragmatic approach to treatment may need to be adopted, whilst paying attention to issues such as drug–drug interactions.

z-Drugs

Zolpidem and zaleplon are now available for managing insomnia. They have pharmacological similarities to benzodiazepines and produce similar side-effects, but have relatively shorter half-lives and are in some cases more selective for specific GABAA receptor subtypes.

Like benzodiazepines, these drugs are licensed for short-term use only. Where the effects are selective on certain GABAA receptor subtypes, the anxiolytic effects are few. However, the Z-drugs may have some limited advantages over traditional benzodiazepines in terms of dependence and withdrawal, and should be considered as an alternative, particularly if there seems to be a potential need for longer-term treatment or in patients presumed to be at increased risk of dependence.

Anticonvulsants

Benzodiazepines have anticonvulsant and muscle relaxant effects that are considered to be independent of their anxiolytic actions. These effects can be valuable in the emergency treatment of seizures or in the management of spasticity or muscle spasms, or movement disorders associated with the use of antipsychotic drugs. Tolerance may develop with long-term use, particularly to their anticonvulsant effects, and they are therefore not generally recommended for prophylactic use in epilepsy, other than in some rare childhood syndromes. They are sometimes used as part of induction procedures prior to anesthesia.

Alcohol Withdrawal

Benzodiazepines – notably diazepam and chlordiazepoxide – are useful in managing withdrawal from alcohol in patients with alcohol dependence, especially in the prevention of epileptic seizures and delirium tremens. There is only limited evidence to suggest that benzodiazepines may be useful in the management

of patients with acute confusional or delirious states, and their use in these conditions is not recommended. There is little evidence that previously alcohol dependent patients may derive benefit from benzodiazepines in helping to facilitate continuing abstinence from alcohol.

Rapid Tranquilization

Although the evidence for potential benefit is rather mixed, some patients with excitement, agitation or severe psychotic symptoms may be prescribed short-term benzodiazepines as part of acute 'rapid tranquillization', or as an adjunct to the use of antipsychotic drugs. In these situations, the dose and duration of treatment needs to be monitored closely. Certain benzodiazepines such as clonazepam can be used in the treatment of patients with acute mania. When these compounds are no longer required, patients should be withdrawn from them, in a tapered manner.

Adverse effects

Subjectively, sedation with feeling of heaviness and dysphoria is closely dose-related. It usually quickly subsides due to tolerance to the subjective effects. At higher doses, unsteadiness, slurring of speech and disorientation indicate over-sedation particularly when the BZD is combined with alcohol. Cognitive and psychomotor impairment can be detected even at ostensibly therapeutic doses. This can ensue during the whole day when the BZD is prescribed several times during the day as an anxiolytic, or a long acting BZD the night before as a hypnotic. It will be confined to the morning following a short acting sleeping pill. These objective effects can persist in long term users [4]. Memory appears to be particularly sensitive to BZD action, again augmented by co-administration of alcohol. The more complex the memory task, the greater the impairment following a BZD. These effects persist into the long term [5]. A meta-analysis that combined several rather diverse trials found definite impairments across a range of tests especially with respect to verbal memory [6].

Many useful data should accrue by measuring various functions before, during and after the administration of a BZD anxiolytic or hypnotic preferably with random allocation to drug or placebo and under double-blind conditions. Such studies are the exception, with usually only two out of the three time phases. The above meta-analysis of neuropsychological tests revealed improvement in several cognitive functions, up to 6 months after BZD discontinuation, but ex-users of BZDs still performed poorly [6]. Older adults are at particular risk [7]. Overall, steady withdrawal usually culminates in improvement, if not immediately.

As well as these laboratory-based investigations more complex skills, such as driving, have been assessed for the practical safety implications [8]. Epidemiological studies also show an association between BZD use and road traffic accidents [9]. Increased age and alcohol use are contributing factors, and a meta-analysis estimated the risk of accidents to be increased by over 50% [10][11][12].

Other accounts and injuries are also more common in people using BZDs. Falls and hip fractures have excited most attention. In the elderly the incidence of hip fractures may be increased by 50% or more, particularly when other medication such as antihypertensives and antidepressants are co-prescribed [13].

However, disorders such as anxiety and insomnia can themselves impair a range of functions. Treatment with a sedative drug may improve the deficits with associated improvement in performance but counteracted to some extent by the direct drug-induced impairment –'confounding by indication'.

Paradoxical excitement is an unwanted effect which also has possible legal implications. This disinhibitory effect of the BZDs can produce increased anxiety, acute excitement and hyperactivity. Aggressive impulses may be released with the emergence of hostility and rage and criminal acts such as assault and rape have been recorded [14].

The hazards of long term use have been touched on earlier. Some adverse effects such as cognitive and psychomotor impairments can persist into the long term, although sensitive techniques may be needed to detect them. Others such as sedation wane probably reflecting tolerance. A confounding issue is that patients taking psychotropic medication may lose sight of their original level of feeling and functioning as time elapses. Only when the medication is discontinued does the person realize that their feelings and performance have been sub-optimal. Comparisons with non-users can be problematic because allocation to treatment was never in a rigorous random way [15].

As long-term benzodiazepine users grow older, they became more sensitive to their medications. This is probably because of reduction in neuronal numbers and receptors and hence a greater receptor occupancy for a constant dose. Increasing impairment can lead to a mistaken diagnosis of dementia, so-called 'pseudo-dementia' [16].

Long term hypnotic use, even at a low dosage level, has been reported to be associated with increased mortality hazards (see below), but subjective effects also alter [17], and many users want to stop.

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Cognitive effects

Controlled studies and systematic reviews have shown that benzodiazepine administration can result in sedation and drowsiness, mental slowing and anterograde amnesia (difficulty in forming new memories). These effects are all dose-dependent. Some but not all of these adverse cognitive effects reduce with continued administration – for example, sedation and drowsiness become less prominent with continued use, but memory problems are likely to continue. Withdrawal from benzodiazepines may be associated with some improvement in cognitive performance after abstinence.

It has been argued that these untoward effects can reduce the likelihood of responding to psychological interventions, although the evidence of this is limited. Similar concerns have been expressed about impairment in the ability to adjust to psychological traumas such as bereavement; despite this, it remains common (although not necessarily best) practice to provide a benzodiazepine to the recently bereaved. However, this may defer the emergence of a bereavement reaction until the benzodiazepine is stopped.

Psychomotor effects

Benzodiazepine administration can result in an impairment of performance whilst driving similar to that seen with blood alcohol levels below the current UK legal limit, the magnitude of effects being influenced by the drug, dosage and other factors. There is also an interaction with alcohol that potentiates the degree of impairment seen with either drug alone.

Pharmacoepidemiological studies suggest that benzodiazepine use is associated with an increased risk of road traffic accidents, over and above that seen with untreated mental disorders. Patients should be advised to contact the Driver and Vehicle Licensing Agency (DVLA) when they are taking medications that may impair driving performance, and to avoid drinking alcohol. Due to drug accumulation, use of drugs with longer half-lives may be more hazardous than use of drugs that have a shorter half-life.

Elderly patients are more vulnerable to the cognitive and psychomotor effects of benzodiazepines and eliminate long-acting drugs more slowly than younger patients, and an increased risk of falls should be considered when contemplating possible benzodiazepine prescription to such patients.

Tolerance

Tolerance to the effects of benzodiazepines can occur; this is more pronounced for the anticonvulsant and sedative effects. Tolerance to the hypnotic and anxiolytic effects can also develop, but probably less often and more slowly. It is unusual for patients to steadily increase their dosage, but this can occur in some patients, particularly those with a history of alcohol dependence or other substance misuse. Should tolerance occur, possible reasons for his need to be explored, and the possibility of misuse considered.

Patients with affective disorders

Benzodiazepines may reduce early adverse drug effects in the treatment of depression and bipolar affective disorder. However, they may sometimes appear to worsen depressive symptoms, perhaps by reducing prominent anxiety symptoms and thereby 'revealing' underlying depression. They have minimal effects in reducing the severity of mild depressive symptoms and in some patients may reduce the likelihood of responding to antidepressant treatment. Stopping benzodiazepines can also be associated with the emergence of depressive symptoms. Benzodiazepines are no substitute for effective continuation treatment with antidepressant drugs in patients with recurrent unipolar depression.

Patients with psychosis

Lorazepam (either orally or intramuscularly) is commonly prescribed in inpatient settings for the management of patients with psychosis and prominent behavioral disturbance. If regular benzodiazepine prescription is required, clonazepam may be preferable, as its long half-life makes it suitable for once-daily dosage.

'Disinhibition'

There is some controversy about whether benzodiazepine use alone can result in disinhibited or impulsive behavior. Studies in patients with personality disorders suggest that benzodiazepines may increase the risk of suicidal behavior, especially when combined with alcohol. In theory, use of benzodiazepines by predisposed individuals may 'release' aggressive behavior towards others, but it is hard to distinguish this possible effect from the features of an underlying disorder.

Dependence

Probable dependence on benzodiazepines is usually manifest by the emergence of withdrawal symptoms on either stopping or too rapidly reducing treatment. Withdrawal symptoms can be physical (such as flu-like complaints and muscle cramps) or psychological (such as irritability, insomnia, nightmares, perceptual changes, and depersonalization or derealization). Symptoms can be prolonged and are sometimes hard to distinguish from those of underlying anxiety disorders, although perceptual disturbances are relatively infrequent in untreated patients with anxiety disorders. Withdrawal reactions are generally short-lived, typically lasting less than one month, although duration is influenced by individual pharmacokinetic factors. There is controversy about whether symptoms persisting for many months (reported by approximately one-quarter of patients) are withdrawal reactions, or simply the features of an underlying disorder, or worsening of that condition triggered by treatment withdrawal.

Established benzodiazepine dependence is preferably treated by advice, pharmacological optimization or substitution, gradual withdrawal and psychological support. In some patients, pharmacological and psychological interventions will be of only limited benefit, so certain individuals will be unable to stop benzodiazepines.

Risk factors for continuation include a history of substance misuse, comorbid depression, dependent personality disorder and physical ill-health. In patients with persistent symptoms, a joint decision should be made about whether they are generally better off with or without treatment.

Abuse of benzodiazepines

Benzodiazepines are widely misused [26], although the pattern varies greatly from country to country [29]. According to one Dutch study, correlates of ‘inappropriate’ use include mentally or physically vulnerable subjects, particularly the elderly [31]. The literature suggests that the elderly, women, poor perceived health status and poor actual physical health are associated with long term use, especially with hypnotics. Long term users at particular risk of becoming dependent include those with depression and those with previous alcohol problems.

Some individuals abuse benzodiazepines (especially temazepam, flunitrazepam and diazepam) and/or related drugs, as part of a wider drug (e.g. heroin, crack cocaine) and/or alcohol problem. Intravenous injection of temazepam can result in emboli and gangrene. Altering the formulations of certain drugs has made them less easy to inject, and restricting the previously most widely abused drug (temazepam) has

probably limited its use by this route. Some 'benzodiazepines' sourced through the Internet are of uncertain nature and strength, and may contain hazardous contaminants. Clinicians should be aware of the increased risks in overdose when benzodiazepines are mixed with other respiratory depressants.

Benzodiazepines are often used as an alternative when supplies of other drugs of abuse are scarce. Benzodiazepines are also sometimes used by young people to 'come down' after taking stimulant 'party drugs'. Prescriptions of benzodiazepines should be subject to regular review. Doctors should be aware that the medication they prescribe may be diverted into the wrong hands and enter the 'black market', and so should be wary of prescribing to certain individuals, such as those with a history of multiple drug abuse. Prescription of benzodiazepines in conjunction with methadone is no longer regarded as good clinical practice.

Benzodiazepines should be prescribed in as low a dose as possible to afford adequate symptom relief. It is difficult to produce a 'risk table', but compounds with higher potency and shorter half-life are associated with a greater likelihood of developing dependence. Unless there are clear risks of more severe problems if the drug is stopped, patients should be encouraged to withdraw gradually after long-term use. Many patients who were previously treated with benzodiazepines over long periods have already withdrawn successfully, but newly dependent patients are still accruing, as prescriptions for benzodiazepines are not declining. Many of those who remain on benzodiazepine anxiolytics will have trouble stopping unless expertly and sympathetically managed, including being offered psychological and other alternative therapies.

Concerns about the use of benzodiazepines as hypnotics are different from the concerns in patients with anxiety disorders. The sudden withdrawal of a long-established treatment can be extremely distressing and possibly dangerous, for example through inducing epileptic seizures. Dependence is more likely with higher dosages but can also occur with low doses, and formulations of compounds at lower strengths and with longer half-lives may be useful in helping patients reduce from higher doses. Even after short-term use, a tapering-off regime (i.e. at least two weeks at reduced dosage) should be considered to minimize the risk of rebound phenomena, that is, the reappearance of symptoms present prior to treatment. After longer-term use this reduction period should probably be extended, sometimes to several months

in patients who have been treated for many years. Where benzodiazepine dependence is diagnosed but a considered decision is made that continued prescription is nonetheless appropriate, they should be prescribed at gradually reducing doses wherever possible.

Mortality

Regular use of benzodiazepines seems to be associated with increased risk of mortality according to a meta-analysis [28]. Even low usage of hypnotics seems associated with excess mortality [27]. Even occasional hypnotic users had over three times the background risk of dying in 2.5 years. Selective prescription of hypnotics for ailing patients was ruled out as the main explanation.

Withdrawal Symptoms

The antecedents of BZD withdrawal syndromes are varied. Many people are started on a BZD but find it insufficiently effective and ask for the prescriber to increase the dose, often at a time of stress. Usually the patient settles on to that dose and remains there for months, years or even decades. A minority escalate the dose and become high dose users. Attempts to withdraw are accompanied by a BZD withdrawal syndrome which is in the same class as barbiturate or alcohol withdrawal [19, 20]. The patient is regarded as being dependent on the BZD and this group constitutes around 20% of the original users – the remainder can discontinue their medication without difficulty [21]. High dosage, the use of high potency compounds and prolonged continuous use is associated with evidence of dependence.

Withdrawal symptoms can include anxiety, insomnia, nightmares, memory and concentration impairments, and muscle spasms. Perceptual hypersensitivity such as photophobia and hyperacusis are common; the patient feels ill and loses weight. The symptoms generally subside in 2–4 weeks but can be prolonged. More serious but rare reactions include fits and psychosis. Most cases are anecdotal and few case series exist [22].

A recent prospective study of tapered withdrawal identified four symptom patterns – gradual decrease in severity, initial worsening followed by a decrease after discontinuation, a later increase in severity, and no change [23]. High prevalence has been reported [24]. Numerous protocols for withdrawal exist (e.g. [25]), but minimal interventions often suffice in primary care. Psychological treatments are usually helpful.

About two-thirds of patients stop completely with a slow tapering schedule. Most of the rest achieve some dose reduction. Repeated failure, however, becomes demoralizing, and support on a low dose may be the optimal outcome. Comorbid depression, alcohol use and older age are poor prognostic factors.

Discontinuation

Discontinuation of many medications may be accompanied by problems. With respect to BZDs, the most common phenomenon is rebound with hypnotics and this can be quantified with polysomnography [18]. After stopping the sleeping tablet, the insomnia can return in an exaggerated form, time to sleep onset is prolonged, sleep is more disturbed and it is shorter in duration. Rebound is generally short lived lasting a night or two, but can panic the patient into resuming the medication.

Gradual tapering of the medication is regarded as not particularly effective and combination with cognitive-behavioral therapy seems superior [43]. Another strategy is to substitute another medication as an aid to withdrawal; many have been tried, usually in small scale studies. No firm conclusions can be drawn [44]. Pregabalin has shown recent promise [45] as has prolonged release melatonin [46].

The success rate in terms of reducing or ceasing BZD use can be quite high with simple measures, such as advice from the GP [47]. Only the failures need specialist referral. Some long-term users have taken their BZDs for decades. Withdrawal attempts may be fruitless, but monitoring of symptoms and functioning must be instituted and maintained. Flumazenil has been investigated as an aid to withdrawal, success has been claimed, but few clinics anywhere offer this service.

The rate of tapering has become a contentious issue. Some long-term users require protracted withdrawal regimens over months or years, but it is difficult to predict the duration in any one case. Indeed, some chronic users can discontinue with surprisingly little upset. It is probably a better clinical strategy to aim to withdraw over 2–3 months but to slow down if the symptoms become too severe.

Harm minimization is a well-known concept in the wider field of addiction [48]. A fundamental change in attitude led to the encouragement of drug using habits, such as availability of sterile water for injection in order to minimize serious adverse events such as the development of local abscesses and the contagion of viral diseases such as HIV and hepatitis. Similar but less extreme measures are appropriate to benzodiazepine abuse.

Prescriber’s Dilemma

In some people, it may be difficult to prevent short term use (less than 4 weeks for anxiolytic use and 2 weeks for hypnotic use) from being prolonged insidiously into long term use. However, in clinical experience, if one takes the time to get more background information and a good sense of the patient’s needs and wants, as well as a feel for the personality traits, benzodiazepines can be prescribed quite safely

to those who need them and when they need them for a medical reason. Informing the patient about the dangers that might occur on longer-term use is nevertheless essential.

No significant declines have occurred in benzodiazepine prescribing over the past 20 years [30], which also points to the need for effective anxiolytic and hypnotic alternatives. Psychotherapy should always be considered if a patient presents with anxiety and/or insomnia. There is good clinical and empirical evidence that it works in the majority of people. However, medication may still be needed as a support for a, sometimes lengthy, period of time.

Conclusions

Benzodiazepines have, like any other medication, desired and undesired effects. They may be prescribed safely in the short-term and can be effective treatments in many patients whose quality of life is significantly affected by distressing anxiety symptoms or troublesome insomnia.

It is always advisable to consider alternatives to prescribing benzodiazepines. Consideration of alternatives should include a balanced appraisal of the relative benefits and risks of the range of options, in the short- and, if needed, in the long-term. Psychotherapy should always be considered in combination with or without combination.

The potential risks of long-term treatment need to be considered prior to starting short-term treatment. Dependence to benzodiazepines is understood to be more of a risk if the medication is taken regularly for a month or more. However, this depends on the individual case, as some patients do not seem to develop dependence even after many months or even years.

Dependence can become a long-term problem. Often, however, this may not necessarily be due so much to the medication but because there are still pressing unresolved issues which were never resolved within a psychotherapy.

All patients should be made aware of the risks of dependence if they continue benzodiazepines in regular dosage over a longer period. A clinical judgement has to be made as to whether alternatives may be more suitable, for each patient, and for each proposed medication.

Many patients are able to take short courses of benzodiazepines or on an ‘as needed’ basic quite safely and to stop them when no longer needed. In these cases, it can make good clinical sense to continue the medication even beyond four weeks.

If there is no history of drug dependence, and positive indicative 'lifestyle' factors are present, a conscious decision to continue benzodiazepine treatment may be more reasonable than the alternatives, provided the patient periodically attempts to slowly reduce the dosage at regular intervals and tries to stop altogether when or if possible.

If the alternative to benzodiazepine treatment is the use of another form of treatment, either psychological or pharmacological, which proves to have little benefit in practice, a patient may return to the prescriber and ask to be put back on a benzodiazepine. This request should not be automatically declined but there should be a sympathetic consideration of whether or not this is appropriate.

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