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Review

Do benzodiazepines still deserve a major role in the treatment of psychiatric disorders? A critical reappraisal

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ABSTRACT

Discovered in the late 1950s by Leo Sternbach, the first benzodiazepine (BZD) chlordiazepoxide was followed by several congeners, which rapidly constituted one of the largest and most widely prescribed classes of psychotropic compounds. After 50 years, BZDs are still routinely utilized not only in psychiatry but, more generally, in the whole of medicine. Despite their high therapeutic index which makes BZDs safer than other compounds like barbiturates, as well as their rapidity of onset, psychiatrists and family physicians are well aware about the controversy that surrounds the wide use – often not adequately based on scientific evidence – of BZDs in many psychiatric disorders. In this overview of international treatment guidelines, systematic reviews and randomized clinical trials, the aim was to provide a critical appraisal of the current use and role of BZDs in psychiatric disorders and their disadvantages, with specific emphasis on anxiety and affective disorders, sleep disorders, alcohol withdrawal, violent and aggressive behaviours in psychoses, and neuroleptic-induced disorders. In addition, specific emphasis has been given to the extent of usage of BZDs and its appropriateness through the assessment of available international surveys. Finally, the entire spectrum of BZD-related adverse effects including psychomotor effects, use in the elderly, paradoxical reactions, tolerance and rebound, teratologic risk, dependence, withdrawal and abuse issues was examined in detail.

1. Introduction

1.1. Historic background

The development of BZDs is closely related to the career of their discoverer, Dr Leo Henryck Sternbach. Son of a pharmacist, born in 1908 in Opatija (currently located in Croatia and at the time in Austro-Hungary), he received his doctoral degree in organic chemistry at the University of Krakow [11,14]. In 1940, he started working for Fritz Hoffmann-La Roche in Basel who helped him to flee to the U.S. (New Jersey) in 1941 to escape the Nazis due to his Jewish origins. In the early 1950s, Dr Sternbach's employer was competing with Wallace Pharmaceuticals which had already developed a $GABA_A$ receptor binding compound, meprobamate (Miltown), with remarkable tranquilizing/sedative effects. Dr Sternbach was, therefore, required to develop something with similar efficacy and he decided to revert to his previous student research into a class of compounds now called benzodiazepines (BZD). He thought that he might make synthetic dyes with them, despite suspecting they might also affect the central nervous system (CNS). Over 2 years, he tested approximately 40 compounds, which, however, proved to be pharmacologically inert. Nonetheless, in 1956, Dr Sternbach, experimenting with another BZD, decided to treat it with methylamine, created a white crystalline powder, and labelled it "Ro 5-0690" [11,14]. However, he was instructed by his employer to stop working on the BZDs, since he had been unsuccessful so far, and to begin to develop an antibiotic instead. However, when he tested the powder on mice and other laboratory animals, he saw a remarkable tranquilizing effect with no side-effects. Chlordiazepoxide (Librium) discovered by Sternbach in 1956, was approved for clinical use in 1960. In 1963, its improved congener, diazepam (valium), was marketed and became astonishingly popular. In the following years, Sternbach was credited with the discovery of many other compounds including flurazepam, flunitrazepam and clonazepam [11,14]. Between 1969 and 1982, valium was the most prescribed drug in America, with over 2.3 billion doses sold in 1978.

1.2. Main pharmacological profile of BZDs

BZDs are allosteric modulators of $GABA_A$ receptors, binding to the chloride-channel molecular complex. This possesses five transmembrane glycoprotein subunits arranged around the central chloride channel (ligand-gated ion channel). The $GABA_A$

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receptor incorporates a rich pharmacology, having multiple allosteric modulating sites as part of the complex (e.g. for BZDs, barbiturates, alcohol and neurosteroids) (Fig. 1). In addition, different $GABA_A$ sub-units exist which, in turn, result in different receptor isoforms that are variably distributed across the CNS [7,170].

BZDs, however, do not bind to the specific GABA binding site thereby enhancing gabaergic transmission. Rather, they are supposed to increase the affinity of GABA for its own binding site. GABA is one of the most abundant neurotransmitters in the CNS (more than 200–1000 times more abundant than acetylcholine or serotonin). Ultimately, GABA binding leads to opening of the chloride channel followed by hyperpolarization of the target cell. The pharmacodynamic action of BZDs is significantly different from that of the barbiturates, which prolong, rather than intensify, GABA response and, moreover, at high doses, they may be GABA-mimetic, directly activating chloride channels. Indeed, the theoretical dose-effect curves of sedative-hypnotics comparing BZDs with barbiturates show that with increasing doses, the final part of the curve plateaus for BZDs (in contrast to barbiturates) making it difficult for BZDs to induce coma, for instance [7,170]. It is easier, however, to induce such an adverse event when BZDs are associated with other psychotropic compounds that are able to depress the CNS, such as alcohol. Nevertheless, BDZs are characterized by a high therapeutic index. In addition, it is important to remember that the action of BZDs, which are full agonists of the BZD receptor located within the $GABA_A$ receptor, may be blocked by compounds with antagonist effect (i.e., flumazenil) and this aspect may contribute to their overall safety.

BZDs may be subdivided on the basis of their chemical structure into different subgroups including 2-keto (e.g., diazepam), triazolo (e.g., alprazolam), 7-nitro (e.g., clonazepam) and 3-hydroxy (e.g., lorazepam) compounds. BZDs also differ in terms of potency, onset of action, duration of action (which depends on the elimination half-life), route of administration and metabolic pathways. On the other hand, BZDs have similar efficacy as well as pharmacological and clinical activity [7,170].

From a pharmacokinetic perspective, BZDs are generally well absorbed and highly protein-bound (95%). Depending on their half-life, they may be subdivided in short (i.e., < 6 hours; e.g., triazolam), intermediate (i.e., 6–20 hours; e.g., alprazolam, lorazepam) and long half-life compounds (i.e., > 20 hours; e.g., diazepam, clonazepam). According to their chemical structure, BZDs may undergo different types of metabolism including glucuronidation (e.g., lorazepam and alprazolam), nitroreduction (e.g., clonazepam) demethylation and oxidation (e.g., diazepam). Furthermore, BZD metabolites may be active (e.g., nordiazepam) or inactive, and may, in turn, be subdivided according to their half-life [170].

2. Method

Literature for this narrative overview was identified by searching Medline and Cochrane Libraries in three steps. First, a search was carried out identifying articles published in English and related to the use of BZDs in psychiatric clinical practice. Specifically, the keyword "benzodiazepine" was variably combined with the terms "anxiety disorders", "affective disorders", "sleep disorders", "delirium", "alcohol withdrawal", "psychoses", "neuroleptic-induced akathisia" and "neuroleptic-induced tardive dyskinesia". A second search was conducted in the area of extent of "usage of BZDs", identifying relevant published surveys in the field. A third search targeted the area of "adverse effects of BZDs" with the keyword "benzodiazepine" variably combined with the terms "side-effects", "tolerability" and "adverse events".

The publication search included meta-analyses, randomized clinical trials (RCTs), naturalistic and retrospective studies and clinical reviews. When several RCTs were available, only pivotal trials were reviewed, prioritizing meta-analytic data and guidelines indications. Furthermore, a hand search for relevant articles was conducted examining the reference list of the publications retrieved in the primary search. Additional information was explored in recently published guidelines on BZD treatment.

3. Results

3.1. The use of BZDs in psychiatric clinical practice

It is difficult to overview the current use of BZDs in psychiatric disorders given that these compounds are frequently used outside

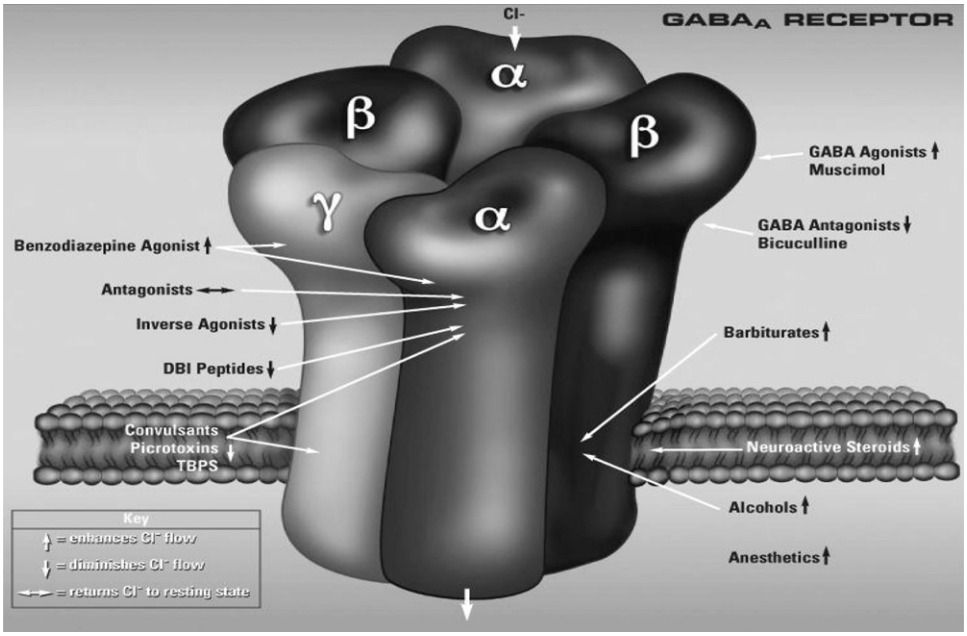

Fig. 1. The GABAa receptor complex.

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their licensed indications (''off-label'') and that formal regulatory approvals are lacking for the majority of disorders for which they are commonly prescribed.

However, according to available guidelines and recommendations, meta-analyses, systematic reviews and RCTs, the following conditions seem to represent the areas of more frequent use for BZDs: anxiety and affective disorders, sleep disorders, alcohol withdrawal, delirium, violent and aggressive behaviours in psychoses and neuroleptic-induced disorders [7,15,47,89] (Fig. 2).

3.1.1. Anxiety Disorders

Over the past decade, different compounds have been investigated for the treatment of anxiety disorders and international guidelines [15,46,89,92] currently recommend selective serotonin reuptake inhibitors (SSRIs) and serotonin/norepinephrine reuptake inhibitors (SNRIs) as the drugs of first choice, relegating BZDs to a second-line option as well as not being recommended for long-term therapy due to the limited amount of data beyond the acute phase. Nevertheless, the quality of evidence of efficacy for some BZDs varies from condition to condition. On one hand, BZDs are generally considered effective and safe, with rapid onset and favourable tolerability. On the other hand, BZDs have no antidepressant action, a major disadvantage as comorbidity between anxiety and depressive disorders is the rule rather than the exception in patients presenting with affective syndromes [15,46,89,92]. In addition, BZDs may cause physiological dependence, sedation, cognitive and coordination problems, memory and psychomotor impairment – particularly in the elderly – as well as dependence and abuse potential.

3.1.1.1. Generalized Anxiety Disorder. The efficacy of BZDs in GAD has been assessed in several RCTs. One of the first trials in the field, conducted in 1993 by Rickels and his co-workers, comparing diazepam vs. trazodone vs. imipramine vs. placebo over 8 weeks, had shown that patients treated with diazepam showed the most improvement in anxiety ratings during the first 2 weeks of treatment, with somatic symptoms being most responsive. However, from weeks 3 to 8, trazodone achieved comparable, and imipramine somewhat better, anxiolytic efficacy than diazepam, with psychic symptoms being more responsive to the antidepressants. Among completers, moderate to marked improvement was reported by 73% of patients on imipramine, 69% of patients on trazodone, 66% of patients on diazepam, and 47% of those on placebo. It is noteworthy to highlight that patients on antidepressants reported a higher rate of adverse effects than diazepam-treated patients [141].

Alprazolam showed positive results in placebo and active comparator-controlled studies [57,58,80,109,115]. Diazepam, in turn, was found to be effective in studies containing a placebo condition [6,26,63,139,140,143] as well as studies using a comparator with established efficacy [57,61,63,88,142,144]. WFSBP guidelines have rated both compounds with a category of evidence "A" (which is the highest). However, the overall recommendation grade is lower compared to the category of evidence, given that long-term treatment studies with BZDs in GAD are lacking and these compounds should only be used when other drugs or CBT have failed. Such a recommendation is consistent with those included in a recently published psychopharmacological treatment algorithm for GAD [46].

Other BZDs have also been investigated with lower levels of evidence (i.e., lorazepam [62] and bromazepam [105]). Of note, the authors of a recent meta-analysis, assessing the efficacy and tolerability of different compounds in GAD including lorazepam as BZD, could not recommend it among first-line treatments on the basis of response and remission rates. Moreover, it was the drug associated with the highest percentage of study withdrawals [13].

3.1.1.2. Obsessive Compulsive Disorder. The use of BZDs in OCD is poorly supported by available literature and guidelines, if not actually contraindicated [82,92]. In fact, only a few studies with mixed/negative results are available, mostly in augmentative therapeutic regimens and in treatment-resistant OCD. In a first pivotal trial comparing clomipramine, clonazepam and clonidine to a control medication in OCD, clonazepam showed mixed benefits [76].

More recently, in a 10-week, double-blind, parallel design trial of clonazepam vs. placebo, the active compound did not evidence any superiority suggesting that clonazepam is likely not effective as monotherapy in treating OCD [81].

In a double-blind, randomized, parallel, placebo-controlled study, when clonazepam was added to sertraline, it showed no additional benefit [38].

Finally, no benefit was reported for lorazepam in a double-blind crossover study vs. morphine and placebo [91].

3.1.1.3. Social anxiety disorder. Several trials have been conducted with BZDs – clonazepam, in particular – in the treatment of SAD. Munjack et al. [117], in an 8-week pilot study, found clonazepam of greater clinical benefit than non-treatment in a control group. Initial sedation, experienced by 70% of the treated subjects, was the most common side effect. Gelernter et al. [66] found a very modest effect for alprazolam over placebo and a generally inferior picture for alprazolam as compared with phenelzine in a study comparing a cognitive-behavioral group treatment (CBGT) program with pharmacotherapy or placebo. The response rate with alprazolam, at a mean dose of 4.2 mg/d, was 38% as contrasted with 20% in patients on placebo. In a subsequent study, clonazepam and placebo were administered under double-blind conditions to 75 outpatients and continued for up to 10 weeks. Superior effects of clonazepam were detected on most measures with response rates for clonazepam and placebo being 78.3 and 20.0%, respectively. Drug effects were apparent on performance and generalized social anxiety, fear and phobic avoidance, interpersonal sensitivity, fears of negative evaluation, and on disability measures. Clonazepam was well tolerated, though unsteadiness and dizziness were more severe and persistent than with placebo [45]. Otto et al. [127] found that patients randomized to clonazepam or CBGT were equally likely to respond to acute treatment, and pretreatment measures of symptom severity provided no guidance for the selection of one treatment over another. Seedat and Stein [151],

Fig. 2. Spectrum of clinical use of BZDs in psychiatric clinical practice.

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assessing the efficacy of coadministration of clonazepam + paroxetine vs. placebo + paroxetine, found mixed results. More recently, Knijnik et al. [90] in a study with 58 adult outpatients with GAD, randomized to 12 weeks of psychodynamic group therapy plus clonazepam vs. clonazepam alone, found that the former treatment resulted in significantly greater improvement.

Taken as a whole, published studies indicate BZDs (clonazepam, in particular) to be efficacious compounds in SAD. However, they do not find favour as first-line medications because of their limited spectrum of action, potential withdrawal difficulties as well as limited amount of data in the prevention of relapse [7,15]. However, they work rapidly, they are well-tolerated, and they may be particularly useful for individuals with episodic performance-related social anxiety [7].

In the WFSBP 2008 guidelines, BZDs have been rated with a "recommendation grade" of 3 and with a "category of evidence" B (i.e., trials without comparators, abuse potential) [15].

3.1.1.4. Post-traumatic stress disorder. Along with OCD, PTSD is one of the anxiety disorders with the lowest level of evidence supporting the use of BZDs. In a pivotal crossover study, subjects received 5 weeks of either alprazolam or placebo followed by 5 weeks of the alternative therapy. The active compound could show only minimal improvement in overall anxiety symptoms, with no improvement in the core symptoms of PTSD [27].

In a subsequent open-label study with 13 trauma survivors, alprazolam and clonazepam were administered up to 6 months. Thirteen other trauma survivors, matched with subjects in the active treatment group for gender and symptom severity in the first week after the trauma, comprised the control group. Subjects in the BZD group did not differ from controls in 1-month and 6-month PTSD and anxiety scores [67].

Indeed, according to recent studies in animal models, BZDs have not only been indicated as ineffective but as potentially damaging. In a recent study by Zohar's group, alprazolam, given immediately after stress exposure, interfered with the normal HPA-stress response, thereby increasing vulnerability to subsequent stress in the animal model [112].

Thus, taken as a whole, the available evidence does not support the use of BZDs as monotherapy in PTSD (Class "F" for WFSBP guidelines) [15] and doubts persist on the potential benefit in combination therapy.

3.1.1.5. Panic disorder. Panic disorder (PD) is probably the anxiety disorder with the most robust evidence of BZD efficacy in the short-term treatment in light of the number and extent of RCTs. In the late 1990s, in fact, alprazolam received an FDA approval for the treatment of PD, making it the first product to be so licensed. One of the first double-blind controlled studies assessing the effect of BZDs in patients with PD was conducted with 50 outpatients who were randomised to alprazolam or placebo for 8 weeks. The efficacy of the active compound was found in a diagnostic category usually then treated with tricyclic antidepressants or MAO inhibitors [32]. In a subsequent study, 48 patients experiencing panic attacks were randomly assigned to double-blind treatment with alprazolam, diazepam, or placebo. Results indicated that both active treatments appeared equally effective in reducing the frequency and severity of panic attacks and generalized anxiety compared with placebo [55]. Over the following years, many trials have been conducted with alprazolam, clonazepam, diazepam and lorazepam, which have attested to the short-term efficacy of these compounds in assuaging the core symptoms of PD. These compounds have been rated with "recommendation grade" of 2 and "category of evidence" A by the WFSBP guidelines [15]. This rate is consistent with their acute efficacy as well as with the poor evidence of efficacy in the long-term treatment – in particular in terms of relapse prevention – along with the well-established cognitive side-effects and dependence potential [7,15].

3.1.2. Affective disorders

BZDs are not recommended in the treatment of depressive disorders as they have no antidepressant effects [13,89]. The literature on the usefulness of BZDs in the field, however, is extremely heterogeneous. Historically in the 1960s, BZDs were commonly used as the earliest augmentation strategies to enhance the anxiolytic or sedative/hypnotic effects experienced by patients taking TCAs or MAOIs [169]. For instance, evidence from studies performed then indicated that anxiolytic medications rapidly and reliably reduced anxiety symptoms and insomnia associated with depressive episodes and, when administered from the outset, might hasten treatment response. However, concomitant prescription of BZDs did not greatly increase the likelihood of response or symptom remission and, moreover, their longer-term utility (in combination with antidepressants) has never been systematically confirmed [168]. Nevertheless, many experts believe that concerns about the risk of BZD addiction in this instance have been overstated [94,153] and a large number of patients with refractory forms of depression continue to receive palliative benefit from concomitant prescription of BZDs. In this perspective, a review conducted by a Cochrane group [65] aimed to determine whether, among patients with major depression, adding BZDs to antidepressants could bring any benefit in terms of symptomatic recovery or side-effects in the short ($<$ 8 weeks) and long term ($>$ 2 months) as compared with antidepressants alone. After excluding studies with antidepressant dosage of less than 100 mg/day of imipramine or its equivalent and duration of trial shorter than 4 weeks, the authors identified nine studies with a total of 679 patients. Of note, the results showed that patients in the combination treatment group were less likely to drop out compared to those taking antidepressants alone. Furthermore, the combination group was more likely to show improvement in depression, even though between-group differences were no longer significant at 6 to 8 weeks. The authors concluded that the potential benefits of adding a BZD to an antidepressant must be balanced judiciously against possible harms including development of dependence and accident proneness, on the one hand, and against continued suffering following no response and drop-out, on the other. Beyond these studies, positive reports on the use of some augmenting BZDs in treatment-resistant depression and anxious depression have been published [116,157]. However, recent meta-analyses on the use of BZDs alone or in augmentation in depressive disorders such as minor depression [18] have not found any evidence to support this use. In addition, the question of whether sedative/hypnotics may prevent or provoke suicide in anxious depressed patients has been recently put forward [182]. Taken as a whole, most recent international treatment guidelines [5,89] recommend to limit the use of BDZs in patients with primary major depression only to those with pronounced anxiety or persistent insomnia not adequately relieved by an SSRI or SNRI.

3.1.3. Sleep Disorders (Insomnia)

The treatment of sleep disorders and insomnia, in particular, is complex and depends on numerous patient-related factors, including age, proposed length of treatment, primary or secondary sleep complaint, psychiatric and medical comorbidity, history of drug or alcohol abuse and costs [166]. In particular, a crucial issue for clinicians is to distinguish whether insomnia is a symptom of another comorbid (psychiatric or medical) disorder or a primary disorder per se. BZDs and related BZD-receptor agonists, however, are the most effective pharmacological therapies for insomnia [129]. The latter compounds are considered non-BZD agents active

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at the level of the BZD receptor ("z" drugs belonging to the classes of imidazopyridines, pyrazolopyrimidines and cyclopyrrolones) and are among the most commonly used hypnotic agents today. "Z" drugs (i.e., zolpidem, zopiclone, eszopiclone and zaleplon), in fact, are also positive allosteric modulators of the $GABA_A$ receptor. A detailed review of the use of BZDs in sleep disorders is beyond the scope of the present article and, herein, only basic principles are provided.

In general, most hypnotics are FDA-approved and indicated only for short-term use (e.g., less than 1 month) and not recommended for chronic treatment [137]. However, as a group, the "z drugs" share characteristics of safety, efficacy and low abuse potential. Furthermore, some agents of this class have shown safety and efficacy in a context of polytherapy over observation periods up to 6 months, without development of tolerance or rebound insomnia after discontinuation [59,93]. However, acute treatment of chronic insomnia often leads deliberately or inadvertently to long-term use. In this perspective, it is noteworthy to highlight that short (e.g., zolpidem, triazolam, etc.) and medium (e.g., lorazepam) half-life compounds may be useful in the short-term also in relation to their rapid absorption. On the other hand, all long half-life compounds (e.g., diazepam, clonazepam, etc.) present higher risk of daytime sedation and impairment because of delayed accumulation and elimination. In addition, risk of increased falls and confusion are present and, taken as a whole, discourage the use of BZDs even in the short-term. It is noteworthy to highlight that until recently, hypnotics were only available as immediate-release formulations. Therefore, when a longer duration of action was required, agents with longer half-life or increased doses were selected with increased risk of next-day residual effects. In this perspective, a modified-release formulation has been developed to provide a more suitable pharmacokinetic profile for some agents (zolpidem extended release) [59,93] and this approach might offer significant benefit in the development of novel hypnotic compounds.

With respect to BZD use in the elderly, prescribing guidelines continue to emphasize short-term, low-dose use, with short-half-life medications along with non-pharmacological treatments, including appropriate sleep hygiene practice, and treatment of other medical or psychiatric causes of disturbed sleep [148].

3.1.4. Alcohol withdrawal

Alcohol abuse and dependence represent a worldwide medical and social problem and BZDs have been widely used for the treatment of alcohol withdrawal symptoms [84]. In a recent review conducted by a Cochrane group [2], the authors evaluated the effectiveness and safety of BZDs in this specific condition. They identified 64 studies (4309 participants) and examined effectiveness, safety and risk-benefit of BZDs in comparison with placebo or other pharmacological treatment and with comparisons among themselves. A protective benefit for BZDs against alcohol withdrawal symptoms, in particular seizures, compared to placebo and a potentially protective benefit for many outcomes compared with other drugs used in this disorder were found. In conclusion, BZDs seem to play an important role in treating alcohol withdrawal according to this recent and updated revision, even though heterogeneity of the trials limited the confidence in the results. This is not surprising considering the overlapping pharmacological properties between the BZDs and alcohol.

3.1.5. Delirium

Delirium may occur in up to one-third of hospitalised patients, being associated with prolonged hospital stay and increased morbidity and mortality [10]. Some open studies have suggested that BZDs may be useful in controlling non-alcohol related delirium. A recent review by the Cochrane initiative [106] was conducted in order to determine the effectiveness and incidence of adverse effects of BZDs in the treatment of such conditions. Selection criteria allowed the identification of only one trial comparing the effect of lorazepam with dexmedetomidine, a selective alpha-2-adrenergic receptor agonist, on delirium among mechanically ventilated intensive care unit patients. In this trial, dexmedetomidine was associated with an increased number of delirium- and coma-free days compared with lorazepam treated patients. One partially controlled study showed no advantage for alprazolam over neuroleptics in treating agitation associated with delirium, and another partially controlled study showed decreased effectiveness for lorazepam and increased adverse effects compared with neuroleptics (haloperidol, chlorpromazine) for the treatment of acute confusion. The authors, actually, could not find any adequately controlled trial to support the use of BZDs in the treatment of non-alcohol withdrawal related delirium among hospitalised patient. Therefore, at this time, BZDs cannot be recommended for the control of this condition and further research is required.

3.1.6. Schizophrenia and agitated, aggressive and violent behaviours in psychoses

BZDs are commonly used in the context of psychotic disorders and schizophrenia as adjunctive treatment, particularly when patients display agitated, violent and aggressive behaviours. A recent review by the Cochrane Collaboration [178] reviewed the effects of BZDs as monotherapy or as an adjunct to antipsychotics for the treatment of schizophrenia and schizophrenia-like psychoses. The analysis included 31 studies with over 2000 participants. Most studies were small-scale, of short duration (1 to 13 weeks) and inconsistently and/or incompletely reported. Eight studies compared BZD monotherapy vs. placebo, finding that more participants on BZDs showed a clinically significant response. Some adverse events observed in these studies suggested that BZDs were more harmful than placebo even though data were incompletely reported. Thirteen studies examined the effects of BZDs in comparison to antipsychotics as monotherapies. In terms of clinical response, no advantage for any treatment group concerning improvement of the participants' global state was found, except for a small study that analysed the mean Clinical Global Impression (CGI) scale severity score at one hour. This comparison was significantly limited by the low numbers of studies reporting on global function and the short trial duration. Two studies showed a statistically significant superiority of antipsychotics in terms of relapse prevention at one year. Desired sedation occurred significantly more often among participants in the BZD group than among participants on antipsychotics at some time-points. Other outcomes relating to the general or specific mental state showed no significant differences between groups. With respect to reported adverse events, there were no data in favour of any group. Sixteen studies examined whether the augmentation of antipsychotics with BZDs was more effective than antipsychotics alone. During the first hour of treatment, the combination treatment group benefited from the augmentation in terms of global state. However, this benefit diminished over time and was not reproducible at 2 hours or longer. No superior efficacy of BZD augmentation could be detected in terms of general mental state. Specific aspects of the mental state showed no group difference except for desired sedation at 30 and 60 minutes. Somnolence affected the combination treatment group significantly more than the control group. Of clinical interest, the use of antiparkinsonian medication was found to be reduced in the combination treatment group. Adverse events were poorly documented and the results were based on scant data. The authors concluded that available randomised trial-derived evidence was insufficient to recommend BZDs either as a sole or

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adjunctive agent in schizophrenia or schizophrenia-like psychoses. The only significant effects were seen in terms of short-term sedation, at best. Therefore, the existing evidence on augmentation of antipsychotics with BZDs seemed to the authors to be inconclusive.

A previous review by the Cochrane Collaboration [69] had specifically examined the effects of BZDs, alone or in combination with antipsychotics, when compared to placebo or antipsychotics, to control disturbed and psychotic behaviours in people with acute psychosis. Selection criteria allowed the identification of 11 studies with a total of 648 participants. When comparing BZDs with placebo, sedation was equally prevalent; however, fewer people allocated to lorazepam remained excited at 24 hours. The lorazepam and placebo groups experienced similar non-significant, low levels of adverse effects. In the comparison of BZDs vs. antipsychotics, without use of anticholinergics/antihistamines, patients allocated to BZDs did not clearly need additional medication compared with those given antipsychotics alone. The numbers sedated were also similar between groups as were mental state ratings. Extrapyramidal symptoms were significantly higher in the antipsychotic treatment group. Two trials (total $n = 83$) comparing lorazepam plus haloperidol with lorazepam alone found no clear difference for the need for additional medication or "not being improved" at one hour. There was no difference in the incidence of extrapyramidal symptoms. Finally, when the BZD plus antipsychotic combination was compared with antipsychotics alone, there was no difference between groups in the need for additional medications or for mental state ratings. Extrapyramidal symptoms were significantly lower for people receiving both BZD and antipsychotics compared with those receiving antipsychotics alone. No significant difference was found in the number of participants unfit for early discharge. The authors concluded that insufficient data were available to support or refute the use of BZDs with or without antipsychotics where emergency drugs are needed. In fact, studies were not large enough to identify any serious adverse effects of BZDs (such as respiratory depression) and more informative research is needed.

3.1.7. Neuroleptic-induced conditions

BZDs are commonly used for some neuroleptic-induced conditions [37] such as neuroleptic-induced tardive dyskinesia and neuroleptic-induced acute akathisia [87].

A review by the Cochrane group [22] was aimed to determine the effects of BZDs for neuroleptic-induced tardive dyskinesia in people with schizophrenia or other chronic mental illnesses. Selection criteria allowed only three trials to be identified (total $n = 80$). The use of BZDs as adjunctive treatment produced no clear changes for a series of tardive dyskinesia medium-term outcomes. One trial ($n = 24$) found better final scores for abnormal movement for patients receiving adjunct BZDs. The reviewers concluded by stating that only 1 small study reports preliminary evidence that BZDs may have some positive effect in neuroleptic-induced tardive dyskinesia. However, inconclusive results from other studies mean routine clinical use is not indicated and these treatments remain experimental.

Neuroleptic-induced akathisia is one of the most common and distressing early-onset adverse effects of antipsychotic drugs, being associated with poor compliance and increased risk of relapse. A Cochrane review [103] attempted to determine the effects of BZDs versus placebo for people suffering from this condition. Selection criteria, however, could identify only two small trials (total $n = 27$). By 7 to 14 days, a symptom reduction for patients receiving clonazepam compared with placebo was found. No significant difference was detected for adverse events or the need for anticholinergic medication. Stressing the lack of larger controlled trials, the authors concluded that over a short follow-up period, the use of BZDs may reduce the symptoms of antipsychotic-induced acute akathisia.

3.2. Extent of Usage of Benzodiazepines and its Appropriateness

A selection of the more informative and representative studies is summarised relating to usage in the UK, Europe, North America and elsewhere around the world [53]. It is generally acknowledged that the high rate of prescription of BZDs is a matter for general concern for health professionals, patients and regulatory bodies [34].

3.3. Surveys of UK usage

Surveys of UK BZD usage in primary care have shown clear changes over time with an initial decline followed by recent increases. A sample of almost 5000 non-institutionalised individuals, 15 years or older, was interviewed by telephone [124]. Overall, 3.5% of the sample reported current use of psychotropic medication, with 63% of the medicines prescribed being BZDs. Consumption by women (4.6%) was twice that of men. Consumption rose significantly from the age of 35 and increased considerably again over the age of 65.

A total of 8580 subjects aged 16–74 years participated in a national survey designed to investigate the co-morbidity with, and impact of, hypnotic use [123]. The usage of medication increased sharply with the reported level of insomnia and with age. BZD hypnotics were used in about 1.2% of those with any report of insomnia and 4.4% of those who met diagnostic criteria for insomnia.

The 1946 British birth cohort database was addressed in order to describe antidepressant, anxiolytic and hypnotic drug use over a 22-year period [35]. Over 3000 of this cohort had been asked about psychotropic medication use at several time points between the ages of 31 and 53. The prevalence of prescribing of all three groups of medication increased significantly from 1977 when it was 30.6 per thousand to 1999 when it had almost doubled to 59.1 per thousand. However, less than 30% of this cohort diagnosed with mental disorder used antidepressants, BZD anxiolytics or hypnotics.

Data from the UK National Health Service over 20 years (Fig. 3) at first sight seem to show a decline in BZD use [135]. However, the use of anxiolytic BZDs has actually increased somewhat. The use of hypnotic BZDs has been replaced by increasing use of the z-drugs. The upshot is no change.

3.3.1. Surveys of European usage in primary care

A survey in Ireland twenty years ago using data obtained from 16 community pharmacies found that the prescribing rates for BZDs increased tenfold from the age of 20 to 70 and was higher in women than in men [120]. Almost all of the patients reported the drugs to be effective in the treatment of anxiety or insomnia.

A Norwegian study in primary care reviewed 3452 prescriptions for BZD hypnotics prescribed by general practitioners over 2 months [164]. Of these, two thirds were for women and just over half were for patients aged 65 and/or older. The quantity of drug per prescription increased with the patient's age: thus, those aged 65 and over received on average 70 defined daily doses (DDD) per prescription compared with only 34.4 for young adults aged 22–29.

A national telephone survey in France in 2001 in a representative sample of non-institutionalised adults estimated the prevalence of BZD use to be 7.5%, almost twice as high among women than men, increasing with age and among the unemployed [100]. The duration of usage was more than 6 months in three-quarters of users and also increased with age.

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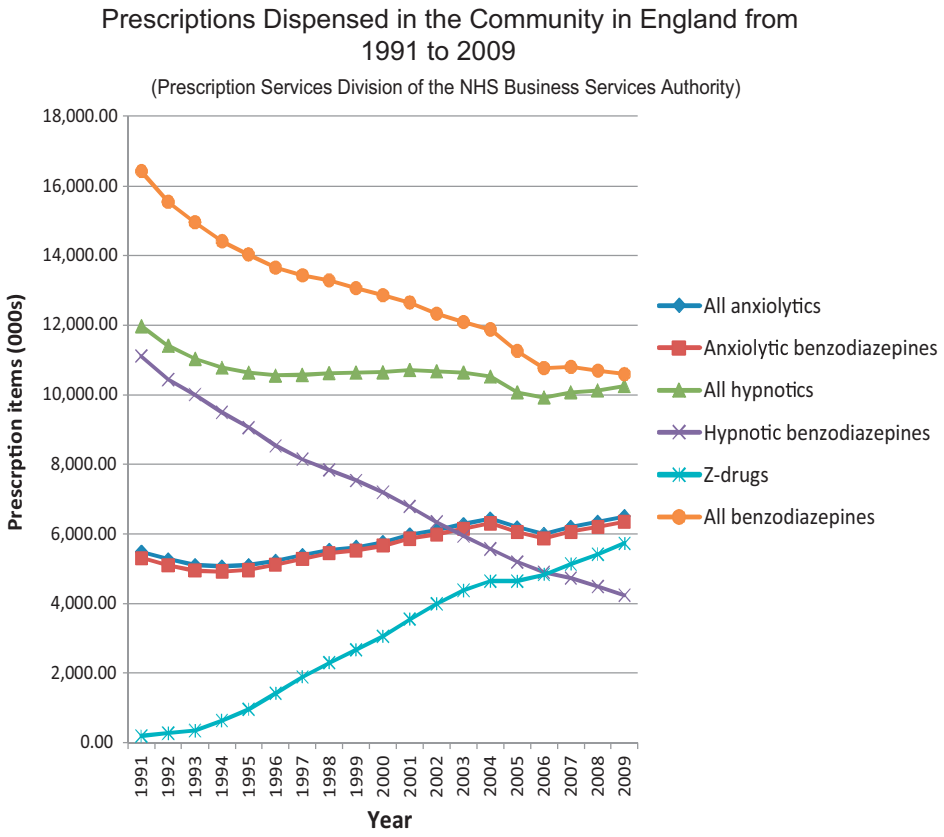

Fig. 3. Prescription Services Division of the NHS Business Services Authority [135].

An Italian study examined the recent trends in BZDs and antidepressant consumption over the years 1995–2003 [33]. BZD consumption over these 9 years remained substantially stable whereas there was almost a three-fold increase in antidepressant consumption from 9 to 26 DDDs.

Another Italian study evaluated all 1771 individuals who were exposed to BZDs during 2005 [176]. Of these, 535 (30%) were BZD users. Of clinical interest, lower level of education, diagnosis of affective illness, longer length of illness and higher service use were significantly associated with BZD exposure. An increase in dosages over time to maintain the drug's effectiveness was not evident from the analysis of the relationship between daily dose and length of therapy. Only 17.3% (93/535) of patients exposed to BZDs discontinued treatment. Age and length of illness were negatively associated with the probability of discontinuing therapy, while the concomitant use of antipsychotics and mood stabilisers was positively associated with discontinuing therapy.

3.3.2. Surveys of usage in primary care in other countries

Psychotropic drug usage was evaluated using data from the prospective, longitudinal Harvard/Brown Anxiety Disorder Research Project (HARP) [174]. Prescribing patterns had remained stable over 12 years. BZDs were the commonest medications, being taken by a half of those diagnosed as suffering from GAD. After 12 years, a third of these patients were still taking them, although a quarter of GAD-diagnosed patients received no medication over the 12 years. The investigators concluded that the various guidelines promulgated over the 12 years of study had had a relatively limited impact on the prescribing patterns.

A Canadian population survey interviewed responders at 2 years intervals with respect to long-term BZD use [119]. Four percent of the Canadian population used BZDs at any time; they were more likely to be female, elderly, smokers, non-English speaking and to have completed high school education. Long-term use was predicted mainly by previous BZD use. Another in British Columbia examined changes in usage over the years 1996–2006 [40]. Long-term usage was associated with being poor, in poor health and being over 65. The authors concluded that despite increased awareness of risks associated with BZD use, little had changed with respect to usage.

More BZDs are prescribed in Japan than in any other major country. An electronic database of prescriptions was examined covering 600,000 outpatient visits [118]. Of 644,444 prescriptions, 6.1% were for anxiolytic and 5.8% for hypnotic BZDs, with internal medicine, surgery and neurology departments being the heaviest users and the psychiatric units relatively light users. Antidepressants were prescribed far less frequently.

3.3.3. Surveys of usage in elderly populations

The extent and appropriateness of BZD use in an elderly community in the UK have been evaluated [168]. People from the same community in Liverpool were sampled between 1982 and 1983 and again in 1989–1991. In the first survey there was a total of 1070 elderly with 660 females and 410 males. In the later sample the total was 5222 with a more even age distribution. Those using BZDs comprised 12.8% in the first study, and 10.8% in the second. Usage by females was higher than by males in the ratio of 2.2 to 1. It was concluded that the continued usage in this study showed that the type of treatment was often inappropriate. The authors recommended: "under such condition, long-term use of these drugs should be actively discouraged".

Whether the usage is appropriate or inappropriate is a value judgement. In a study of elderly medical inpatients in 17 hospitals in England and Wales, an algorithm was developed to divide prescriptions into those, which were given in an acceptable way and those, which were not appropriate [20]. Prescribing data were

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collected concerning 1391 patients. In only a third was it concluded that the BZDs were prescribed appropriately with an acceptable indication and no contraindications.

Data from the Berlin Aging Study showed that BZDs were taken by 19.9% of the 70-85 year olds, and by 15.2% of those over 85 [104]. Usage in males was 15.6% and in females 20.1%. The commonest indication was insomnia. Most patients were long-term users: 26% had taken their BZD for less than a year; 33.8% for 1–5 years; and 40.3% for over 5 years.

Drug dispensing data between 1991 and 2003 were available in the Netherlands for over 5000 people [108]. The investigators found that 17.7% of the users in the cohort eventually proceeded to chronic use after the first prescription. The predictors of long-term usage included depressive symptoms, hypertension, painful joints and a self-perception of being in poor health. Conversely, living alone protected against long term BZD use. Hypnotic medication was more likely than anxiolytic medication to result in chronic use.

Prescriptions in the elderly population were evaluated for over 1 million residents of Ontario covered by the provincial universal drug benefit programme [171]. The annual prevalence of BZD prescriptions dispensed decreased from 25.1% in 1993 to 22.5% in 1998. The dispensing prevalence increased with age, with about a fifth of those aged 65–69 and approximately 30% of those aged 85 and over receiving a BZD.

The use of BZDs in elderly Australians was assessed by analysing data for 2002 in 3970 individuals aged 65 or more in a general practice database [180]. Overall, 15.7% had received a prescription in that year. The percentages rose from 11.1% in those aged 65–69 to 21.8% in those aged over 85. Females received more prescriptions than male, the ratios varying between 1.5 and 3, but not generally according to age, though one-quarter of females over 85 were prescribed a BZD.

3.3.4. Hospital studies

The influence of admission to hospital on the prescribing of BZDs was evaluated in a background population of 29672 subjects [114]. The main outcome measure was any change in community BZD prescribing following hospitalisation. Of the 2628 subjects admitted to a general hospital, 59 (2.2%) started BZDs but 45 (1.7%) discontinued them. Admission to a psychiatric hospital resulted in 17 (6.7%) of the 254 subjects starting and 40 (16.7%) discontinuing BZDs. Yet, when compared to the overall extent of BZD prescribing in the study population, these were minor effects.

One study assessed patients in the emergency room of a general hospital [159]. Elderly patients used more psychotropic drugs, particularly BZDs and antidepressants than did younger patients. BZDs were most widely used by the psychiatrists on duty.

3.4. Adverse effects of benzodiazepines

An unusual way of assessing adverse effects was utilised by Martin et al. [110]. They used an indirect measure of tolerability, namely the number of withdrawals from a trial for any reason. They carried out a meta-analysis of 23 short-term trials. Although withdrawal from the trials for "lack of efficacy" significantly favoured the BZDs over placebo, such differences for withdrawal "for any reason" showed no conclusive results. This could be interpreted as showing that the efficacy advantages for the BZDs are cancelled out by adverse effects, yielding a neutral risk/benefit ratio.

3.4.1. Cognitive effects

Stewart [161] reviewed the acute and chronic cognitive effects of the BZDs. She noted that acute administration induced sedation, drowsiness, impairment of learning, psychomotor slowing, and anterograde amnesia [16]. Sedation and memory impairment are probably distinct BZD effects [41]. Chronic cognitive effects are modified by tolerance to some, but not all, of the acute effects. Sedation and impaired attention appear to wane [28,107]. A wide range of cognitive and psychomotor effects show persistent impairment during long-term use and may persist after withdrawal [19,70,72,167]. The main methodological problem is trying to distinguish the effects of the BZDs from impairments associated with any underlying psychopathology such as anxiety. Visuo-spatial impairments have been the most consistent findings. Another complication is that impairments may be related to peak plasma concentrations. BZDs may differ in the severity of their effects with lorazepam and alprazolam often being singled out [42]. It has also been suggested that the cognitive effects of the BZDs may interfere with psychological treatments such as counselling [74].

An epidemiological study in France recruited 1389 people aged 60–70 from the electoral rolls of the city of Nantes and followed them up at 2 and 4 years [130]. Of the 1176 subjects who participated in the three examinations, 10% were episodic, 6% recurrent and 7% chronic BZD users. A range of cognitive tests showed significantly lower scores than in non-users. The results were independent of age, sex, education, alcohol and tobacco use, anxiety and depression scores, and the use of psychotropic drugs other than the BZDs.

An extensive study comprised a meta-analysis of the cognitive effects of long-term BZD use [19]. Thirteen studies were identified and the data were combined so that each study only contributed one outcome variable relating to cognitive function. The duration of BZD use ranged from 1 to 34 years. These users were consistently more impaired than controls across all of the cognitive categories evaluated. The mean weighted effect size was -0.74 ($SD \pm 0.25$) and all these differences were significant. The authors point out the relative paucity of studies but conclude that long-term BZD use and the cognitive impairment associated with this use, "has numerous implications for the informed and responsible prescription of these drugs".

That long-term use of BZDs can induce persistent cognitive impairment that can be demonstrated on withdrawal. In a controlled study, BZDs were gradually withdrawn from a group of elderly nursing home residents [148]. Compared with similar residents who were maintained on their BZD medication, measures of cognitive performance and memory showed significant improvement. By contrast, anxiety, agitation and sleeplessness were unaffected.

3.4.2. Psychomotor effects

One aspect of psychomotor functioning that has received a great deal of attention because of its real-life implications is driving ability. A review some years ago concluded that epidemiological studies, albeit sparse, indicated that BZD use was associated with an increase in relative risk of being involved in a traffic accident of about 1.5 to 6.5 [173]. Relevant factors included dose, number of BZDs and recency of use. The authors equated this increased risk to that of 0.6 to 1 g/L of alcohol. Compounds with a long elimination half-life tended to accumulate and increased the risk. This implies that tolerance may supervene to the therapeutic effects but not so, or to a definitely lesser extent, to complex perceptual and psychomotor effects. Elderly patients may be more at risk. Concomitant use of alcohol is particularly dangerous, and patients should be warned appropriately [24].

One meta-analysis evaluated 27 studies of driving, either on the road or on a simulator [136]. While no consistent effects were noted in the driving simulator, BZDs increased the deviation in the lateral position ($p < 0.004$). A similar study incorporating 22 studies [126] was more cautious, pointing out that potential confounding could occur from the underlying pathology.

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A recent paper reviewed the effects of BZDs, antidepressants and opioids on driving ability [44]. Two meta-analyses showed that BZDs are associated with a 60–80% increase in the risk of traffic accidents and a 40% increase in "accident responsibility". Taking alcohol and BZDs together increased the accident risk 7.7 times. The increased risk of an accident in the elderly taking BZDs (pooled OR 1.13) was lower than that in younger drivers (OR 2.21). Daytime anxiolytics impaired driving performance irrespective of half-life. Both short- and long-acting BZDs taken as hypnotics impaired driving at least during the first 2–4 weeks of ingestion.

Another study dealing with road traffic accidents and BZDs, used dispensed prescribing as a measure of exposure in a case-control study of drivers in Tayside, Scotland, who were involved in a road traffic accident, and had used psychotropic medication [17]. Rates were compared in these drivers while taking and off their medication. Antidepressants of various types were not associated with a significantly increased odds ratio. By contrast, the risk with BZDs was 1.62 (95% confidence limits 1.24–2.12; $p = 0.01$). The risks were age-related, younger drivers being particularly at risk. Most had not combined their BZD with alcohol. Long half-life BZD anxiolytics were more risky than shorter-acting compounds. Among short-acting hypnotics, zopiclone seemed to be overrepresented. The authors concluded that users of anxiolytic BZDs and zopiclone should be advised not to drive.

3.4.3. The elderly

For both pharmacokinetic and pharmacodynamics reasons, the elderly are more sensitive to the effects of BZDs [29,149]. The adverse effects are well known and include tolerance, withdrawal syndromes, over sedation, increased falls and cognitive effects. With anxiolytic use, the over sedation can be a major problem and "pseudo-dementia" may develop. Hypnotic use is often accompanied by a feeling of "hang-over", again particularly in the elderly. Carers may note a dramatic decrease in alertness and mental functioning in an elderly person whose hypnotic dose is increased. This may be compounded by interactions with other medications, for example, analgesics and antihypersensitive agents [96].

Accordingly, the risk/benefit ratio is less favourable in this age group [12,44]. One disturbing problem is cognitive impairment, which masquerades as dementia [85,175]. The Verdoux study identified six studies, which explored the association between BZD use and cognitive decline. Three studies found an increased risk of cognitive decline but two showed a lowered risk, suggesting methodological problems. The Hulse study was also inconclusive.

A classic paper published many years ago contrasted the efficacy and adverse effects of nitrazepam with placebo in healthy, young and old people [30]. Ten milligrams of nitrazepam given for three successive nights improved subjective ratings of sleep but both groups of subjects tended to feel less alert at 12 and 36 hours. Elderly subjects made significantly more errors than the young despite similar plasma concentrations of nitrazepam and similar half-lives in both groups. The investigator attributed these differences to an increasing sensitivity of the ageing brain in the elderly. Presumably, the number of BZD receptors declines so that receptor occupancy increases.

Elderly in-patients appear to be at particular risk [36]. The hypnotic and residual effects of nitrazepam 5 mg and temazepam 20 mg were compared in 58 elderly in-patients after seven nights of administration. Patients reported a better night sleep after the first use of either drug, but this effect had disappeared by night seven. Reaction time was unchanged after the first night but was prolonged significantly after the seventh dose as the drugs accumulated. Another psychometric task was impaired after the first night in both groups, and this effect had increased after the seventh night. Patients of low intelligence tended to be more affected.

One particular hazard concerns the risk of hip fractures in older people taking BZDs [39]. An extensive review designated the use of psychotropic medications as an established risk factor for hip fractures. Eleven primary epidemiological studies were identified but differences in research design led to some inconsistencies. The outpatient studies showed clear deleterious effects of the BZDs, with no difference between short- and long-acting compounds. Higher doses were a definite risk factor, as was recent initiation of use. The overall increased risk was estimated at 50%.

Several studies have investigated the possible relationship between BZD usage and falls. Hypnotic use in the elderly has been assessed as a particular risk [1]. However, poor sleep can itself result in daytime dysfunction [163]. In the evaluation of new hypnotics, postural sway and reaction time should be evaluated.

3.4.4. Paradoxical reactions

Paradoxical excitement is an unwanted effect, which has important legal implications [131]. The disinhibitory effects of the BZDs can produce increased anxiety, acute excitement and hyperactivity. Aggressive impulses may be released with the emergence of hostility and rage; criminal acts such as assault and rape are possible. Estimates of incidence range from less than 1% to at least 20% of those taking BZDs; the variation depends on the patient sample. High-risk patients include those with borderline personality disorders, impulse control disorder and persistent alcohol problems. The combination of a BZD and alcohol is particularly likely to lead to paradoxical reactions. The patient may have complete or partial amnesia for the event such as an episode of "air-rage" in an airplane. Disinhibitory reactions to sedative drugs are related to type of BZD, dose and mode of administration [25]. Thus, preoperative intravenous administration of high doses of high potency BZDs poses a particularly enhanced risk.

Recently, attention has been drawn to increasing use of BZDs in France and their propensity to induce paradoxical reactions wherein increases rather than decreases in emotional feelings and behaviour can occur [147]. Journalists have described aggressive feelings, agitation, and disinhibition and even violence, suicide and rape. Risk factors include borderline personality and drug misuse, especially polydrug abuse, learning difficulties, the under – 18's and over 65's [25,131]. High dosage is an important risk factor [54].

3.4.5. Teratology

There has been some controversy concerning possible teratogenic effects of BZDs. The general consensus is that they have low teratogenic potential but may rarely cause cleft palate [4,52]. Neonatal withdrawal reactions have been described [3,86]. The last reviewers conclude that minimising the risk involves using the drugs at the lowest effective dose for the shortest possible duration, avoiding use in the first trimester and avoiding polydrug use.

3.5. Rebound, tolerance, dependence and withdrawal

3.5.1. Rebound and tolerance

The mildest form of withdrawal is rebound. Rebound comprises the original symptoms recurring transiently at a greater intensity. Withdrawal involves the onset of new symptoms not previously experienced by the patient.

An important review article was published in 2001 by Dikeos and Soldatos [51] who concentrated on rebound insomnia on discontinuation and on efficacy and tolerance. They concluded that all licensed hypnotic drugs have been shown to be efficacious initially for the amelioration of insomnia, irrespective of the elimination half-lives. A meta-analysis of sleep laboratory studies with five hypnotics showed "clear-cut loss of efficacy" by 2 weeks

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following nightly use [158]. The meta-analysis found that tolerance to triazolam was intense, but slight for midazolam and zolpidem. Zopiclone also probably demonstrated tolerance. Another meta-analysis showed that triazolam was associated with rebound and tolerance, whereas zolpidem, also short-acting, caused a milder degree of rebound insomnia. Nor did preliminary data suggest that it might be a problem with the ultra-short acting zaleplon.

A study of zolpidem, 5 and 10 mg, as compared with placebo, for seven nights in 24 healthy elderly volunteers detected no residual effects or tolerance [60].

Very few medium- or long-term studies have been conducted that attempt to evaluate efficacy of the BZDs as anxiolytics or hypnotics, and systematically assess adverse effects. One such study compared the hypnotic efficacy and psychometric effects of either chlormethiazole or triazolam in the elderly over 9 weeks of treatment [21]. Both were similarly effective in short-term use but triazolam lost its efficacy over 9 weeks. Furthermore, daytime withdrawal effects were reported with triazolam but not with chlormethiazole.

3.5.2. Dependence and withdrawal

Dependence is defined by the World Health Organisation as a strong desire or sense of compulsion to take a substance, a difficulty in controlling its use, the presence of a physiological withdrawal state, tolerance of the use of the drug, neglect of alternative pleasures and interests and persistent use of the drug, despite harm to oneself and others.

Withdrawal comprises a group of symptoms that occur on stopping or reducing the use of a psychoactive substance that has been taken repeatedly, usually for a prolonged period. The syndrome may be associated with signs of physiological disturbance. A withdrawal syndrome is one of the indicators of a dependence syndrome.

People who misuse or become dependent on BZDs or on z-drugs are usually seeking medical help during increased periods of anxiety or sleeplessness: they persist with their prescription beyond the generally recommended time frame or attain doses above the licensed range. They are then continued by their prescriber – so-called "involuntary" or iatrogenic dependence. A second group of patients actively seek the sedative/hypnotic for its intentional abuse because of its rewarding psychoactive properties. The latter are more likely to have a comorbid diagnosis of another substance-misuse disorder, and to procure their drugs from several sources such as prescriber, illicit sales of diverted supplies, or Internet sites [102].

As far back as 1961 the potential problem with BZD dependence, at least at high doses, was adumbrated by Hollister and his colleagues [83]. Prisoners were given 300–600 mg/day of chlordiazepoxide (several times the usual dose) for several months. On placebo substitution, 10/11 developed depression, psychosis, agitation, insomnia, loss of appetite, and nausea within 2–8 days: two suffered seizures. The investigators warned that patients would escalate their dose. However, it transpired that less than half of users in practice did so. In other words, most of the patients using BZDs, who show clear signs of dependence, are still taking the original dose. Only a minority take a dosage above recommended therapeutic levels. These individuals usually have a more severe form of dependence than those patients keeping to the therapeutic dosage range.

The similarities between BZD withdrawal and the syndromes accompanying alcohol and barbiturate withdrawal were recognised early on [9]. Severe syndromes can result [73,78,97,98]. Protracted withdrawal has been described but the nature of these symptoms has been disputed [78]. The occurrence of the withdrawal syndrome is related to high dosage and long-term treatment, but the severity of the withdrawal syndrome is not so closely related [95]. However, severe withdrawal syndromes may still supervene despite slow withdrawal over several months or even years [97].

Even modest dosage reductions as well as complete withdrawal can result in withdrawal symptoms. These comprise physical symptoms such as muscle tension and spasm, or weakness, pins and needles in the extremities, and flu-like symptoms. Perceptual hypersensitivity and depersonalisation/derealisation are common. Anxiety and insomnia may worsen, nightmares may disturb the patient, memory and concentration are impaired, and depressive symptoms arise for the first time. Occasionally, epileptic fits, total or partial, a paranoid or a confusional psychosis may occur [133,181]. The symptoms appear within 2–3 half-lives of the BZD being withdrawn and usually lessen and then disappear within a few weeks [150]. Some patients claim that their symptoms have persisted for months or indefinitely [145].

Withdrawal symptoms from BZDs can ensue after 4–6 weeks of use, but only in about 15–30% of patients [97]. Why some long-term users can withdraw without difficulty even after years of continuous use while others undergo protracted agonies remains unclear [8]. More serious or life-threatening symptoms may occasionally occur [133], including delirium tremens, delusions, status epilepticus which may end in death, catatonia, which may also result in death, depression (often severe), suicidal ideation, self harm, and attempted suicide. Many of these are reported anecdotally and few case series exist. High levels of neuroticism, lower educational level and lower quality of life were associated with higher levels of distress during withdrawal [121], and with higher doses, and low levels of social support [122].

A recent prospective study revealed four patterns of withdrawal symptoms over time [177]: a gradual decrease over the 50-week time period; an increase in the severity of symptoms at the onset of tapering and a decrease in severity post-tapering; an increase in the severity of symptoms 4 weeks after the cessation of BZD tapering; no symptoms detectable.

Russell and Lader [146] published a stepped care approach to BZD discontinuation. It began with a minimal intervention with advice from the GP, and progressed to a planned tapering of doses by the GP for patients if the first stratagem was unsuccessful. Hospital-based BZD discontinuation was then considered necessary if these two stages were repeatedly unsuccessful.

Quite minimal interventions are often helpful [99]. A 10-year follow-up used medical records of patients in the Netherlands who had successfully discontinued BZD use after advice about discontinuation in a letter from their GP. Of these patients 60% continued abstinent. Those who were not able to maintain their abstinence usually continued on lower or average doses of BZDs [48].

Withdrawal schedules are widely available and involve tapering usually after substituting diazepam [179]. However, such substitution has little evidence to support its efficacy [50]. The rate of taper is not based on good empirical evidence but on the clinical experience of the prescriber [79]. The initial stages of withdrawal are easier for the patient to tolerate than the later and last stages. It is usual to start fairly briskly and then slow down. Patients may not feel better until fully withdrawn [79]. Stopping tapering in the middle of withdrawal is counter-productive.

Substitution of a long-acting BZD such as diazepam or chlordiazepoxide is often used to assist withdrawal. Also the formulations that are available such as liquid preparations facilitate small decrements. Other drugs, which have been substituted, include antidepressants, serotoninergic anxiolytics, anticonvulsants and beta-blockers; these may help in management without reducing the severity of the withdrawal [138]. In general, psychological treatments are helpful but some believe

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only when dosage tapering has ceased [160]. A recently-published meta-analysis of 24 intervention studies compared routine care with gradual dose reduction (GDR) and GDR with psychological techniques or pharmacological substitutions [128]. Routine care was less effective than the interventional procedures.

A recent descriptive review of studies evaluating methods of expediting withdrawing BZDs in primary care concluded that there are few objective data on the optimal rate of benzodiazepine withdrawal; that the optimal duration of withdrawal is undetermined; and may vary for each patient [99].

The prognosis with a slow tapering schedule is usually fairly good with about two-thirds of patients achieving total cessation. Others achieve a reduction in dosage but this is an inadequate outcome as there is a high rate of relapse. Those that fail to discontinue have a poor prognosis and repeated failure may ensue, demoralising the patient. Predictive factors include previous failed attempts, co morbid depression or physical conditions, a personality problem, a history of alcohol-related problems, an unsympathetic general practitioner, lack of family or social support and older age. Patients prescribed medication by their usual GP are more likely to respond positively to brief intervention than those whose medication was prescribed by another medical practitioner [75]. Those that achieve a successful total withdrawal should never risk a relapse by taking BZDs again, even for short periods [77]. Even alcohol should be avoided because of cross-tolerance and dependence.

A different approach using the BZD antagonist and partial agonist, flumazenil, has been tried with some success [68]. One obvious hazard is precipitating dangerous withdrawal in chronic users, particularly those on high doses. Studies are still in progress but large-scale RCTs remain to be carried out.

The teratogenic risk with the BZDs is low [see above]. However, pregnant women are often withdrawn from their BZD treatment. This should never be abrupt [56]. If BZDs are continued into late pregnancy, neonatal withdrawal syndromes may occur in the baby and can be severe [113].

In summary, most patients do not escalate their dose yet physical dependence on the BZDs is apparent as manifested by unpleasant symptoms on discontinuation. This comprises a characteristic withdrawal syndrome "sedative/alcohol", with often bizarre symptoms. The withdrawal can be hazardous with fits, psychosis and depression. There have been copious reports of a prolonged syndrome. The outcome is usually favourable with tapered withdrawal but the elderly have a worse prognosis.

3.5.3. *Official guidelines on benzodiazepine and z-drug withdrawal*

Several official guidelines are available. For example, the Drug Misuse and Dependence: UK Guidelines on Clinical Management provide information suitable for a long-term BZD and z-drug withdrawal regimen in the community [172]. The guidelines recommend converting the medications into an equivalent dose of diazepam based on clinical experience of withdrawal schedules. Diazepam is recommended because it has a relatively long half-life and is available in different strength tablets and in liquid form. Being long-acting, it can be prescribed as a once-daily dose that can be titrated according to the patient's withdrawal symptoms.

3.6. *Abuse of benzodiazepines*

The prevalence of sedative misuse has been calculated from data from the National Comorbidity Study in the US [71]. The lifetime prevalence of non-prescribed sedative use among adults was estimated at 7.1%. Unfortunately, the type of sedative was not specified in this study and other similar surveys suffer from the same drawback. Abuse of BZDs is likely to be higher in countries where they are easily obtainable, often without prescription, such as some regions of Asia and South America. However, much of the literature relates to the US and European nations where misuse often results from diverted prescriptions.

Patients who are prescribed BZDs for problems with anxiety or sleep usually do not escalate their doses even over a lengthy period of use. However, high dose BZD mono-dependence has been reported [101,152], with doses ranging up to 100 s of milligrams per day of diazepam and equivalent doses of lorazepam or alprazolam [73,111]. Laboratory studies of abuse liability show that although BZDs in general have the potential for abuse, this is at a much lower level than for heroin, cocaine or the barbiturates [49]. Primary BZD abuse is therefore less common than secondary abuse with alcohol or other drugs. High doses are taken as part of a pattern of polydrug abuse [165]. Patients with problems with alcohol abuse or dependence are more likely to use higher doses of BZDs. Sometimes they are taken regularly but they are also taken in an intermittent binge-type pattern. They are frequently taken with alcohol because the combination results in increased feelings of intoxication or with other sedative drugs such as tricyclic antidepressants or opiates [43,132]. They are used by heroin dependent individuals and by patients in opioid substitution treatment to prolong and enhance the opiate effects [162]. BZDs can also be used when preferred drugs are scarce. They are used by stimulant users to alleviate the increased jitteriness and anxiety after a binge and to induce sleep. They are usually taken orally but both intranasal [23,154] and intravenous abuse does occur, the pattern of use varying according to compound, formulation and country. Snorted flunitrazepam has high abuse liability and this type of abuse was popular in Chile. Other BZDs have been abused intravenously.

BZDs like most drugs of abuse and are associated with increased mortality in misusers, although data are limited [31,97,98,125,134]; in general BZDs can increase the respiratory depressive effects of opioids but perhaps not as much as alcohol can. There is an increased risk of fatal overdose but the underlying mechanism is complex.

4. Conclusions

Over approximately 50 years, BZDs have become one of the best known and most widely prescribed classes of psychotropic compounds. BZDs are used in a variety of psychiatric and non-psychiatric disorders. In most cases, such a wide use is not supported by scientific evidence but is mostly empirical.

The level of evidence for each BZD needs to be differentiated on the basis of the disorder: for instance, in anxiety disorders levels of evidence for the short-term use is robust for PD and GAD, intermediate for SAD and poor in PTSD and OCD. On one hand, rapid onset of efficacy and safety issues (e.g., overdose) make it difficult to even contemplate renouncing BZDs in clinical practice [36,64]. On the other hand, side-effects, particularly in the long-term, and abuse and withdrawal concerns, recommend a more cautious use of BZDs (short-term) than previously achieved [64]. The risk/benefit ratio is positive in short-term use but debatable once treatment exceeds the recommended duration, In particular, the controversy over whether the short-term benefits outweigh the possible risk of dependence has never been resolved. The advent of other effective agents in the treatment of anxiety and insomnia is changing the parameters of this debate, as the BZDs no longer appear as indispensable as originally thought when they superseded the barbiturates. Not only psychiatrists, but primary care physicians, who are the main BZD prescribers should acknowledge these developments, and recognize inappropriate use (e.g., chronic and with undocumented response) [155]. Intervention approaches to improve the use of BZDs including education, audit and feedback, and alerts have been implemented

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with the ultimate aim of raising the awareness of potentially inappropriate BZD use [156].

Research should be aimed at trying to identify individuals who are at particular risk of becoming dependent and/or escalating their dosage. Better stratagems for helping patients to withdraw should be explored such as the use of flumazenil.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

Dr Lader has been involved in giving general medico-legal advice on the benzodiazepines to claimants and defendants, but has not appeared in court.

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