Clinical management of withdrawal from benzodiazepine anxiolytic and hypnotic medications

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Declaration of interests

I am President-Elect of the British Association for Psychopharmacology (2020-22) and a Councillor of the European College of Neuropsychopharmacology (2019-22). I have been a Medical Patron of Anxiety UK since 2002 onwards, was Chair of the Psychopharmacology Committee of the Royal College of Psychiatrists (2017-20) and was Clinical Advisor to the National Clinical Audit of Anxiety and Depression (2017-20). I have researched, prescribed, and taken antidepressants. I adhere to no particular ideology about the nature, causes or treatment of mental disorders.

ABSTRACT

Benzodiazepines continue to be prescribed widely in the management of patients with insomnia or anxiety disorders, despite the availability and acceptability of alternative pharmacological and psychological treatments. Many patients will experience adverse effects during treatment and considerable distress when the dosage is reduced and stopped. Management of benzodiazepine withdrawal includes measures to prevent the development of dependence, careful attention to underlying medical conditions, medication consolidation and gradual dosage reduction, accompanying psychological interventions, occasional prescription of concomitant medication, and relapse prevention with on-going support to address psychosocial stressors. There is a need for easier patient access to services with refined expertise, and further research to optimise strategies for preventing dependence and facilitating withdrawal.

Key words: benzodiazepine; anxiolytic; hypnotic; dependence; withdrawal

INTRODUCTION

Benzodiazepines became widely prescribed for treating patients with anxiety disorders and insomnia over fifty years ago, long before the awareness that alternative approaches such as cognitive-behaviour therapy (CBT) or selective serotonin reuptake inhibitors (SSRIs) are often effective in managing common mental health problems. Like most medicines, benzodiazepines have a range of beneficial and untoward effects. Beneficial effects include reduction of anxiety, induction of sleep, muscle relaxation, and prevention of epileptic seizures; untoward effects include drowsiness, mental slowing, memory disturbance and the risk~~s~~ of dependence ~~and abuse~~. The balance of benefit and risk is disputed and undergoes periodic reconsideration [1-3]. Meta-analyses demonstrate the efficacy of benzodiazepine anxiolytics in some patients with certain anxiety disorders [4-6] but tolerability and safety concerns should limit their use in routine clinical practice. A recent evidence review by Public Health England noted the following: prescriptions for benzodiazepines are declining; they are associated with a risk of dependence and withdrawal syndromes; clinical guidelines specify that benzodiazepines should not usually be prescribed for more than 2-4 weeks; the limited number of high-quality recent studies of optimal strategies for managing withdrawal; and the need to improve the support from healthcare systems to patients experiencing benzodiazepine dependence or withdrawal [7].

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PHARMACOLOGICAL PROPERTIES OF BENZODIAZEPINES

Some knowledge of the pharmacodynamic and pharmacokinetic properties of benzodiazepines is needed to understand both the origins of problems such as tolerance and dependence, and the principles of management of their withdrawal in clinical practice. Benzodiazepines enhance the effects of the major inhibitory neurotransmitter γ-aminobutyric acid (GABA) which is the endogenous ligand at $GABA_A$ receptors (ligand-gated chloride and bicarbonate ion channel complexes, comprising five glycoprotein sub-units surrounding a central transmembrane channel) and at $GABA_B$ receptors (G-protein-coupled metabotropic receptors which stimulate the opening of inward-rectifying potassium channels). Benzodiazepines act as 'positive allosteric modulators' at $GABA_A$ receptors resulting in anticonvulsant, anxiolytic, hypnotic and myorelaxant effects, but they have no effects on $GABA_B$ receptors, at which baclofen and gamma hydroxybutyrate (GHB) are agonists [8].

The $GABA_A$ receptor has a well characterised molecular structure [9]. At $GABA_A$ receptors, GABA binds at the interface between α and ß sub-units (the same site binds the antagonist bicuculline and the agonists gaboxadol and muscimol). Most $GABA_A$ receptors are benzodiazepine-sensitive, with specific binding sites at the interface between α and γ sub-units, where benzodiazepines act as positive allosteric modulators changing the receptor conformation to allow increased *frequency* of opening of the ion channel, so enhancing the inhibitory effect of GABA. The cyclopyrrolone hypnotic zopiclone appears to bind at the same site as benzodiazepines, suggesting that differences between zopiclone and benzodiazepines result from effects occurring elsewhere [10]; its metabolite desmethylzopiclone has partial agonist properties. The receptor has multiple additional binding sites, including those for barbiturates (which increase the *duration* of chloride ion channel opening when GABA is bound), neurosteroids such as pregnanolone, and some inhaled anaesthetics. $GABA_A$ receptor sub-units have varying distributions and may mediate differing effects of benzodiazepines: α-1 sub-units may mediate sedation and tolerance, and α-5 sub-units may mediate memory disturbance, whereas α-2 and α-3 sub-units may mediate anxiolysis, suggesting that novel $GABA_A$

receptor sub-unit selective ligands could prove anxiolytic whilst avoiding some tolerability concerns, although not all evidence supports this notion [11, 12]. The imidazopyridine hypnotic zolpidem (which as monotherapy has minimal anxiolytic effects) binds relatively selectively to α-1 sub-units, with very low affinity for α-2 or α-3 sub-units, and no appreciable affinity for α-5 sub-units [13]. Zaleplon, a low-potency, ultra-short acting and only weakly effective pyrazolopyrimidine hypnotic, has higher affinity for α-1 sub-units than for α-2 or α-3 sub-units [14].

Currently available benzodiazepines differ in chemical structure and pharmacokinetic properties but share a common mechanism of action and produce a range of similar clinical effects. They differ in potency, time to effect and duration of action, and degree of lipophilicity and volume of distribution [15]. Some need repeated daily dosing but others once-daily dosing to achieve their desired effects (see Table 1). With the exception of the 3-hydroxy-substituted benzodiazepines lorazepam, oxazepam and temazepam (which are conjugated with glucuronic acid) all benzodiazepines undergo extensive hepatic metabolism, so concomitant medications which act as either inducers or inhibitors of hepatic enzymes can change plasma levels in potentially clinically significant ways. As examples, the SSRIs fluoxetine and fluvoxamine can impair the elimination of alprazolam and diazepam, through inhibition of CYP2C19 (diazepam) and CYP3A4 (both drugs) [16]. Many benzodiazepines have long-lasting active metabolites, which can accumulate with repeated dosing; especially in elderly patients, those with physical health problems (such as liver disease), and those with genetic variants leading to reduced activity of relevant cytochrome P450 metabolising enzymes.

FEATURES AND MECHANISMS OF BENZODIAZEPINE TOLERANCE, DEPENDENCE, AND WITHDRAWAL

Tolerance to the effects of benzodiazepines can occur and is probably more pronounced for the anticonvulsant and hypnotic-sedative effects than for the anxiolytic effects: it is unusual for patients with anxiety disorders to incrementally increase their daily dosage [17]. Development of tolerance may arise from multiple though poorly understood underlying mechanisms; including $GABA_A$ receptor uncoupling (whereby benzodiazepines exhibit decreased ability to facilitate GABA-induced ion flux), modifications in $GABA_A$ sub-unit expression, and compensatory glutamatergic, monoaminergic and neurosteroidal influences [18-20].

Although initially considered to be relatively free of dependence and withdrawal effects, a steadily emerging awareness of distressing symptoms after abrupt discontinuation [21], rebound anxiety and insomnia after concluding medium-term treatment [22], indications of psychological and physical dependence [23], and troublesome clusters of symptoms which often persist months after stopping treatment [24] together led to a re-evaluation of potential hazards associated with benzodiazepine anxiolytics and hypnotics [25].

The neural basis of the habit-forming properties of benzodiazepines is not fully understood, although they increase the firing of dopaminergic neurones in the ventral tegmental area through effects on α1 sub-unit containing $GABA_A$ receptors on nearby interneurons: this triggers drug-evoked synaptic plasticity in excitatory afferents onto dopaminergic neurones and underlies drug reinforcement [26]. The mechanisms underlying the experience of withdrawal symptoms are also not fully established, although down-regulation of benzodiazepine binding sites, and increased calcium ion flux and serotonergic activity may be relevant: supporting evidence in pre-clinical models includes findings that verapamil (a calcium channel antagonist) [27-29], baclofen [27, 30], and

zacopride (a 5-HT_3 receptor antagonist and 5-HT_4 agonist) [30] can all attenuate withdrawal responses.

Dependence on benzodiazepines can be revealed following the emergence of withdrawal symptoms on either abruptly stopping or rapidly reducing the dosage after long-term treatment. A broad range of physical and psychological symptoms has been described (see Table 2) [31]. Some features can be hard to distinguish from the symptoms of underlying anxiety disorders, though perceptual disturbances such as a sensation of 'tilting' are infrequent in untreated patients. Differential diagnoses reflect the presented clinical features, so can include alcohol and drug intoxication or withdrawal, hypoglycaemia, cerebrovascular events and epilepsy [31]. Withdrawal phenomena are usually short-lived (lasting less than four weeks) although their duration is influenced by individual pharmacokinetic factors, and some individuals describe markedly distressing symptoms long after stopping benzodiazepines [7]. Some volunteered illustrative personal narratives are included as supplementary material in Box 1.

Identified risk factors (some disputed, and some rather weak) for the development of benzodiazepine dependence include demographic, clinical, pharmacological and health service use characteristics. Starting benzodiazepines at a younger age, lower length of education, minority ethnic group status, higher levels of anxiety and depressive symptoms, history of alcohol or drug dependence, higher daily dosage, longer duration of benzodiazepine use, shorter drug half-life, and participation in self-help groups for medication dependence may all be important [32]; as may concomitant prescription of other psychotropic drugs [33]. Reported behavioural features such as perceived 'reliance' on benzodiazepines to perform daily activities, continued use beyond the original treatment indication had passed, taking of extra tablets before anticipated stressful events, and 'doctor shopping', private (i.e. non-state service) prescriptions and reports of lost prescriptions may also be relevant [31]. Systematic review and meta-synthesis of the differing experiences of patients suggests that problems with benzodiazepines (and the 'Z-drugs' zopiclone and zolpidem) are perpetuated by lack of knowledge of side effects and absence of psychosocial support, but could be ameliorated by education about medication, an increased range of alternative forms of care, and targeted extended dialogue between patients and clinicians [34].

A range of scales are available to assess the severity of benzodiazepine dependence and withdrawal. Features suggestive of dependence can be evaluated reliably through the condition-specific self-report Benzodiazepine Dependence Questionnaire [35] or the Benzodiazepine Dependence Self-Report Questionnaire [36], or the more generic Severity of Dependence Scale [37] [38]. Aspects of craving can be assessed reliably with the self-report Benzodiazepine Craving Questionnaire [39]. Severity of benzodiazepine withdrawal phenomena can be estimated through the self-report Ashton check-list [14] and a visual analogue scale [40], and assessed reliably through the self-report Benzodiazepine Withdrawal Symptom Questionnaire [41] or Benzodiazepine Hypnotics Withdrawal Symptoms Scale [42, 43], the observer-rated Clinical Institute Withdrawal Assessment Scale-Benzodiazepines [44], and the Penn Physician Withdrawal Checklist [45].

'GOLD-STANDARD' CURRENT PRACTICE

Key aspects of current practice are summarised in Table 3. There is much scope for the *primary prevention* of dependence, with an emphasis on limiting benzodiazepine anxiolytic or hypnotic prescriptions to short-term treatment and exercising considerable caution when considering

prescriptions in older patients [46]. Physicians may underestimate the importance of factors which can be helpful in avoiding inappropriate prescribing, such as patients' concerns about potential side effects, and their dislike of taking multiple medications [47]. *Secondary prevention* measures include systemic approaches to reducing the renewal of prescriptions, regular practice-based auditing, and implementation of alerting systems to prompt discussions between prescribing physicians and dispensing pharmacists [48]. *Tertiary prevention* focuses on tapering approaches and support of patients before, during, and after withdrawal.

A series of systematic reviews have examined the strength of evidence guiding the clinical management of benzodiazepine dependence [49-51]. An overall view is that benzodiazepines should be withdrawn gradually with the aim of minimising withdrawal symptoms, often at a rate based on the ability of the patient to tolerate emerging symptoms [31]: although a recent review recognised that more high-quality research into strategies for optimising management was needed [7]. Recommendations on the pace of dosage reduction range widely, from reducing the initial benzodiazepine dose by 50% approximately every week, to reducing the daily dose by between 10% and 25% every 2 weeks [31]. *British National Formulary* guidance suggests that once a patient has been switched to diazepam (see following paragraph), the daily dosage can be reduced by 1-2 mg every 2-4 weeks (or by one-tenth of the dosage every 1-2 weeks in patients taking high-doses)[52]. Brief psychological interventions may enhance the efficacy of gradual dose reduction [49], including reductions in older patients [50]. It is contended that most patients will be able to withdraw over a period of between 4-8 weeks [27]; and that prolonged reductions (over many months) should generally be avoided in order to prevent the withdrawal of treatment from becoming the patient's main preoccupation [53].

It is uncertain whether switching from a shorter-acting drug (such as lorazepam) to a longer-acting drug (such as diazepam or clonazepam) is advantageous, though patients who are taking multiple benzodiazepines should whenever possible first be 'converted' to taking a single drug [31]. Approximate dosage equivalents are shown in Table 4 [54], although there is much variation between individuals in drug metabolism. Benzodiazepines subject to extensive hepatic metabolism should be avoided in patients with evidence of liver disease. Higher treatment drop-out rates may occur during withdrawal from shorter-acting than from longer-acting benzodiazepines, though switching to drugs with a longer half-life does not always appear associated with improved outcomes [55]. Inpatient admission may be needed for the initial stages of withdrawal in patients taking very high doses (equivalent to 100 mg/day of diazepam, or greater) [56]: but there seems to be little difference in outcome between fixed schedule or symptom-triggered dosage reduction [56].

Certain medications (some anticonvulsants, antidepressants, antihistamines, beta-blockers, gabapentinoids, and melatonin) have been evaluated to establish whether they exert beneficial effects in easing symptoms and improving outcomes in benzodiazepine withdrawal, but the evidence of benefit is limited [49, 57]. Whereas carbamazepine and oxcarbazepine can be effective in reducing symptoms associated with alcohol withdrawal [58], the evidence of benefit in facilitating benzodiazepine withdrawal is limited [59]. Substitute pharmacotherapies given alone appear inferior to gradual dose reduction, and in combination probably do not enhance its efficacy [49]. Subcutaneous or slow intravenous infusion of the $GABA_A$ receptor antagonist/partial agonist flumazenil has been found helpful in some patients, although its use can precipitate panic-like symptoms, seizures and psychosis-like experiences [60, 61].

Psychological interventions are aimed to facilitate withdrawal, support subsequent abstinence, and address any underlying disorders. CBT is used widely although supporting evidence appears rather limited [31]. A randomized controlled trial showed that a 3-month taper off benzodiazepines, with or without concomitant CBT, was superior to 'usual care': short-term abstinence rates were 21% for usual care, 62% for tapering without CBT, and 58% for tapering with CBT [62]. Simpler measures may be all that is needed in some patients: for example, among those who discontinued benzodiazepines successfully after receipt of a GP letter advising them to stop, the abstinence rate at 10-year follow-up was 59% [63]. Such simple brief interventions (such as providing advice and information leaflets) can facilitate an initial reduction in benzodiazepine use, but should probably be accompanied by other psychosocial interventions [64]. A detailed analysis of theoretical domains and behavioural change techniques among evaluations of the effectiveness of brief interventions suggests that components such as provision of information about health consequences and instilling confidence in gradual dosage reduction strategies may be important [65].

The utility of urine drug screening in monitoring the progress of benzodiazepine withdrawal is disputed [66-68]. This is partly because the large volume of distribution of some compounds can cause a prolonged 'leaching out' well beyond the end of drug intake, and partly because certain benzodiazepine metabolites are themselves parent compounds: as examples, temazepam and oxazepam are metabolites of diazepam, which may lead the screener to conclude that the patient had been taking other benzodiazepines during diazepam withdrawal. It has been argued that urine drug screening should be use to engage the patient rather than as a punitive measure [69].

MANAGEMENT OF 'COMPLEX CASES'

Withdrawal of benzodiazepines is rarely simple, but it may be especially challenging in certain groups of patients, such as those with comorbid mental disorders such as major depression or schizophrenia, or those who are taking other potentially habit-forming prescription medicines or non-prescribed drugs. For these reasons, individualised treatment rather than generic protocol-driven approaches is often necessary [70]. Although a substantial proportion of individuals taking long-term benzodiazepines have major depressive disorder [71], concomitant antidepressant prescription appears to have limited impact on the success of benzodiazepine withdrawal [72-75]. Many patients with the diagnosis of schizophrenia receive long-term prescriptions of benzodiazepines [76], despite the lack of compelling evidence of their efficacy in this condition, or concerns about a potential contribution to its increased mortality [77], or the evidence that tapering down of benzodiazepines can reduce some of the associated cognitive impairments in this patient group [78]. A range of pharmacological approaches to facilitating benzodiazepine withdrawal in patients with schizophrenia have been evaluated (including studies with melatonin, paroxetine, pregabalin and valproic acid) but there is insufficient evidence to support their widespread adoption in routine clinical practice [79]. Benzodiazepine dependence is a frequent comorbid condition among individuals with alcohol use disorders [80], but studies of the influence of alcohol use disorders on outcomes relating to continued use or withdrawal from benzodiazepines have generated inconsistent findings [81-83]. Simultaneous withdrawal from alcohol and benzodiazepines requires particularly careful attention and probably should only be undertaken in inpatient settings [84]. In patients receiving concomitant benzodiazepines and opioid maintenance, the dose of the opioid (usually methadone or buprenorphine) should preferably be kept stable throughout the benzodiazepine reduction, though high enough to prevent symptoms of opioid withdrawal:

buprenorphine may carry a lower risk of benzodiazepine-related overdose than methadone [85]. Concurrent opioid detoxification and benzodiazepine withdrawal is not advised [86].

PROGNOSIS AFTER BENZODIAZEPINE WITHDRAWAL

Short-term patient outcomes following benzodiazepine withdrawal appear to vary markedly, and long-term outcomes have not been investigated extensively although many patients will remain troubled by psychological symptoms long after withdrawal [31]. Early studies and commentaries identified a marked variation in the duration and severity of withdrawal symptoms [87, 88]. In primary care settings, approximately 20% of long-term users will stop benzodiazepines successfully after only minimal interventions such as receipt of advisory letters or provision of information during a consultation [89-92]. Four differing patterns of symptoms - decline, early emergence, late emergence, and persistence - were identified in a one-year prospective study involving long-term benzodiazepine 'users' undergoing inpatient detoxification [93]. A prospective primary care study involving over 2000 long-term (more than three months) users followed over two years after receipt of advice to taper their use found that 49% of patients had remained completely abstinent [94]. Poorer outcomes have been associated with a range of factors: encompassing pharmacological (higher dosage, longer duration of treatment, shorter half-life, more rapid taper); demographic (lower educational attainment); and clinical (greater anxiety and depressive symptom severity, panic disorder diagnosis, 'neuroticism', maladaptive personality traits) variables [95-99]. Some patients who undergo withdrawal from benzodiazepines report persistent psychological symptoms even after five years [100], in the absence of psychophysiological disturbances often seen in patients with anxiety [101].

PREVENTION OF RELAPSE

Investigations of the risk of relapse (i.e. the resumption of benzodiazepine use after withdrawal) are limited. Predictors of relapse include high-dose use (more than 10 mg diazepam equivalent per day) and poor general health perception [94]; persistent insomnia and psychological distress in long-term hypnotic users [102]; greater self-reported severity of dependence, and daily alcohol consumption [82]; and craving for benzodiazepines [103]. It seems reasonable to state that many of those who develop problems with benzodiazepines do so from a background of childhood adversity, comorbid physical and mental health conditions, strained inter-personal relationships, precarious employment, financial difficulties, and housing uncertainties; if these associated factors persist beyond benzodiazepine withdrawal, individuals will naturally remain vulnerable to relapse.

NEW DEVELOPMENTS

Many problems relating to benzodiazepine dependence and withdrawal can be reduced through the primary, secondary, and tertiary prevention measures described above. The development and clinical availability of novel pharmacological and psychological interventions, with efficacy in anxiety disorders and insomnia but without the tolerability and safety concerns of current treatments, could also reduce the recourse to prescription of benzodiazepine anxiolytics and hypnotics, and so reduce the likelihood of dependence and withdrawal syndromes.

9.1. Pregabalin. This branched chain amino acid has structural similarities to GABA, and has anticonvulsant, analgesic and anxiolytic properties. Its mechanism of action is complex: it shows high affinity binding to the α2δ sub-unit of the P/Q type of voltage-gated calcium channels and reduces

glutamate release; and may also reduce the synthesis of excitatory synapses and block the 'trafficking' of new voltage-gated calcium channels to the cell surface. It does not bind directly to $GABA_A$ or $GABA_B$ receptors or to binding sites allosterically linked to GABA, but increases GABA transporter protein density and extracellular GABA in the brain through a dose-dependent increase in L-Glutamic acid decarboxylase activity [104]. Detectable anxiolytic effects can occur within a few hours in patients anticipating stressful clinical procedures [105]. It has efficacy in acute treatment and relapse prevention in patients with generalized anxiety disorder (GAD) [106], for whom the most common reported treatment-associated adverse events are dizziness and somnolence [107]. Due to the early onset of effect, relative rarity of adverse effects more commonly seen with SSRIs (such as sexual dysfunction), and seeming low incidence of withdrawal symptoms after acute treatment, pregabalin was rapidly and widely adopted into clinical practice [108]. Although it can reduce withdrawal symptoms from benzodiazepines and zolpidem [109-112], iterative observations of its ~~abuse potential~~effects in a range of pre-clinical, clinical and pharmacoepidemiological studies [113] led to its scheduling as a controlled drug. Individuals with a history of psychiatric illness or substance use disorders [114] or personality disorders [115] seem to be at higher risk for pregabalin misuse ~~and abuse~~, and its role in managing patients with benzodiazepine dependence or withdrawal must now be considered to be minimal.

Melatonin agonists

The pineal gland hormone melatonin has a role in synchronizing various circadian rhythms, including regulation of sleep and wakefulness. Its release is affected by light-dark information from retinal photosensitive cells relayed through the suprachiasmatic nuclei, secretion being regulated by noradrenaline; effects mediated through M_1 and M_2 receptors lead to drowsiness and facilitation of sleep. Immediate-release melatonin is included within some over-the-counter remedies for insomnia and has been used to manage sleep disturbance in children, but a prolonged-release formulation (containing 2 mg of melatonin) is available for short-term use in older patients (55 years and above) troubled by primary insomnia characterised by poor quality sleep. The M_1/M_2 receptor agonist ramelteon has some efficacy in reducing subjective sleep latency (by around 13 minutes), but not in increasing total sleep duration, in randomized controlled trials lasting up to 24 weeks [116]. ~~It appears to lack abuse potential~~Non-prescribed usage is considered unlikely [117]. Short-term ramelteon administration may sometimes facilitate dosage reduction and withdrawal of benzodiazepine hypnotics, although a range of investigations in disparate clinical groups have produced inconsistent findings [118].

Orexin receptor antagonists

Orexinergic neurones originate in lateral and posterior hypothalamic areas and have wide projections to brain nuclei involved in wakefulness. Orexin-A and orexin-B integrate circadian, metabolic and sleep debt influences to determine the balance of wakefulness and sleepiness (and are also involved in regulation of food intake and lipid metabolism). Suvorexant exerts antagonist effects at orexin type 1 and type 2 receptors, suppressing wakefulness: its elimination half-life is approximately 12 hours. Meta-analysis reveals its only limited efficacy in reducing subjective time-to-sleep-onset (by 6 minutes) and increasing subjective total-sleep-time (by 16 minutes) in patients with primary insomnia [119]. Pre-clinical studies suggested suvorexant ~~has limited abuse potential~~is unlikely to be misused [120], although it ~~has~~ had demonstrable ~~abuse potential~~'liking' properties in recreational polydrug users [121]. It is uncertain whether suvorexant can facilitate withdrawal from

benzodiazepines, although a retrospective study suggested that switching to suvorexant was sometimes beneficial in dosage reduction and withdrawal of benzodiazepine hypnotics [122].

$GABA_A$ sub-type selective ligands

It is conceivable that the development of $GABA_A$ receptor sub-unit selective ligands could result in the availability of novel efficacious anxiolytics which may avoid the sedation and liability for dependence seen with benzodiazepines, [11],[123]. The compounds TPA023 (an imidazotriazine) and AZD7325 (a cinnoline) are positive allosteric modulators at $GABA_A$ α-2 and α-3 sub-units, were found to be non-sedating, and showed some anxiolytic effects among patients with GAD before further development was stopped, due to concerns relating either to toxicity in rodents (TPA023) or to sub-optimal adherence or pharmacokinetics in patients (AZD7325) [124]. It is premature to judge whether the possible entry of $GABA_A$ sub-type selective ligands into clinical practice might facilitate benzodiazepine withdrawal.

ASIC-IA receptor antagonists

An alternative route to the development of novel anxiolytics focuses on agents which target central chemosensors involved in the anxiety response to carbon dioxide (CO_2) challenge (in experimental medicine models, inhalation of 35% CO_2 can induce panic attacks, whereas inhalation of 7.5% CO_2 can mimic the features of GAD). Chemosensors include lactate-sensitive orexin-expressing neurones in hypothalamus, pH-sensitive serotonergic neurones in the raphe nuclei, and acid-sensing ion channels activated by extracellular acidosis [125]. The acid-sensing ion channel 1A ($ASIC\text{-}1_A$) is a voltage-insensitive H^+-gated cation channel, highly expressed in the amgydala, dentate gyrus, cortex, striatum, and nucleus accumbens [126]. Drugs which target central chemosensors but with no effects at $GABA_A$ receptors might potentially exert anxiolytic effects [127] whilst avoiding tolerability and safety problems associated with benzodiazepines [128].

Novel psychological, neuromodulatory and complementary interventions

Approaches based on CBT principles and practice are often beneficial in patients with anxiety disorders and insomnia, but many do not improve substantially: there is a need for improved psychological interventions in managing these conditions, as well as for easing the psychological distress associated with benzodiazepine dependence and withdrawal. The efficacy of cognitive behaviour therapy for insomnia (CBT-I) in discontinuing benzodiazepine and related hypnotics over three months is established, but it is unclear whether these benefits are sustained over longer periods [129]. Whilst neuromodulatory approaches are sometimes beneficial in facilitating withdrawal and reducing craving in patients with substance use disorders [130], their effects in patients with benzodiazepine dependence are unknown. Although probably not as effective as CBT-I in patients with insomnia, complementary interventions are sometimes helpful in reducing sleep disturbance [131], and herbal preparations [132] and balneotherapy [133], but not acupuncture [134] may help in reducing dosage and psychological symptoms during and after benzodiazepine withdrawal.

CONCLUSIONS

The widespread availability of frequently effective and generally acceptable treatments for patients with anxiety disorders or insomnia, and an increased awareness of problems such as sedation and dependence, have together gradually reduced the recourse to prescribing of benzodiazepine

anxiolytics and hypnotics. However, many prescriptions for benzodiazepines are still issued each year [7], and in most individuals, alternatives such as CBT-I or SSRIs would probably be advantageous, as it is often hard to prevent the justifiable short-term use from extending indefinitely, with an accompanying gradual change in the balance of risk and benefit [135]. A relatively small sub-group of patients with severe, persistent, distressing and disabling symptoms which have proven refractory to a succession of evidence-based psychological and pharmacological treatments may still benefit from benzodiazepine anxiolytic or hypnotic medication, for longer than merely short-term treatment, although regular attempts should be made to reduce the dosage when this seems appropriate [2]. A gradual reduction in dosage of benzodiazepines, when coupled with simple psychological interventions, can be accomplished safely and prove effective in primary care settings, although many patients find the process very unsettling and some will remain troubled by distressing and impairing symptoms for many months after the withdrawal of medication. Hard-pressed and under-resourced secondary care mental health services often struggle to offer the degree of support and expertise which is necessary for this patient group. There is a persistent need for easier patient access to services with refined expertise, together with an imperative for further research into optimising strategies for preventing the development of dependence and for facilitating withdrawal and maintaining abstinence from benzodiazepines [7].

Acknowledgements

Many thanks to Dr Mary Houston for her help with manuscript preparation. I wish to acknowledge the encouragement of Professor Malcolm Lader (1936-2020), previous President of both the Society for the Study of Addiction (1982-1992) and of the British Association for Psychopharmacology (1986-1988), whose work on benzodiazepine dependence and withdrawal still informs clinical practice: many cohorts of patients have benefited from his consistent dedication to raising awareness of the need to accurately assess the potential risks and benefits of psychotropic drug treatment.

Table 1.

Pharmacokinetic parameters and prescribing correlates in some benzodiazepines

Compound	Bioavailability	Time to peak level (hrs)	Biological half-life (hrs)	Dosage and use(s)	Onset of effect
Midazolam	96% (IM route)	1.5-2.5	1.5-2.5	Single dose, sedation prior to anaesthesia	Very fast
Temazepam	96%	2-3	8-20	Night-time sleep induction	Fast
Flunitrazepam	64-77%	1-2	18-26	Night-time sleep induction	Fast
Lorazepam	85%	2	10-20	As required, panic attack	Fast
Alprazolam	80-90%	1-2	4-6 (IR) 10-16 (XR)	3 times daily, anxiolysis	Intermediate
Diazepam	76%	0.5-1.5	20-100	Twice daily, anxiolysis, management of alcohol withdrawal	Intermediate
Oxazepam	95%	1.5-3.0	6-9	3-4 times daily, anxiolysis	Intermediate -slow
Chlordiazepoxide	~100%	~4	5-30	3 times daily, anxiolysis, management of alcohol withdrawal	Slow
Clonazepam	90%	1-8	19-60	Once daily, anxiolysis, anticonvulsant	Intermediate -slow, but sustained

Table 2.

Clinical features reported or observed after benzodiazepine withdrawal

Psychological symptoms	Physical symptoms	Complications
Increased anxiety	Trembling	Increased risk of seizures
Nervousness	Sweating	Poor motor coordination
Sleep disorders	Nausea and vomiting	Cognitive impairment
Inner restlessness	Motor agitation	Impairment of memory
Depressive symptoms	Dyspnoea	Perceptual impairments
Irritability	Increased heart rate	Hyperacusis
Psychosis-like conditions	Elevated blood pressure	Photophobia
Depersonalisation-derealisation	Headaches	Hypersomnia
Confusion	Muscle tension	Dysaesthesia and dyskinesia

Adapted from Soyka, 2017 [31]

Table 3.

Key aspects of clinical management in benzodiazepine dependence and withdrawal

1. Prevention
    - *Primary*: avoidance of benzodiazepines; identification and treatment of psychological illness; awareness of at-risk patient groups; sensitivity to patient concerns about medication; restriction of benzodiazepine prescriptions to short-term treatment
    - *Secondary*: restriction on automatic renewal of benzodiazepine prescriptions; practice-based clinical audits focused on prescribing practice; implementation of practice-based alerting systems to prompt discussion between prescribers and dispensers
    - *Tertiary*: familiarity with and implementation of treatment withdrawal protocols; support of patients before, during and after withdrawal
2. Medication consolidation and gradual dose reduction
    - conversion of benzodiazepine polypharmacy to monotherapy; inpatient admission for very high dose users; dosage tapering at mutually agreed rate; avoidance of very prolonged reductions; avoidance of simultaneous withdrawal from benzodiazepines and opioids
3. Accompanying psychological interventions
    - techniques based on psychoeducation; motivational interviewing and instillation of confidence and optimism; CBT to support withdrawal and maintain abstinence, and psychological treatment of underlying conditions
4. Concomitant psychotropic drug prescriptions
    - pharmacological treatment of underlying conditions such as major depressive disorder and generalised anxiety disorder; medication for facilitating abstinence in alcohol use disorder; occasional use of short-term administration to facilitate withdrawal; rare use of flumazenil in specialist services
5. Relapse prevention
    - approaches to managing persistent insomnia; continued treatment of underlying conditions; support in reducing alcohol consumption; attempts to address risk factors such as interpersonal discord, precarious employment, and housing problems

Table 4.

Approximate dosages of common benzodiazepines and Z-drugs equivalent to 5 mg of diazepam.

Drug	Dose
Chlordiazepoxide	12.5-15 mg
Clonazepam	0.25-1.0 mg
Loprazolam	0.5-1.0 mg
Lorazepam	0.5 mg
Lormetazepam	0.5-1.0 mg
Nitrazepam	5 mg
Oxazepam	10-15 mg
Temazepam	10 mg
Zaleplon	10 mg
Zopiclone	7.5 mg
Zolpidem	10 mg

Data taken from a range of sources, summarised in http://www.sussexpartnership.nhs.uk/sites/default/files/documents/bdz_equivalent_doses_spt_guidance_update_-_0714.pdf. Accessed 10/08/2021 [54].

Box 1. Personal accounts of the experience of benzodiazepine withdrawal

The following paragraphs are extracted from personal accounts received following publication of the 2013 British Association for Psychopharmacology statement on benzodiazepines: in each case, the sender gave permission for extracts from these accounts to be shared in public fora.

Individual A. First prescribed diazepam for insomnia in 2005 - no previous history of significant mental or physical illness. Complained of a loss of efficacy and dose was gradually increased. Over time complained of depression, vomiting, nausea, anxiety, balance problems, derealisation, depersonalisation and other symptoms, additional medication prescribed. Diazepam dose increased to 40 mg a day in 2011. Body and mind almost entirely ceased to function and went off work ill. Had a fall down the stairs at home in 2012 due to balance problems and suffered a fractured skull and a traumatic brain injury. Iatrogenic drug addiction missed in the hospital despite a call to the ward from the prescribing GP, therefore sudden cessation of high benzodiazepine dose (40 mg daily). Immediately entered the early stages of the benzodiazepine withdrawal syndrome. After discharge in June 2012, suffered hallucinations, psychosis and other mental and physical problems (see symptom list in the Ashton Manual). Readmitted to hospital in July 2012 suffering from psychosis and seizures, benzodiazepine withdrawal syndrome not identified and levetiracetam was prescribed for suspected epilepsy. Received discharge from the neurosurgical multidisciplinary team in October 2013, indicating full recovery from TBI. Still suffering many protracted benzodiazepine withdrawal symptoms after 20 months, including balance problems, tinnitus, depersonalisation, derealisation and loss of sensation in some limbs. Symptoms are episodic and the recovery is capricious.

Individual B. I am an ex-addict of 10 years re. benzodiazepine drugs and have been left permanently physically disabled with brain atrophy, neuropathic pain in right leg, hypothyroidism, COPD (never smoked) chronic fatigue syndrome, violent daily headaches. I have suffered these prescribed drug injuries ever since I withdrew myself nearly 28 years ago. I am a victim of permanent damage caused as a direct result of iatrogenic addiction over a 10-year period and on repeat prescriptions.

Individual C. Many patients like me became addicted to prescribed benzodiazepines through no fault of our own and were prescribed them for decades by doctors ignoring the 1988 CSM 2 – 4 week guidelines. My withdrawal symptoms following 32 years of being prescribed Ativan by GPs were as follows and lasted for 2 years before starting to let up: constant sleep disturbances including persistent nightmares, feeling a sense of dread all the time, depersonalisation, derealisation, loud constant tinnitus, hypersensitivity to light and sound, visual distortions like the ground and surroundings moving like liquid, hot and cold flushes, sweating, crushing headaches, a tight band around the head, breathlessness, intrusive unwanted thoughts, retching and nausea, muscle aches, cramps, burning sensations in muscles, chronic fatigue, agoraphobia and claustrophobia, panicky feelings and palpitations, loss of appetite, dizziness and loss of balance, no concentration, confusion, the inability to perform simple tasks or plan things, comprehension problems, spontaneous itching feelings all over body, dry mouth and metallic taste, restless legs and muscle twitches, flu like symptoms with sore tight throat, jelly legs feeling as if they will collapse under you, short term memory loss and teeth hurting.

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