

Long-Term use of Benzodiazepines: Tolerance, Dependence and Clinical Problems in Anxiety and Mood Disorders

S. Michelini, G. B. Cassano, F. Frare, G. Perugi

Institute of Psychiatry, School of Medicine, University of Pisa, Italy

This paper reviews the literature on the epidemiological, biological and clinical features of benzodiazepine dependence and withdrawal syndrome, focusing on clinical problems associated with the long-term use of benzodiazepine (BZs) in mood and anxiety disorders. These conditions represent the most frequent mental disorders for which BZs are overprescribed. In addition to dependence and withdrawal phenomena, the presence of chronic subtle toxicity and the interference with the underlying psychopathology observed with BZ use suggests a need for a more careful evaluation of the risk-benefit ratio in the long-term administration of BZs.

Introduction

Introduced over 20 years ago, benzodiazepines (BZs) quickly became the most widely used of all psychotropic drugs. Their marked anxiolytic, hypnotic, and muscle relaxant properties and their relative safety rapidly elevated BZs to treatment of choice for common and recurrent conditions such as anxiety states, tension, insomnia, and vague psychosomatic complaints. These symptoms also frequently occur in non-psychiatric disorders; in fact, most prescribing of BZs is by general practitioners and internists. Compared with older anti-anxiety agents such as barbiturates, chloral hydrate, meprobamate, paraldehyde, and alcohol, BZs are more specific anxiolytics and less lethal in acute toxicity and overdose.

For many years, the BZs were thought to be a safe and effective long-term treatment for anxiety and insomnia. However, during the last few years, the attitude toward these compounds has greatly changed, and growing awareness and concern about dependence liability, withdrawal phenomena, short and long-term side effects has brought the long-term use of these compounds into question. Inappropriate use and therapeutic long-term use of BZs has become especially apparent with increasing data on the development of physical dependence. The dependence potential of BZs has been discussed by the American Psychiatric Association (APA) (1990), who established a task force to gather and report on the available information regarding these widely prescribed drugs. The APA's task force concluded that "concern is justified regarding BZ appropriate

therapeutic use, toxicity, abuse and risk of inducing drug dependent state". (American Psychiatric Association, 1990).

There are no data to suggest that long term therapeutic use of BZs commonly leads to dose escalation or to recreational abuse (Woods et al., 1987; Cole and Chiarello, 1990; Kleber, 1990). Addiction, in the sense of loss of control over use and continued despite harm, is almost exclusively limited to patients with preexisting and/or concomitant alcohol, opiate, cocaine, or other sedative hypnotic abuse (Woods et al., 1987; American Psychiatric Association, 1990; Cole and Chiarello, 1990; Kleber, 1990; Kales et al., 1991). However, there is no doubt that even therapeutic doses of BZs taken over prolonged periods can lead to physical dependence and specific withdrawal syndrome (Busto et al., 1986; Royal College of Psychiatrists, 1988; American Psychiatric Association, 1990; Lader, 1990; Rickels et al., 1990; Schweizer et al., 1990; Petturson and Lader, 1991; Marriot and Tyrer, 1993). Moreover, several observations seem to indicate that sporadic, non-continuous consumption of BZ may "sensitize" a patient to future withdrawal effects (Kales et al., 1991).

Data on the incidence rate of an inappropriate use and abuse of BZs are relatively scarce. Epidemiological studies have suggested that about 2% of all adults in the United States (Balter et al., 1984; Mellinger et al., 1984), 3% of those in the United Kingdom, and 5% of those in France have taken tranquilizers continuously for over a year (Balter et al., 1984). There are a significant number of people who start to take BZs from non-medical sources such as patient's relatives or friends; this use is usually intermittent, brief and for the symptoms relief, usually insomnia. Most long-term users are elderly, female and suffer from chronic psychiatric as well as physical illnesses. These patients report that their drug use is therapeutic and under medical supervision (American Psychiatric Association, 1990). Hellerstein et al. have recently reported that patients seeking BZs were predominantly impoverished minority women with a diagnosis of a mood disorder or anxiety disorder (Hellerstein et al., 1994).

In the last few years, several reviews of the literature have been performed on BZ dependence, abuse and withdrawal

(Ayd, 1983; Owen and Tyrer, 1983; Noyes et al., 1988; Royal College of Psychiatrists, 1988; American Psychiatric Association, 1990; Lader, 1990; Petturson and Lader, 1991). In this paper we review the main clinical and biological characteristics of BZ withdrawal syndrome, focusing our attention on the problems associated with the long-term use of these compounds in mood and anxiety disorders. These conditions are the most frequent mental disorders for which BZs are overprescribed and utilized. Clinical and therapeutic problems arising from the interaction between mood and anxiety disorders and long term utilization of BZs are discussed.

Biological Basis of the BZ Withdrawal Syndrome

BZs are thought to exert their anxiolytic effect by enhancing GABA neurotransmission in the central nervous system. These compounds behave like allosteric agonist modulators, acting at a specific recognition site (rBZ) located in the GABA-A receptor complex (rGABA-A) (Morrow et al., 1988). Two other classes of ligands are known to bind to rBZ: the inverse agonist modulators, which decrease GABAergic transmission, and the antagonist modulators, which prevent binding of agonists and inverse agonists at rBZ. Inverse agonists show an anxiogenic and proconvulsant effect, while antagonist modulators have little or no intrinsic activity in physiological conditions (Haefely, 1990).

The molecular mechanisms responsible for development of BZ tolerance, dependence and withdrawal syndrome are not known (Nutt, 1990). To date, pharmacological, biochemical and electrophysiological studies do not provide an homogenous pattern of modifications of GABAergic transmission during chronic BZ treatment and/or during the withdrawal state. There is no general agreement between studies about this issue. Authors have found that chronic BZ treatment may result in a down-regulation of rBZ (Gallager et al., 1984), in a down-regulation of rGABA-A (Concas et al., 1984; Little et al., 1987; Miller, 1991), or in a long-lasting impairment of allosteric modulation system (Gonsalves and Gallager, 1987; Gallager and Wilson, 1988; Hu and Ticku, 1994), or in no alteration at all (Gallager et al., 1984; Wilson et al., 1987; Stephens et al., 1988; Gallager et al., 1989). The pharmacological profile of BZs seems to affect their liability to induce dependence on chronic administration (Schoch et al., 1993). In fact, neurochemical studies have showed that partial and receptor subtype 1-selective agonists induce a less severe GABAergic transmission dysfunction (Schoch et al., 1993) than full, non-selective agonists.

Animal studies have also shown that concurrent administration of PK 11195, a peripheral site benzodiazepine antagonist, attenuates discontinuation effects of BZs, suggesting a common role of the central and peripheral benzodiazepine receptor during withdrawal (Byrnes et al., 1993; Martinez et al., 1992).

An increase in Ca^{++} flux and 5-HT release from the hippocampus, during benzodiazepine withdrawal has also been observed (File and Andrews, 1993). In this perspective File and Andrews showed that the calcium channel antagonist verapamil prevented withdrawal response in rats treated with diazepam chronically (File and Andrews, 1993). The same effect was obtained by the GABA-B agonist baclofen and

the 5-HT₃ receptor antagonist zacopride (File and Andrews, 1993).

Little (1988) suggested that BZ chronic receptorial stimulation induces a shift in the allosteric modulation of rBZ. Several studies (Nutt, 1986; Little et al., 1987a, and 1987b; Little et al., 1988) confirmed this hypothesis showing reduced efficacy of agonists, increased efficacy of inverse agonists, and the occurrence of a partial inverse agonist activity for antagonists. Such a withdrawal-shift may dramatically increase the capacity of an hypothetical endogenous inverse agonist to inhibit GABAergic transmission. However, despite many promising data, there is no clear evidence of the existence of endogenous inverse agonist in human brain. Such a withdrawal-shift in receptor modulation, resulting in a reduction of inhibitory efficacy of GABAergic transmission, may be a biochemical explanation of the clinical manifestations of the withdrawal syndrome.

Tolerance

The development of tolerance to the sedative and psychomotor effects of BZs is well documented (Greenblatt and Shader, 1978; Fabre et al., 1981; Hollister, 1981; Aranko et al., 1983; Busto et al., 1986; Lucki et al., 1986; Haefely et al., 1990; Gorenstein et al., 1994), but there are conflicting reports about the development of tolerance to the anxiolytic and memory effects (Gorenstein et al., 1994).

Even though tolerance may develop to the sedative effect after approximately two to four weeks (Rickels et al., 1990), patients continue taking BZs mainly to avoid rebound insomnia and withdrawal symptoms.

Tolerance to the sedative and psychomotor effects does not usually lead to significant dosage increases over time or to high-dose abuse (Balmer et al., 1981; Garvey and Tollefson, 1986). On the contrary, patients often decrease their doses, especially those patients affected by panic disorder (Sheehan, 1987; Burrows et al., 1990), who need high doses of BZs in the early phases of the treatment.

Tolerance to BZ is receptor related and is not due to pharmacokinetic changes (Christensen, 1973; File, 1982; Crawley et al., 1987; Haigh and Feeley, 1988). The extensively documented heterogeneity in the expression of BZ receptor subtypes (for review see Olsen and Tobin, 1990) may explain the lack of uniformity of the nervous system's response to chronic treatment with different compounds acting via the GABA-A receptor complex (Haefely et al., 1990). New drugs such as imidazopyridines (Bassi et al., 1989; Sauvanet et al., 1988), cyclopyrrolones (Morishita et al., 1987; Piot et al., 1990) and the anxiolytic beta-carbolines (Krause et al., 1991) seem to induce less or no tolerance (Miller et al., 1990).

Clinical Features of BZ Withdrawal Syndrome

Withdrawal symptoms

Although the phenomenon of BZ withdrawal syndrome is generally accepted, controversy remains regarding its incidence, severity and the type of symptoms experienced. The reported incidence range from 40% to 100% of the chronic users (Rickels et al., 1988, and 1990; Schweizer et al., 1990).

This wide variability can be explained by methodological issues such as differences in the definition criteria for withdrawal syndrome, selection of subjects, and length of observation period.

BZ withdrawal symptoms have been singled out and specified in the context of a well-defined syndrome with a predictable onset, time course and duration (Busto et al., 1986; Royal College of Psychiatrists, 1988; American Psychiatric Association, 1990; Lader, 1990; Rickels et al., 1990; Schweizer et al., 1990; Petturson and Lader, 1991). Psychic, physical and perceptual symptoms can be observed, and these manifestations can be suppressed by resuming BZ. Anxiety, insomnia, restlessness, agitation, irritability, muscle tension, and tremor represent the most common symptoms. Nausea, coryza, diaphoresis, lethargy, increased sensitivity to light, touch, sound and smell, metallic taste, aches, pains, blurred vision, depression, nightmares, hyperreflexia, ataxia are less frequent. Severe clinical features such as psychosis, seizures, persistent tinnitus, confusion, paranoid delusions, and hallucinations are uncommon and usually appear after abrupt discontinuation of high doses, high-potency, short-acting BZs (American Psychiatric Association, 1990; Lader, 1990, and 1991). Nevertheless, these severe features do occur in polydrug abusers, in alcoholic patients and in older patients (Noyes et al., 1988; American Psychiatric Association, 1990; Lader, 1990; Petturson and Lader, 1991).

The available literature reports a wide variability in BZ withdrawal symptoms, due to drug factors and patient characteristics, which influence the clinical presentation of the syndrome. Among the drug factors, length of use, doses and rate of discontinuation appear to be the most important. A gradual tapering reduces the contribution to withdrawal severity of other drug factors such as BZ daily dose, half-life, and potency (Schweizer et al., 1990; Nutt, 1990; Lader, 1991). Short-acting BZs induce dependence more readily than long-acting ones and their abrupt discontinuation results in more severe symptoms (Lader, 1990; Rickels et al., 1990; Schweizer et al., 1990; Greenblatt et al., 1990). There are no major qualitative differences in withdrawal symptomatology between long half-life and short half-life BZs, but some authors report a higher frequency of perceptual symptoms and tinnitus after abrupt discontinuation of short half-life compounds (Rickels et al., 1990). Daily dose represents an important factor which influences the severity of symptomatology. More severe symptoms such as psychosis, seizures, persistent tinnitus, confusion, paranoid delusions, hallucinations follow abrupt discontinuation of high doses (American Psychiatric Association, 1990; Lader, 1990, and 1991).

Another relevant drug factor is the BDZ potency. There is the clinical impression that high potency compounds induce dependence more frequently than low potency ones (American Psychiatric Association, 1990; Lader, 1991); however, reliable data on this issue are still lacking.

The minimum time after which clinically significant withdrawal symptoms develop is not well established, but clinical studies suggest that just three to six weeks of treatment with therapeutic doses can induce a mild withdrawal syndrome in some patients (Fontaine et al., 1984; Power et al., 1985; Pecknold et al., 1988). However, a period of time ranging from four months to one year seems to represent the duration threshold

for developing a meaningful dependence with therapeutic doses.

Patient factors which are thought to influence the clinical presentation of withdrawal symptomatology are the presence of psychiatric comorbidity, personality disorder, organic brain damage, and polysubstance abuse. Some physiological differences such as age and sex may represent adjunctive factors.

On discontinuing BZs, patients may present rebound as severe as the original symptoms or relapse in the pre-existing disorder in addition to abstinence syndrome (Mellinger et al., 1984; American Psychiatric Association, 1990; Lader, 1990; Greenblatt et al., 1990). The major problem in differentiating these phenomena is that the symptoms of the BZ withdrawal syndrome closely resemble those for which the drug was taken in the first place, mainly anxiety and insomnia. Apart from seizures and delirium, there are few withdrawal symptoms that do not also occur in anxiety disorders or in healthy subjects. Moreover, symptoms considered specific of withdrawal syndrome, such as perceptual or motor problems, may be experienced by tranquilizer-free subjects suffering from anxiety. Early worsening of symptoms may be sign of rebound and withdrawal, and there is a considerable overlap between them. Both rebound and withdrawal symptoms probably reflect an acute expression of new changes induced by the drug at receptor level. A delayed occurrence of symptoms and their persistence over time are more likely to represent a sign of return of the original disorder.

The presence of a particular mental disorder can interfere in several ways with the onset, course and severity of withdrawal-related phenomena. The relationships between withdrawal phenomena and different underlying psychopathologic conditions are still not adequately explored and require further attention.

Old age appears to be an important factor in increasing sensitivity to BZ effects. In the elderly, long-term treatment may be associated with increased toxicity and dependence. The presence in older people of reduced metabolic inactivation and excretion of the drug is a possible explanation of this phenomenon (Power et al., 1985). However, in our clinical experience, toxicity and dependence are also increased by the presence of even minimal brain damage, which may represent a common condition in the elderly.

Onset and time course

The onset and time course of the different symptoms arising during withdrawal appears extremely variable (Noyes et al., 1988; American Psychiatric Association, 1990; Lader, 1990) and drug and patients' factors seem to play a pivotal role in this process (Rickels et al., 1990; Schweizer et al., 1990). The abrupt discontinuation of short-acting BZs results in the rapid onset of symptomatology soon after the end of the treatment, while the abrupt interruption of long-lasting BZ results in a delayed onset.

The withdrawal syndrome of short-acting BZs usually starts after 24 hours, peaks at approximately 96 hours, and returns close to baseline by the third week (Rickels et al., 1990). With long-acting BZs withdrawal starts later, usually after two to

three days, with a peak at approximately six to seven days (Rickels et al., 1990). Some patients experience symptoms up to six months after discontinuation (Tata et al., 1994). It is not clear whether this long-lasting withdrawal is determined by a permanent structural modification of the GABA-A receptor or whether it depends on more complex individual constitutional factors.

Dependence and Withdrawal-Related Phenomena in Mood and Anxiety Disorders

The effects of long-term BZ use and withdrawal there from are not merely pharmacological events, but a complex interweaving of pharmacology with the psychopathology, personality, and the drug metabolism of each patient.

The use, abuse and withdrawal-related phenomena show different patterns of severity and time course in various mental disorders. In spite of the clinical relevance of these aspects, relatively scarce research has been devoted to assessing the contribution of non-drug factors such as personality and baseline psychopathology to BZ withdrawal severity and outcome. A pre-existing mental disorder may determine different attitudes toward the drug use modalities, such as passive dependency and different therapeutic expectancy, which might worsen the perceived withdrawal or even result in pseudo-withdrawal. Moreover, differences in specific neurochemical functional systems related to a particular mental disorder may interfere in a peculiar way with the GABAergic transmission, influencing the clinical features of withdrawal syndrome.

Because of their clinical characteristics and prevalence, anxiety and mood disorders represent diagnostic categories with a high risk of BZ dependence (Rickels et al., 1986). Not all anxious patients tend to develop BZ dependence: the risk is greater for patients affected by panic and generalized anxiety disorders, than for social phobias and obsessive-compulsive disorder (Rickels et al., 1986; Salzman, 1993). The latter two groups show either negligible or little improvement after consumption of BZs and consequently are at low risk for dependence.

The BZ withdrawal syndrome shows special characteristics in patients with panic disorder. During withdrawal, these patients may experience severe anticipatory anxiety, more serious and more frequent attacks as well as an increase of avoidance, which in turn reinforce BZ dependence (Burrows et al., 1990). As pointed out by Otto et al. (1992), panic patients may re-enter a cycle of catastrophic interpretation of symptoms, increased vigilance and fear, and panic. Two studies have investigated the effects of tapering alprazolam discontinuation in panic disorder. Fyer et al. (1987) treated 17 patients with alprazolam for a mean of 29.4 weeks. The treatment responders received a mean of 5.25 mg/day and the nonresponders 6 mg. After treatment, medication was reduced at a rate of 10% of the baseline dose every three days. Fifteen of the 17 patients experienced recurrence of panic attacks or an increase in the frequency above pretreatment baseline, 14 patients experienced at least two new symptoms such as insomnia, tachycardia, dizziness, light-headness, malaise and debility, and six patients failed to complete the study and were treated with imipramine. Pecknold et al. (1988) interrupted the administration of alprazolam in double-blind fashion, after eight weeks of treatment, in 20 patients with panic disorder. During the

period in which alprazolam was withdrawn, 28% of the treated patients and 2% of the placebo group showed a "rebound" of anxious symptomatology accompanied by a partial return of panic attacks. Twenty-one patients (35%) who took alprazolam experienced a transitory withdrawal syndrome, which was mild in 15 cases. In the other six cases (10%) the withdrawal syndrome was severe and characterized by symptoms such as tremor, insomnia, impaired concentration, muscle aching, metallic taste, nausea, motor impairment, increased sensitivity to light, touch, sound and smell, depersonalization, tiredness, paresthesias, hot and cold flashes and blurred vision.

The long-lasting anxious symptomatology of GAD encourages the prolonged use of BZs. These patients usually self-administer anxiolytics because of occasional exacerbation of their symptoms or because drugs are prescribed by the general practitioner. It is likely that in a large proportion of cases this treatment regimen helps in controlling patient anxiety for a long period. However, an increasing number of these subjects are referred to a specialist for the problem of BZ dependence rather than for their baseline anxiety. In these cases, chronic anxiety appears to be worsened by symptoms such as irritability, depression and insomnia, that usually disappear after drug discontinuation.

In our experience, the relationship between BZ dependency and mood disorders is even more complex. Long-term use of BZ seems to induce chronic dysphoric mood, with persistence of anxiety, irritability, difficulty in concentration and memory impairment. The relationship between manic-depressive cycles and the long-term use of BZs is difficult to interpret. During BZ withdrawal we have observed manic switches and the occurrence of mixed states, characterized by anxiety, tension, with psychomotor agitation, depressed mood, insomnia, irritability, hostility, anger and aggressiveness directed towards themselves and others (unpublished data). However, these clinical observations need to be supported by controlled data in large clinical studies.

Clinical and Therapeutical Considerations

As suggested by Lader (1990), the evaluation of risk-benefit ratio in prescribing BZs should be assessed in relation to clinical practice and should not be exclusively based on data derived from the more artificial conditions of the controlled trials. In the last few years an increasing number of patients have referred themselves to psychiatric services for BZ dependence and are aware of the difficulties arising from drug discontinuation. Among patients with anxiety and mood disorders interepisodic chronicity and residual symptoms often appear to be related to inappropriate long-term use of BZs. These phenomena are usually relieved by drug discontinuation and, after a period of exacerbation related to withdrawal, the mood conditions clear up. Recent studies seem to show that chronic BZ users, who succeed in terminating drug administration for at least five weeks, significantly lowered their levels of anxiety (Rickels et al., 1990).

Drowsiness and sedation, the most common side effects of BZs at the beginning of treatment, especially with high doses of high potency BZ (American Psychiatric Association, 1990; Lader, 1990, 1991; Nutt, 1990), do not present a problem for

most patients. These side effects quickly disappear because of the rapid occurrence of tolerance. On the other hand, anterograde amnesia, irritability, anger, hostility, depression and the impulse dyscontrol with high suicidal risk are clinically relevant findings in a well-defined number of long-term users with mood and anxiety disorders. In spite of this, these symptoms are often interpreted as an exacerbation or as a natural evolution of previous disorders and the chronic use of sedatives is overlooked. The amount of patients suffering from BZ misuse-related problems is difficult to determine, since research in this field is lacking or is conducted in specialist contexts mainly concerned with the care of chronic and resistant conditions. A large number of individuals who take low doses of BZ continuously for decades without problems may be easily found outside the psychiatric setting (American Psychiatric Association, 1990). Most general practitioners and some psychiatrists base their long-term BZ prescriptions on the experience of subjects who have successfully achieved substantial relief from their anxiety or insomnia with low doses of BZs taken for several years.

Unfortunately, the main focus of clinical research into long-term use of BZs has been on identifying and characterizing withdrawal syndrome, and little attention has been attracted by those patients showing marked worsening of their mood and/or anxiety disorder during such treatment. In our experience, such events may be associated with recurrent mood disorders, panic disorders, or comorbidity conditions.

Further attention should be focused on subjects in whom BZ tolerance, dependence and withdrawal may represent an adjunctive risk factor favoring the onset of a new disorder. In our experience it is not unusual for BZ-dependent patients who have taken these drugs for many years for insomnia or generalized anxiety to exhibit onset of mixed states, depressive episodes or panic attacks after abrupt drug discontinuation.

Physical dependence should be treated by gradual tapering of the BZs in order to attenuate drug factors which contribute to the severity of the withdrawal (Rickels et al., 1990; Schweizer et al., 1990). Cognitive-behavioral interventions are also crucial to ameliorate discontinuation-associated difficulties. Physical examination, as well as accurate evaluation of the social and interpersonal context, should represent a preliminary step. The underlying psychopathology and patient reliability and compliance should be considered in the choice of treatment setting. Since most patients are treated as outpatients, a strong support system is required. Relatives should be adequately informed and involved in the planning of treatment. The medical staff should provide continuous assistance and a doctor should be always available by telephone.

When a short half-life BZ has been utilized, it is preferable to switch the patient to a compound with long half-life to allow gradual discontinuation because of the slower clearance (Noyes et al., 1988; American Psychiatric Association, 1990; Lader, 1990; Burrows et al., 1990; Smith and Landry, 1990). A tapering schedule should be set up and then modified according to an accurate and frequent evaluation of the clinical features. Usually the rate of discontinuation is higher in the initial stages of tapering than in the final ones, as the majority of the withdrawal symptoms occur in the last half of tapering (Rickels et al., 1990; Schweizer et al., 1990).

The length of time needed for the drug tapering procedure is not predictable, and may range from a few weeks to several months, depending on baseline dose, duration of use, type of drug, the patient's physical health, and concomitant psychopathology. In some cases a period of hospitalization may be appropriate if severe complications appear during withdrawal, i.e., worsening of panic, depression with suicidal ideation, mixed and confusional states.

Several pharmacological treatments have been tried in order to alleviate BZ withdrawal syndrome, but none have proved particularly effective (see also Roy-Byrne et al., 1993, for a review). Several studies have shown weak efficacy of beta-blockers (Tyrer et al., 1981), α_2 -agonists (Goodman et al., 1986) and buspirone (Schweizer and Rickels, 1986) in the treatment of withdrawal symptoms. Some reports have indicated the usefulness of carbamazepine (Schweitzer et al., 1991; Neppe and Sindorf, 1991; Swantek et al., 1991) administered in doses ranging from 200 to 600 mg/day. In particular, Schweitzer et al. (1991), in a controlled study of 40 patients with a history of long-term daily BZ therapy, observed that five weeks after drug tapering, significantly more patients who had received carbamazepine than placebo remained drug-free, despite the fact that no statistically significant differences in withdrawal severity could be demonstrated. In our experience low doses of sedative tricyclic antidepressants such as amitriptyline and trimipramine represent a useful tool in lowering anxiety levels and in alleviating insomnia. Rickels et al. (1991) have shown a significant effect of imipramine (25–225 mg/day) in relieving withdrawal symptoms in patients with panic disorder and generalized anxiety disorder.

To detoxify patients with BZs in a poly-drug combination, a proposed protocol is substituting a long-acting barbiturate such as phenobarbitone, followed by its gradual tapering (DuPont, 1990; Lader, 1990; Smith and Landry, 1990).

New drugs such as imidazopyridines (Bassi et al., 1989; Sauvaget et al., 1988), cyclopyrrolones (Morishita et al., 1987; Piot et al., 1990; Lader et al., 1993), benzodiazepines (Rickels et al., 1991), imidazobenzodiazepines (Tricklebank et al., 1990), imidazo(1–2)pyrimidines (Gardner et al., 1987a and 1987b), the anxiolytic beta-carbolines (Krause et al., 1991; Emmett-Oglesby et al., 1993), and quinolizinones (Jenk et al., 1992) seem to have a more selective action than traditional BZs. In addition, they seem to induce fewer side-effects such as oversedation and memory disturbances. Some of these drugs are members of the class of compounds known as partial agonists of benzodiazepine receptors, which display high affinity for the rBZ, and lower intrinsic activity than conventional compounds (Gardner et al., 1987b; Haefely et al., 1990). Long-term use of these partial agonists seems to decrease tolerance phenomena and the risk of dependence (Sellers et al., 1991). However, their value in the prevention and treatment of BZ withdrawal phenomena, although promising, has not yet been fully demonstrated.

Conclusions

In the substance abuse terminology, addiction and physical dependence represent two different concepts. These terms, although used interchangeably, are not synonymous. Addiction refers to a chronic compulsive pattern of drug use, in a manner

that has detrimental consequences for the patient or his social environment. The patient craves the drug and has difficulty stopping. Other aspects of addiction are represented by a loss of control over drug use by a consistent pattern of overuse. Abuse and addiction to BZs are almost exclusively limited to people with history of alcohol-sedative abuse and/or multiple drug abuse, and require specific therapeutic programs in chemical dependence units.

Physical dependence is a state of physiological adaptation with biochemical, physiological and behavioral disruptions. It is usually accompanied by tolerance to the effects of the drug and withdrawal symptoms. The main problem with long-term use of therapeutic doses of BZ is physical dependence with related withdrawal symptoms. In fact, all the studies on BZs show that addiction is not a major problem, and a loss of control over the use of these drugs is an exceptional event among people treated chronically for insomnia, anxiety or mood disorders. Patients who receive prescriptions for BZs tend to decrease their intake over time, despite a loss of efficacy in a substantial proportion of cases (American Psychiatric Association, 1990; Woods et al., 1987; Cole and Chiarello, 1990).

In prescribing and in taking BZs, physicians and patients should be aware that any individual taking these drugs for several months is going to present withdrawal phenomena if the treatment is discontinued abruptly. Withdrawal phenomena can also occur during long-term use of short half-life compounds, especially when utilized as hypnotics.

In conclusion, even if BZs still represent a powerful treatment for several psychopathological conditions accompanied by acute anxiety and agitation, doubts about their long-term use in chronic and recurrent mental disorders have arisen. In addition to dependence and withdrawal phenomena, the presence of chronic subtle toxicity and the interference with underlying psychopathology appears to suggest that a more careful evaluation of the risk-benefit ratio in the long-term administration of BZs is needed.

References

- American Psychiatric Association: Benzodiazepine dependence, toxicity, and abuse. A task force reports of the American Psychiatric Association. American Psychiatric Association, Washington, D.C., 1990
- Aranko, K., M. J. Mattila, T. Seppala: Development of tolerance and cross-tolerance to the psychomotor actions of lorazepam and diazepam in man. *Br. J. Clin. Pharmacol.* 15 (1983) 542–552
- Ayd, F. J.: Benzodiazepine dependence and withdrawal. *J. Psychoact. Drugs* 15 (1983) 67
- Balmer, R., R. Battegay, R. von Marchall: Long-term treatment with diazepam: investigation of consumption habits and interaction between psychotherapy and psychopharmacotherapy: a prospective study. *Pharmacopsychiatry* 16 (1981) 221–234
- Balter, M. B., D. I. Manheimer, G. D. Mellinger, E. H. Uhlenhuth: A crossnational comparison of antianxiety/sedative drug use. *Curr. Med. Res. Opin.* 8 (1984) 5–20
- Bassi, S., M. G. Albizzati, C. Ferrarese, L. Frattola, B. Cesana, R. Piolti, A. Farolfi: Alpidem, a novel anxiolytic drug. A double-blind, placebo-controlled study in anxious outpatients. *Clinical Neuropharmacology* 12 (1989) 67–74
- Burrows, G. D., T. R. Norman, F. K. Judd, P. F. Marriott.: Short-acting vs long-acting benzodiazepine discontinuation effects in panic disorders. *J. Psychiatric Res. (Suppl.)* 2 (1990) 65–72
- Busto, U., E. M. Sellers, C. A. Naranjo et al: Withdrawal reaction after long term therapeutic use of benzodiazepines. *New Engl. J. Med.* 315 (1986) 854–859
- Byrnes, J. J., L. G. Miller, K. Perkins, D. J. Greenblatt, R. I. Shader: Chronic benzodiazepine administration XI: concurrent administration of PK11195 attenuates lorazepam discontinuation effects. *Neuropsychopharmacology* 8 (1993) 267–273
- Christensen, J. D.: Tolerance development with chlozepoxide in relation to the plasma level of parent compound and its main metabolites in mice. *Acta Pharmacologica et Toxicologica* 33 (1973) 262–272
- Cole, J. O., R. J. Chiarello: The benzodiazepine as drug of abuse. *J. Psychiat. Res.* 24 (1990) 135–144
- Concas, A., M. Serra, M. Salis, V. Nurchi, G. Crisponi, G. Biggio: Evidence for an involvement of GABA receptors in the mediation of the proconvulsant action of ethyl-beta-carboline-3-carboxylate. *Neuropharmacol.* 23 (1984) 323–326
- Crawley, J. N., P. J. Marangos, J. Stivers: Chronic clonazepam administration induces benzodiazepine receptors subsensitivity. *Neuropharmacology* 92 (1987) 358–364
- DuPont, R. L.: A practical approach to benzodiazepine discontinuation. *J. Psych. Res.* 24 (1990) 81–90
- Emmett-Oglesby, M. W., D. A. Lytle, S. A. English: Abecarnil used to treat benzodiazepine withdrawal. *Psychopharmacol. Ser.* 11 (1993) 121–131
- Fabre, L. F., D. M. McLemond, A. G. Stephens: Comparison of the therapeutic effect, tolerance, and safety of ketazolam and diazepam administered for six months to outpatients with chronic anxiety neurosis. *J. Int. Med. Res.* 9 (1981) 191–198
- File, S. E., N. Andrews: Benzodiazepine withdrawal: behavioral pharmacology and neurochemical changes. *Biochem. Soc. Symp.* 59 (1993) 97–106
- File, S. E.: Recovery from lorazepam tolerance and the effect of a benzodiazepine antagonist (RO 15–1788) on the development of tolerance. *Psychopharmacology* 77 (1982) 284–288
- Fontaine, R., G. Chominard, L. Annable: Rebound anxiety in anxious patients after abrupt withdrawal of benzodiazepines treatment. *Am. J. Psychiatry* 141 (1984) 848–852
- Fryer, A. J., M. R. Liebowitz, J. M. Gorman: Discontinuation of alprazolam treatment in panic patients. *Am. J. Psychiatry* 144 (1987) 303–308
- Gallager, D. W., C. Heninger, M. A. Wilson: Chronic BDZ agonist exposure and its consequences for GABA-BDZ interactions. In: Allosteric modulation of amino acid receptors: therapeutic implications. Barnard, E. A. and E. Costa (ed.), Raven Press, New York (1989) 91–108
- Gallager, D. W., J. M. Lakoski, S. F. Gonsalves, S. L. Rauch: Chronic benzodiazepine treatment decreases postsynaptic GABA sensitivity. *Nature* 308 (1984) 74–77
- Gallager, D. W., M. A. Wilson: Chronic BDZ agonist exposure: comparison of electrophysiological changes by brain region and BDZ receptor ligand. In: Chloride channels and their modulation by neurotransmitters and drugs. Biggio, G. and E. Costa (ed.), Raven Press, New York (1988) 325–336
- Gardner, C. R., R. Deacon, G. Mann, P. Budhram, A. P. Guy: Agonist and antagonist effects of RU 32514, a new non-benzodiazepine receptor ligand for benzodiazepine receptors. *Br. J. of Pharmac.* 92 (1987a) 655
- Gardner, C. R., R. Deacon, G. Mann, P. Budhram, P. Miller: RU 32698, a new benzodiazepine receptor ligand with anxiolytic but little sedative/myorelaxant properties. *Br. J. of Pharmac.* 92 (1987b) 537

- Garvey, M. J., G. D. Tollefson: Prevalence of misuse of prescribed benzodiazepines in patients with primary anxiety disorder or major depression. *Am. J. Psychiatry* 143 (1986) 1601–1603
- Gonsalves, S. F., D. W. Gallager: Time course for development of anticonvulsant tolerance. *Brain Res.* 405 (1987) 94–99
- Goodman, W. K., D. S. Charney, L. H. Price, S. W. Woods, Heninger: Ineffectiveness of clonidine in the treatment of the benzodiazepine withdrawal syndrome: report of three cases. *Am. J. of Psychiatry* 143 (1986) 900
- Gorenstein, C., M. A. Bernik, S. Pompeia: Differential acute psychomotor and cognitive effects on diazepam on long-term benzodiazepine users. *Int. Clin. Psychopharmacol.* 9 (1994) 145–153
- Greenblatt, D. J., L. G. Miller, R. I. Shader: Benzodiazepine discontinuation syndromes. *J. Psych. Res.* 24 (1990) 73–79
- Greenblatt, D. J., R. I. Shader: Dependence, tolerance, and addiction to benzodiazepines: clinical and pharmacokinetic considerations. *Drug Metab. Rev.* 8 (1978) 13–28
- Haefely, W.: Pharmacology of partial agonists at the benzodiazepine receptors. In: *Biological Psychiatry*. Racagni, G., N. Brunello, T. Fukuda (ed.), Excerpta Medica, Amsterdam, vol.1 (1991) 705–707
- Haefely, W., J. R. Martin, P. Schoch: Novel anxiolytic that act as partial agonist at benzodiazepine receptors. *Trends Pharmacol. Sci.* 11 (1990) 452–456
- Haigh, J. R. M., M. Feeley: Tolerance to the anticonvulsant effect of benzodiazepine. *Trends in Pharmacologic Sciences* 9 (1988) 361–366
- Hellerstein, D. J., D. M. Flansaa, L. D. Zweben-Howland, L. W. Samstag: A clinical profile of patients affected by a state regulation of benzodiazepine prescriptions. *Hosp. Community Psychiatry* 45 (1994) 362–365
- Hollister, L. E.: Pharmacology and pharmacokinetics of the minor tranquilizers. *Psychiatr. Ann. (Suppl.)* 2 (1981) 26–31
- Hu, X. J., M. K. Ticku: Chronic flurazepam treatment produces decreased efficacy of the benzodiazepine ligands and pentobarbital with gamma-aminobutyric acid-A receptors in cortical neurons. *J. Pharmacol. Exp. Ther.* 270 (1994) 485–490
- Jenk, F., J. L. Moreau, E. P. Bonetti, J. R. Martin, W. E. Haefely: Ro 19-8022, a nonbenzodiazepine partial agonist at benzodiazepine receptors: neuropharmacological profile of a potential anxiolytic. *J. Pharmacol. Exp. Ther.* 262 (1992) 1121–1127
- Kales, A., R. L. Manfredi, A. N. Vgontzas, E. O. Bixler, A. Vela-Bueno, E. C. Fee: Rebound insomnia after only brief and intermittent use of rapidly eliminated benzodiazepines. *Clin. Pharmacol. Ther.* 49 (1991) 468–476
- Kleber, H. D.: The nosology of abuse and dependence. *J. Psych. Res.* 24 (1990) 57–64
- Krause, W., F. Reibmann, W. Schunack, Chr. Schobel: Comparative pharmacokinetics of abecarnil in rat following single and multiple intragastric treatment and continuous administration via the diet. *Drug metabolism and disposition* 19 (1991) 29–35
- Lader, M., I. Farr, S. Morton: A comparison of alpidem and placebo in relieving benzodiazepine withdrawal symptoms. *Int. Clin. Psychopharmacol.* 8 (1993) 31–36
- Lader, M.: Benzodiazepine withdrawal. In: *Handbook of anxiety*. Noyes, R., M. Roth, G. D. Burrows (ed.), Elsevier, Amsterdam, Vol. 4 (1990) 57–71
- Lader, M. H.: Low dose therapeutic benzodiazepine dependence: are there differences between benzodiazepines? In: *Biological Psychiatry*. Racagni, G., N. Brunello, T. Fukuda (ed.), Excerpta Medica, Amsterdam, Vol. 1 (1991) 775–777
- Lader, M. L.: Psychopharmacology of benzodiazepines. *J. Psych. Res.* 44 suppl. 2 (1990) 33–34
- Little, H. J., D. J. Nutt, S. C. Taylor: Selective changes in the in vivo effects of benzodiazepine receptor ligands after chemical kindling with FG 7142. *Neuropharmacol.* 26 (1987) 25–31
- Little, H.: Chronic BDZ treatment increases the effect of the inverse agonists. In: *Chloride channels and their modulation by neurotransmitters and drugs*. Biggio, G. and E. Costa (ed.), Raven Press, New York (1988) 307–323
- Little, H. J., D. J. Nutt, S. C. Taylor: Bidirectional effects of chronic treatment with agonists and inverse agonists at the benzodiazepine receptor. *Brain Res. Bull.* 19 (1987 a) 371–378
- Little, H. J., D. J. Nutt, S. C. Taylor: Kindling and withdrawal changes at the benzodiazepine receptor. *J. Psychopharmacol.* 1 (1987 b) 35–46
- Little, H. J., R. Gale, N. Sellars, D. J. Nutt, S. C. Taylor: Chronic benzodiazepine treatment increases the effects of the inverse agonist FG 7142. *Neuropharmacology* 27 (1988) 383–389
- Lucki, I., K. Rickels, A. M. Geller: Chronic use of benzodiazepines and psychomotor and cognitive test performance. *Psychopharmacology* 89 (1986) 555–558
- Marks, J.: The benzodiazepines, use, overuse, misuse, abuse. MTP Press, Lancaster (1978)
- Marriot, S., P. Tyrer: Benzodiazepine dependence. Avoidance and withdrawal. *Drug Saf.* 9 (1993) 93–103
- Martinez, J. A., M. J. Fargeas, L. Bueno: Physical dependence on diazepam: precipitation of abstinence syndromes by peripheral and central benzodiazepine receptor antagonists. *Pharmacol. Biochem. Behav.* 41 (1992) 461–464
- Mellinger, G. D., M. B. Balter, E. H. Uhlenhuth: Prevalence and correlates of the long-term regular use of anxiolytics. *J.A.M.A.* 251 (1984) 375–379
- Miller, L. G., W. Galpern, M. Lumpkin, J. Heller, D. J. Greenblatt, R. I. Shader: Chronic administration of the benzodiazepine partial agonist Ro 16-6028 does not produce tolerance or receptor alterations. *Clinical Pharmacol. and Therap.* 47 (1990) 135
- Miller, L. G., W. R. Galpern, D. J. Greenblatt, M. Lumpkin, R. I. Shader: Chronic benzodiazepine administration. IV. A partial agonist produces behavioral effects without tolerance or receptors alterations. *The J. of Pharm. and Exp. Therap.* 254 (1990) 33–38
- Miller, L. G.: Chronic benzodiazepine administration: from the patient to the gene. *J. Clin. Pharmacol.* 31 (1991) 492–495
- Morishita, H., K. Kushiku, J. Matsuki, T. Tokunaga, T. Inoue, R. Mori, H. Kawamoto, T. Furukawa: Pharmacological effects of the anti-anxiety compound suriclone and its principal metabolites. *Drug Res.* 37 (1987) 1332–1340
- Morrow, A. L., P. D. Suzdak, S. M. Paul: Benzodiazepine, barbiturate, ethanol, and hypnotic steroid hormone modulation of GABA-mediated chloride ion transport in rat brain synaptosomes. In: *Chloride channels and their modulation by neurotransmitters and drugs*. Biggio, G. and E. Costa (ed.), Raven Press, New York (1988) 247–261
- Neppe, V. M., J. Sindorf: Carbamazepine for high-dose diazepam withdrawal in opiate users. *J. Nerv. Ment. Dis.* 179 (1991) 234–235
- Noyes, R., M. J. Garvey, B. L. Cook, P. J. Perry: Benzodiazepine withdrawal: a review of the evidence. *J. Clin. Psychiatry* 49 (1988) 382–389
- Nutt, D. J.: Benzodiazepine dependence in the clinic: reason for anxiety. *Trends Pharmacol. Sci.* 7 (1986) 457–460
- Nutt, D. J.: Pharmacological mechanisms of benzodiazepine withdrawal. *J. Psych. Res.* 24 (1990) 105–110
- Olsen, R. W., A. J. Tobin: Molecular biology of GABA-A receptors. *The FASEB J.* 4 (1990) 1469–1480
- Otto, M. W., M. H. Pollak, S. Meltzer-Brody, J. F. Rosenbaum: Cognitive-behavioral therapy for benzodiazepine discontinuation in panic disorder patients. *Psychopharmacol. Bull.* 28 (1992) 123–130
- Owen, R. T., P. Tyrer: Benzodiazepine dependence. *Drugs* 25 (1983) 385

- Pecknold, J. C., R. P. Swinson, K. Kuch, C. Lewis: Alprazolam in panic disorder and agoraphobia. Results from a multicenter trial discontinuation effects. *Archives of General Psychiatry* 45 (1988) 429–436
- Petturson, H., M. H. Lader: Withdrawal from long-term benzodiazepine treatment. *Br. Med. J.* 283 (1991) 643–645
- Piot, O., J. Betschart, J. M. Stutzmann, J. C. Blanchard: Cyclopyrrolones, unlike some benzodiazepines, do not induce physical dependence in mice. *Neurosc. Lett.* 117 (1990) 140–143
- Power, K. G., D. W. A. Jerrom, R. J. Simpson, M. Mitchell: Controlled study of withdrawal symptoms and rebound anxiety after six week course of diazepam for generalized anxiety. *Brit. Med. J.* 290 (1985) 1246–1248
- Rickels, K., E. Schweitzer, W. G. Case, D. Greenblatt: Long-term therapeutic use of benzodiazepines. I Effects of abrupt discontinuation. *Arch. Gen. Psychiatry* 47 (1990) 899–907
- Rickels, K., W. G. Case, E. Schweitzer, C. Swanson, R. B. Fridman: Low dose dependence in chronic benzodiazepine users: a preliminary report in 119 patients. *Psychopharmacol.* 22 (1986) 407–415
- Rickels, K., W. G. Case, E. Schweitzer: Management of benzodiazepines discontinuation. In: *Biological Psychiatry*. Racagni, G., N. Brunello, T. Fukuda (ed.), Excerpta Medica, Amsterdam, Vol. 1 (1991) 778–779
- Rickels, K.: Long-term treatment of anxiety and risk of withdrawal: prospective comparison of clorazepate and buspirone. *Arch. Gen. Psychiatry* 45 (1988) 444–450
- Roy-Byrne, P. P., M. D. Sullivan, D. S. Cowley, R. K. Ries: Adjunctive treatment of panic and agoraphobic symptoms: use, dependence, toxicity, abuse. *J. Psychiatr. Res. Suppl.* 1 (1993) 143–153
- Royal College of Psychiatrists: Benzodiazepine and dependence: a College statement. *Bull. R. Coll. Psychiatrists* 12 (1988) 107
- Salzman, C.: Benzodiazepine treatment of panic and agoraphobic symptoms: use, dependence, toxicity, abuse. *J. Psychiatr. Res. Suppl.* 1 (1993) 97–110
- Sauvanet, J. P., S. Z. Langer, P. L. Morselli: Imidazopyridines in sleep disorders: a novel experimental and therapeutic approach. Raven Press, New York (1988)
- Schoch, P., J. L. Moreau, J. R. Martin, W. E. Haefely: Aspects of benzodiazepine receptor structure and function with relevance to drug tolerance and dependence. *Biochem. Soc. Symp.* 59 (1993) 121–134
- Schweitzer, E., K. Rickels, W. G. Case, D. J. Greenblatt: Carbamazepine treatment in patients discontinuing long-term benzodiazepine therapy. Effects on withdrawal severity and outcome. *Arch. Gen. Psychiatry* 48 (1991) 448–452
- Schweitzer, E., K. Rickels, W. G. Case, D. Greenblatt: Long-term therapeutic use of benzodiazepines. II Effect of gradual taper. *Arch. Gen. Psychiatry* 47 (1990) 908–915
- Schweitzer, E., K. Rickels: Failure of buspirone and placebo in relieving benzodiazepine withdrawal symptoms. *Am. J. of Psychiatry* 143 (1986) 1590
- Sellers, E. M., U. Busto, H. C. Kaplan: Clinical abuse of partial and full agonist benzodiazepines. In: *Biological Psychiatry*. Racagni, G., N. Brunello, T. Fukuda (ed.), Excerpta Medica, Amsterdam, Vol. 1 (1991) 709–710
- Sheehan, D.: Benzodiazepines in panic disorders and agoraphobia. *J. Affect. Disord.* 13 (1987) 169–181
- Smith, D. E., M. J. Landry: Benzodiazepine dependency discontinuation: focus on the chemical dependency detoxification setting and benzodiazepine-polidrug abuse. *J. Psych. Res.* 24 (1990) 145–156
- Stephens, D. N., H. H. Schneider, R. Weidmann, L. Zimmermann: Decreased sensitivity to BDZ receptor agonists and increased sensitivity to inverse agonist following chronic treatments: evidence for separate mechanisms. In: *Chloride channels and their modulation by neurotransmitters and drugs*. Biggio, G. and E. Costa (ed.), Raven Press, New York (1988) 337–354
- Swantek, S. S., G. T. Grossberg, V. M. Neppe, W. G. Doubek, T. Martin, J. E. Bender: The use of carbamazepine to treat benzodiazepine withdrawal in a geriatric population. *J. Geriatr. Psychiatry Neurol.* 4 (1991) 106–115
- Tata, P. R., J. Rollings, M. Collins, A. Pickering, R. R. Jacobson: Lack of cognitive recovery following withdrawal from long-term benzodiazepine use. *Psychol. Med.* 24 (1994) 203–213
- Tricklebank, M. D., T. Honoré, S. D. Iversen, J. A. Kemp, A. R. Knight, G. R. Marshall, N. M. J. Rupniak, L. Singh, S. Tye, F. Watjen, E. H. F. Wong: The pharmacological properties of the imidazobenzodiazepine, FG 8205, a novel partial agonist at the benzodiazepine receptors. *Br. J. of Pharmacol.* 101 (1990) 753–761
- Tyrer, R., D. Rutherford, T. Huggett: Benzodiazepine withdrawal symptoms and propranolol. *Lancet* 1 (1981) 520–522
- Wilson, M. A., C. Heninger, D. W. Gallager: Response to various BDZ receptor ligands following chronic diazepam exposure in rats: SN reticulata sensitivity and GABA modification of receptor binding. *Soc. Neurosci. Abst.* 13 (1987) 962
- Woods, J. H., J. L. Katz, G. Winger: Abuse liability of benzodiazepine. *Pharmacological reviews* 39 (1987) 251–419

Giulio Perugi, M. D.

Institute of Psychiatry
School of Medicine
University of Pisa
Via Roma 67
I-56100 University of Pisa
Italy