BENZODIAZEPINE TREATMENT FOR ALCOHOL-DEPENDENT PATIENTS

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Abstract — Benzodiazepines (BZDs) are the preferred pharmacological agents for treatment of acute alcohol withdrawal. Treatment with BZDs can be administered on an out-patient basis for subjects experiencing mild to moderate withdrawal and on an in-patient basis for the most severe forms of withdrawal. The efficacy of BZDs for long-term treatment of alcoholism has been more controversial. Controlled studies indicate that BZD treatment does not improve abstinence rate. Most reviews of drug treatment of alcoholism conclude that routine use of BZDs is not indicated on a long-term basis. However, the clinical reality is that many alcoholics are treated by BZDs during detoxification and then continue to receive them for the treatment of anxiety disorders or insomnia, often secondary to alcohol dependence. After a review of the biological properties of BZDs related to their therapeutic issues, this review discusses the major indications for BZD treatment of alcoholism. BZDs are first prescribed to prevent and treat symptoms of alcohol withdrawal. Indication of BZD administration during alcohol withdrawal and criteria of choice of an agent according to its half-life or its route of administration are discussed. The different protocols of BZD treatment during withdrawal are considered (e.g. loading techniques, symptom-triggered therapy). The use of BZDs in the treatment of anxiety associated with alcohol dependence is examined. Among unwanted effects, risk of abuse, memory impairment, confusion, and delirium are described. Finally, practical guidelines for the use of BZDs in the treatment of alcoholism are proposed.

INTRODUCTION

Benzodiazepines (BZDs) are a group of chemical compounds that were first synthesized in the 1880s and shown to have tranquilizing actions in the 1950s (Nutt et al., 1989). In 1960, when chlordiazepoxide, the first BZD, was introduced in the United States (Ciraulo et al., 1988), several highly favourable reviews were published on its efficacy in treating the symptoms observed during alcohol detoxification. Despite the availability of other drugs (i.e. β-blockers, clonidine), BZDs remain the preferred pharmacological agents for the treatment of acute alcohol withdrawal (Fuller and Gordis, 1994). Treatment with BZDs can be administered on an out-patient basis for subjects experiencing mild to moderate withdrawal and on an in-patient basis for the most severe forms of withdrawal. The majority of patients can be treated safely on an ambulatory basis (Shaw, 1995).

The efficacy of BZDs for long-term treatment of alcoholism has been more controversial. The earlier studies were optimistic, but later controlled studies indicated that BZD treatment did not improve abstinence rate. Most reviews of drug treatment of alcoholism conclude that routine use of BZDs is not indicated on a long-term basis. However, the clinical reality is that many alcoholics are treated with BZDs during detoxification and then continue to receive them for the treatment of anxiety disorders or insomnia which are often secondary to alcohol dependence.

General practitioners and psychiatrists are often in the position of evaluating the risks and benefits
of BZD use in the post-withdrawal phase of treatment. The possible inherent danger of prescribing a potential drug of abuse to subjects with a history of abusing one substance should be considered in the light of yet other liabilities, e.g. not using an anxiolytic agent when it could be helpful, a potential increase in quality of life, and adherence to treatment.

This review discusses both biological issues related to the effects of BZDs and their actions on withdrawal symptoms and on anxiety associated with alcohol abuse or dependence, and therapeutic issues concerning their indication in the treatment of alcohol withdrawal and in the long-term treatment of alcohol dependence.

**BIOLOGICAL ISSUES**

BZDs and ethanol share several biological modes of action. These similarities explain how and why ethanol antagonizes symptoms of withdrawal: by acting upon γ-aminobutyric acid (GABA) receptors, noradrenergic systems, activation of the hypothalamic–pituitary–adrenal (HPA) axis, and kindling phenomenon (Table 1). Ethanol and BZDs also undergo pharmacokinetic interactions which influence their actions. The following are brief accounts of all these aspects.

**GABA**

*Effects of ethanol.* Ethanol acts, at least in part, at the BZD/GABA–chloride receptor complex (Tabakoff and Hoffman, 1992). Chronic ethanol administration increases the binding of [3H]Ro-15-4513 (a partial inverse agonist of the BZD receptor) in the cerebral cortex and cerebellum of rats. Using polyclonal antibodies, Mhatre and Ticku (1993) have shown that chronic ethanol ingestion also produces a decrease in the expression of GABA_A receptor subunit. This effect may underlie the molecular basis for alcohol tolerance and withdrawal.

During alcohol withdrawal, the GABA receptor complex becomes acutely devoid of ethanol's enhancing effect on chloride flux, so there is a subsequent decrease in GABA functioning. The alcohol-withdrawal syndrome is characterized by reduced coupling of the GABA_A BZD receptor to the chloride channel (Adinoff, 1994). As GABA is the major inhibitory neurotransmitter in the central nervous system (CNS), this reduction of coupling results in disinhibition. A reduction in GABA-induced chloride flux has been associated with seizures, anxiety, and anxiety-related symptoms such as tremors, diaphoresis, and tachycardia.

*Actions of BZDs.* BZDs may ameliorate the symptoms of alcohol withdrawal by substituting the GABA-enhancing effects of ethanol. BZDs have been demonstrated to decrease the signs of ethanol withdrawal through the GABA/BZD receptor, in that diazepam’s ameliorating effects on withdrawal-associated tremor in rats is antagonized by Ro-15-1788 (Nutt et al., 1989). BZDs also act through the increase in the affinity of GABA to the GABA_A receptor.

**Noradrenergic activity**

*Effects of ethanol.* Acute ingestion of alcohol increases locus coeruleus activity. Locus coeruleus neurons are activated and noradrenaline activity is increased (Valentino and Aston-Jones, 1995). Lactate infusion, which stimulates the

<p>| Table 1. Biological effects of benzodiazepines (BZDs) |
|----------------------------------------|----------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Effect of ethanol</strong></th>
<th><strong>Action of BZDs</strong></th>
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<tbody>
<tr>
<td>GABA</td>
<td>Stimulation of GABA activity</td>
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<tr>
<td>Withdrawal decreases GABA functioning</td>
<td>Increase of affinity of GABA to GABA_A receptor</td>
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<td>Noradrenaline</td>
<td>Blockade of noradrenergic hyperactivity</td>
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<td>Overactivity during alcohol ingestion and withdrawal</td>
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<tr>
<td>Stimulation during withdrawal</td>
<td>Decrease of withdrawal-induced corticosteroid increase</td>
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<tr>
<td>Increase in corticosteroid levels</td>
<td>Blockade of withdrawal reactions and decreased probability of seizure activity</td>
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<tr>
<td>Repeated withdrawals increase neuronal responsivity</td>
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noradrenergic system, triggers anxiety in patients presenting with panic disorder and in alcoholics (John and Miller, 1997).

During withdrawal, signs of sympathetic nervous system overactivity, such as diaphoresis, tachycardia, hypertension, and tremor indicate increased activity of the noradrenergic system (Nutt et al., 1989). This increase has been substantiated by reports of elevated levels of cerebrospinal fluid noradrenaline and its central metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in alcoholics during withdrawal (Hawley et al., 1985). In addition, the β-adrenoceptor blocker propranolol has been shown to be effective in the treatment of anxiety and irritability induced by the alcohol-withdrawal syndrome (Bailly et al., 1992).

**Actions of benzodiazepines.** BZDs interact with noradrenergic neuronal functioning and block withdrawal-induced alterations of noradrenaline and MHPG. Low doses of diazepam have been reported to decrease single-unit activity in the locus coeruleus, which contains approximately 50% of the noradrenergic cell bodies in the CNS. Clinically, acute diazepam pretreatment antagonizes anxiety produced by yohimbine, an α2-adrenoceptor antagonist. BZDs may therefore ameliorate symptoms of ethanol withdrawal such as diaphoresis, tachycardia, anxiety, and tremor through an interaction with noradrenergic neuronal function, resulting in a decrease in noradrenergic activity.

**HPA axis**

**Effects of ethanol.** HPA axis activation (Nutt et al., 1989) has been reported during ethanol withdrawal in human studies. Elevations in corticosteroid levels have been associated with alterations in mood and cognitive impairment. Symptoms of ethanol withdrawal such as fatigue, weakness, hypertension, mental confusion, and depression may be partially related to the excessive glucocorticoid levels observed during withdrawal.

**Actions of BZDs.** BZDs decrease stress-induced elevation of adrenocorticotropic hormone and corticosteroids. This effect is antagonized by the BZD antagonist Ro-15-1788. BZDs may also reduce the severity of ethanol withdrawal by blocking the associated HPA axis activation.

**Kindling effect**

**Effects of ethanol.** The repeated experiences of untreated ethanol withdrawals may produce a 'kindling' effect over time (Ballenger and Post, 1978). Kindling is defined as 'the progressive increase in neuronal responsivity produced by spaced and repeated epileptogenic stimulation'. This mechanism suggests that each additional episode of withdrawal elicits increasingly severe symptoms. Many anxiety crises in alcoholics may be directly induced by kindling related to repeated withdrawals (Brady and Lydiard, 1993).

**Actions of BZDs.** Ulrichsen et al. (1995) studied the effects of diazepam on kindling activity by exposing rats to 13 episodes of alcohol intoxication and withdrawal. In diazepam-treated animals, the withdrawal reactions were blocked. During episodes 10 to 13 of alcohol intoxication and withdrawal, no animal received diazepam. The probability of seizure activity was 0.239 in the control group and 0.066 in animals that had been previously treated with diazepam (difference statistically significant at $P < 0.05$). The increased vulnerability to convulsive behaviour induced by repeated withdrawals was thus prevented by diazepam treatment. This animal laboratory experiment led the authors to suggest that diazepam administration may prevent the progression of kindled alcohol withdrawal behaviour. No study in alcohol-dependent patients has confirmed this hypothesis.

**Pharmacokinetic properties of BZDs and interaction with ethanol**

**BZD metabolism.** All the BZDs are metabolized mainly by the liver. The process of elimination varies; it can occur by oxidation or conjugation. Chlordiazepoxide and diazepam undergo oxidation and the active metabolites formed have long half-lives. Lorazepam primarily undergoes glucuronidation to an inactive form which is rapidly eliminated.

**Interactions between BZDs and alcohol.** According to Castaneda et al. (1996), who reviewed studies concerning the interactions between BZDs and alcohol, brain BZD levels are affected differently by alcohol ingestion. Ethanol minimally influences blood levels of triazolam, yet it significantly decreases its brain concentration. Brain concentration of diazepam is slightly in-
increased, whereas that of chlordiazepoxide is hardly altered, by alcohol.

Van Steveninck et al. (1996) investigated at a cognitive level the pharmacokinetic and pharmacodynamic interactions between diazepam (10 mg) and alcohol. Diazepam plus alcohol often caused subjects to fall asleep during adaptative tracking and eye movements. There was a clear effect of diazepam plus alcohol on smooth eye pursuit, whereas diazepam alone or alcohol alone had no apparent effect. The study by the above authors also investigated the pharmacokinetic and pharmacodynamic interactions between diazepam and alcohol at a controlled alcohol concentration. They did show consistent indications for synergistic, supra-additive pharmacological interactions between alcohol and diazepam except for impairment of smooth pursuit eye movement. Alcohol plus diazepam, however, caused large decreases in subjective alertness and in all measures of performance. The effects of diazepam were also compared to those of placebo and of bretazenil, a partial BZD agonist. The following sequence was found for the magnitude of treatment effects: bretazenil > diazepam > alcohol > placebo.

Effects of liver function and age. As stated earlier, the liver is the major organ for BZD metabolism, where BZDs undergo phase I oxidation and progress to phase II glucuronidation. Liver dysfunction affects BZD pharmacokinetics and oxidative metabolism (Bird and Maleka, 1994). Age and liver disease are known (Peppers, 1996) to alter the pharmacological profile of agents that undergo oxidative metabolism (chlordiazepoxide and diazepam). Primarily, the result is an increased half-life and propensity to cause over-sedation. In the elderly, the clearance rate of these agents undergoes at least a 50% decline with a four- to nine-fold increase in terminal elimination half-life, at least a two- to four-fold increase in volume of distribution, decreased plasma protein binding, delayed appearance of metabolites in the bloodstream and a two-fold decrease in non-protein-bound drug clearance. In patients presenting with alcoholic cirrhotic liver disease, a two- to three-fold decrease in diazepam clearance is observed. Other BZDs, not significantly oxidized by the liver (such as oxazepam and lorazepam), should therefore be considered for patients presenting with liver disease. Giving too high doses of BZDs to patients presenting with liver disease could theoretically lead to an excessive accumulation of the drug or metabolites and enhance pharmacodynamic effects and toxicity (Peppers, 1996).

**THERAPEUTIC ISSUES**

**BZDs in the treatment of alcohol withdrawal**

Treatment of the alcohol-withdrawal syndrome is the first step towards the rehabilitation of alcohol-dependent patients. The objectives of treatment should be the relief of suffering, as well as prevention and/or treatment of complications such as seizures, or delirium tremens. Fulfilment of these objectives ensures a smoother transition into a long-term rehabilitation programme. The ideal drug for alcohol withdrawal should have a rapid onset and a long duration of action, a wide margin of safety, a metabolism not dependent on liver function, and absence of abuse potential (Nutt et al., 1989). Various BZDs offer many of these advantages. BZDs have been found effective in: (1) preventing agitation and alcohol-withdrawal seizures; (2) preventing delirium tremens; and (3) as cross-tolerant agents with ethanol. BZDs, owing to their wide margin of safety and low potential to produce physical dependence and tolerance in short-course therapy, are therefore very effective in the treatment of alcohol-withdrawal syndrome. Their indication represents the drugs of choice (Ozdemir et al., 1993). Their widespread use has decreased the occurrence of life-threatening consequences of alcohol withdrawal, such as delirium tremens (Fuller and Gordis, 1994). Following the use of chlordiazepoxide, many other BZDs have been used successfully. Diazepam, lorazepam, oxazepam, alprazolam, and halazepam have been shown to be safe and effective in the treatment of the alcohol-withdrawal syndrome (Peppers, 1996).

**Indications for BZD treatment of alcohol withdrawal**

There is a debate on the systematic indications for BZDs in alcohol withdrawal. According to Nutt et al. (1989), patients with moderate withdrawal require only minimal pharmacological intervention. Other authors stressed that repeated untreated withdrawals, even of mild intensity,
progressively induce a ‘kindling’ process and the severity of withdrawal increases over time (Booth and Blow, 1993). The risk of delirium tremens and of seizure disorders also increases after repeated withdrawals. Edwards (1992) noted that symptoms of withdrawal, like tremor or anxiety, reinforce the alcohol-dependence syndrome and stimulate the urge to drink alcohol.

If the indications for systematic BZD treatment for mild forms of withdrawal are a contentious issue, more severe cases of withdrawal represent a clear indication for the use of BZDs. For these forms of alcohol-withdrawal syndrome, Nutt et al. (1989) recommend the systematic instigation of treatment with BZDs. For those patients presenting severe symptoms of alcohol withdrawal or delirium tremens (confusion, disorientation, motor agitation, tremor), BZDs should be used as soon as possible during the detoxification phase.

A history of significant withdrawal symptoms in the past, multiple previous detoxifications, recent alcohol drinking at high levels (i.e. above 24 drinks on heavy drinking days) predict a risk of a severe withdrawal syndrome and an increased risk of complications. A previous history of withdrawal (Shaw, 1995) more than quadruples the risk of severe withdrawal (32 vs 7.3%) and a history of more than four previous episodes of withdrawal more than triples the risk (59 vs 16.7%). Patients with a history of severe withdrawal syndrome also represent an indication for systematic treatment with BZDs.

Patients especially at risk of seizure disorders must be systematically treated during alcohol withdrawal. Ethanol withdrawal is the most common cause of adult-onset seizure disorder and the risk is increased when patients have a history of seizures. Mayo-Smith (1997) showed that placebo-controlled trials of benzodiazepines confirm a highly significant reduction of seizures (risk reduction of 7.7 seizures per 100 patients treated, \( P = 0.003 \)). In patients presenting with a history of seizures, doses of a BZD should be increased (20 mg diazepam repeated hourly for the next 2 h) (Nutt et al., 1989).

Choice of a BZD in the treatment of alcohol withdrawal

Arguments for preferentially choosing a particular BZD over another depend upon the pharmacological properties of the agent and especially the route of its administration and its pharmacokinetic properties (half-life) (Bird and Makela, 1994). The two main criteria of choice remain the half-life and the route of administration.

Route of administration. The drug should be available parenterally. When patients are agitated or non-compliant, parenteral administration facilitates safe and rapid control of severe forms of alcohol withdrawal. It is also important that an oral form of administration is available as the withdrawal state improves.

Choice of long or short half-life compounds? There is controversy regarding whether a drug with a long half-life is superior to one with an intermediate half-life for treating the alcohol-withdrawal syndrome. Diazepam and chlordiazepoxide have long half-lives, and following oxidation in the liver, produce active metabolites. Other compounds such as lorazepam and oxazepam have intermediate half-lives (10–20 h) and do not produce active metabolites (Shaw, 1995).

Some studies have warned that the risk of sedation is high with long half-life drugs. Most studies, however, have noted that a long half-life is beneficial and provides for a ‘smoother’ (less anxiety) treatment of withdrawal (Bird and Makela, 1994). In choosing a BZD for a patient with alcoholism it is also important (Frances and Borg, 1993) to consider that BZDs with slow onset have less abuse potential. No study, however, has confirmed that BZDs with slow onset or long half-life facilitate the risk of abuse or dependence more than short half-life agents. Medications with short half-lives can, on the other hand, lead to precipitated and too abrupt withdrawal.

According to most studies, diazepam is the drug of choice for the treatment of sustained withdrawal-induced seizures (Romach and Sellers, 1991). Nutt et al. (1989) also consider that diazepam is the BZD of choice, as it has a wide margin of safety and is quickly absorbed when administered per os. The subsequent rapid uptake of diazepam into the brain allows the patient to be evaluated for signs of toxicity prior to the next dose. The effects of diazepam and its metabolite, desmethyldiazepam, persist for relatively long periods of time (the half-lives of diazepam and desmethyldiazepam are 33 and 90 h respectively on average). This permits a withdrawal relatively free of cyclical variations and eliminates the need for additional doses following the initial dose...
regimen. Mayo-Smith (1997) noted that longer-acting agents may be more effective in preventing seizures; they contribute to an overall smoother withdrawal course with fewer breakthrough or rebound symptoms.

Nutt et al. (1989) recommend the use of 25 mg of chlordiazepoxide instead of 10 mg of diazepam. Chlordiazepoxide is less preferable, because of its slower absorption and distribution. According to Frances and Borg (1993), oxazepam is not dependent on liver metabolism, has slow onset, is less reinforcing, and may be the best choice for treating patients with anxiety and alcohol disorders.

**Controlled comparative studies of BZDs**

Comparative studies of BZDs in alcohol withdrawal are rare. They are limited by the following methodological difficulties: (1) the fact that withdrawal manifestations are transient, their severity and time of occurrence being variable from one patient to another; (2) the significant effect on withdrawal symptoms of non-pharmacological interventions like reassurance and general nursing care; and (3) the ethical difficulty of employing a placebo-compared design in patients exposed to significant risk of severe withdrawal complications.

The first BZD found to be successful in the treatment of alcohol-withdrawal syndrome was chlordiazepoxide. Later, all BZDs have proved efficacious, provided that equipotent dosage regimes and administration routes are employed (Ozdemir et al., 1993).

Adinoff (1994) compared alprazolam, clonidine, diazepam, and placebo in the treatment of alcohol withdrawal. Both diazepam and alprazolam were superior to clonidine and placebo. Adinoff (1994) noted that the efficacy of alprazolam is related to its effect on the BZD receptor and not its α-2-receptor agonist properties. This study which involved only a small sample size, used a placebo-controlled design and clearly confirmed the superiority of alprazolam and diazepam to placebo.

Hoey et al. (1994) compared chlordiazepoxide, lorazepam and diazepam in the treatment of withdrawal in alcohol-dependent in-patients. They prospectively studied 50 patients and concluded that long-acting BZDs, such as diazepam and chlordiazepoxide, may provide a more comfortable withdrawal and less interference with cognitive function than lorazepam. One plausible explanation for this is that the extended half-lives of the parent drug and its active metabolites provide smoother control of symptoms. Short-acting agents may induce rebound insomnia and anxiety, even when they are administered for a short period of time. This study, however, did not compare the different classes of BZDs. It has mainly validated a protocol which defines lorazepam as appropriate therapy for patients 60 years of age and older and those with hepatic dysfunction and chlordiazepoxide for all other types of patients.

There is no experimental evidence that any specific BZD is superior in the management of the alcohol-withdrawal syndrome. Published studies do not indicate clearly a preference for one molecule over another.

**Protocols for treatment**

Three protocol treatments have been proposed for alcohol withdrawal: (1) high dosage and tapering after 3 to 7 days; (2) fixed doses and loading technique; and (3) 'symptom-triggered' therapy.

**High dosage and tapering.** Most often (Shaw, 1995), BZDs are administered at high dosages and tapered off over 4–7 or more days in the light of the patient’s response (Table 2). Diazepam, 10–20 mg every 6 h per os may be administered until adequate sedation is achieved. A dose reduction of at least 25% daily is proposed thereafter. This protocol is easy to institute and is often chosen in routine practice. Patient’s needs, however, are extremely variable and the dosage of medication is therefore difficult to predict accurately. In patients with heavy dependence, at least 40 mg of diazepam or 8 mg of lorazepam will be

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Table 2. Protocol for alcohol detoxification using a high dosage procedure

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage</th>
<th>Duration</th>
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<tbody>
<tr>
<td>High dosage and tapering</td>
<td>Diazepam 40 mg or more, lorazepam 8 mg or more</td>
<td>Dose reduction of at least 25% daily thereafter</td>
</tr>
<tr>
<td>In severe cases:</td>
<td>Diazepam 10–20 mg orally hourly until adequate sedation is achieved</td>
<td>Dose reduction of at least 25% daily thereafter</td>
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</table>

Adapted from Shaw (1995).
required for the first day or two of treatment (Table 2).

**Fixed-dose regimen of diazepam or ‘loading technique’**. This mode of administration has been proposed as a protocol for the prescription of long-acting BZDs, such as diazepam or chlordiazepoxide (Ozdemir et al., 1993). The ‘loading dose technique’ takes advantage of the sustained action of the long half-life BZDs. This technique (Bird and Makela, 1994) consists of loading a long half-life BZD by administering it every 1 to 2 h until the patient either shows clinical improvement or experiences sedation.

Nutt et al. (1989) described the diazepam-loading procedure. In this paradigm, diazepam 10 mg, is administered orally every hour until symptoms are suppressed or the patient becomes sedated. Prior to each administration of diazepam, the patient should be evaluated for response and symptoms of BZD toxicity. Co-existing illness should be considered if withdrawal is not sufficiently reduced after six doses. The re-emergence of symptoms should be treated with 20 mg diazepam every 6 h. In addition to the rapid amelioration of withdrawal symptoms, this treatment strategy therefore tends also to decrease drug-seeking behaviour.

Both diazepam and chlordiazepoxide have active metabolites and repeated administration of a constant dose may result in accumulation of the drug in patients with liver disease. Oxazepam (15–60 mg) and lorazepam (1–3 mg) should be administered to such patients every 6 h. Tapering of lorazepam or oxazepam should begin on the second day. Tapering should be accomplished by decreasing the dose, not by increasing the intervals between doses.

Pycha et al. (1993) proposed an i.v. flunitrazepam loading technique in 25 patients presenting with the alcohol-withdrawal syndrome. Their open trial showed that this treatment was efficient and safe. I.v. flunitrazepam led to quick and complete remission of the alcohol-withdrawal syndrome. Patients were awake and oriented after the last dose and they were treated for a mean time of 85 ± 39 h. Pycha et al. (1993) clearly considered their work as preliminary and stressed that this protocol can only be provided in an intensive care unit.

'Symptom-triggered' therapy. This therapy (Saitz et al., 1994) consists of monitoring patients and providing medication only when symptoms of alcohol withdrawal appear. The use of a simple, objective, standardized scale (Clinical Institute Withdrawal Assessment for Alcohol, revised Scale, CIWA) (Table 3) to monitor patients and to guide the administration of medication appears safe and effective. Sullivan et al. (1991) retrospectively assessed the usefulness of this scale, listing 10 symptoms and signs of withdrawal including nausea, tremor, headache, anxiety, agitation, orientation, sweating, and auditory, visual, and tactile disturbances. Usual prescriptions were for diazepam 20 mg orally or chlordiazepoxide 100 mg orally as needed hourly for a CIWA-Ar score of > 10. Nurses scored the patients at hourly intervals in early withdrawal. Drug doses were repeated until the appropriate therapeutic responses (suppression of symptoms of withdrawal) occurred. Total BZD dosage was calculated in terms of mg diazepam equivalents. Subjects treated according to the CIWA scale required less BZD (median dose 50 mg diazepam equivalent compared with 75 mg, \( P = 0.04 \)). Correlation coefficients revealed a closer relationship between the degree of alcohol exposure (as determined by blood-alcohol levels and transaminases) and BZD requirements during withdrawal for the group treated with the aid of the scale.

Saitz et al. (1994) performed a double-blind controlled trial to compare the efficacy of the symptom-triggered regimen with the standard fixed-schedule approach. Subjects in the fixed-schedule group received 400 mg of chlordiazepoxide every 6 h. The doses were not administered if the patient was somnolent or refused the medication. The symptom-triggered group received 25 to 100 mg of chlordiazepoxide hourly when their

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**Table 3. Clinical Institute Withdrawal Assessment for alcohol (CIWA-Ar)**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Score</th>
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<tbody>
<tr>
<td>Nausea and vomiting</td>
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<tr>
<td>Tremor</td>
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<tr>
<td>Paroxysmal sweats</td>
<td></td>
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<tr>
<td>Anxiety</td>
<td></td>
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<tr>
<td>Agitation</td>
<td></td>
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<tr>
<td>Tactile disturbances</td>
<td></td>
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<tr>
<td>Auditory disturbances</td>
<td></td>
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<tr>
<td>Visual disturbances</td>
<td></td>
</tr>
<tr>
<td>Headache or fullness in head</td>
<td></td>
</tr>
<tr>
<td>Disorientation and clouding of sensorium</td>
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</table>

Adapted from Sullivan et al. (1991).
CIWA scores of withdrawal were above 8. Medication treatment duration was shorter in the symptom-triggered group than in the fixed-schedule group (median 9 vs 68 h respectively). The symptom-triggered group also received less benzodiazepine (100 vs 425 mg). The incidences of delirium tremens, hallucinations, and seizures were equivalent in the two groups. Saitz et al. (1994), however, excluded from the symptom-triggered group patients with any history of seizures. These authors concluded that the symptom-triggered method can be used for the treatment of alcohol withdrawal under the following conditions: (1) where nurses are specifically trained to assess withdrawal symptoms; and (2) patients with history of seizures or patients presenting with acute medical or psychiatric illness must be excluded.

Comparison between the different treatment protocols and especially the loading technique and ‘symptom-triggered’ therapy is difficult. No double-blind design can be applied in this context. The intrinsic efficacy of the methods cannot be differentiated from the impact of the experience of the medical and paramedical team.

**BZD treatment of anxiety associated with alcoholism**

Epidemiological studies have shown that anxiety symptoms are especially frequent in alcohol-dependent patients. Panic attacks with and without agoraphobia are more common among alcoholics than among the rest of the population (Adès, 1989). Noradrenergic activation (Nutt et al., 1989) may play an important role both in conditioning tolerance and panic attacks. In most cases, anxiety is induced by alcohol withdrawal, alcohol intoxication or by the consequences of societal conditions of work, family, and social state (Adès, 1989). Kranzler (1996) noted, as have many other authors, that most cases of anxiety in alcoholics are secondary to alcohol dependence or abuse disorder.

Treatment of anxiety in alcohol-dependent patients (Kranzler, 1996) is thus particularly difficult in the context of a single clinical evaluation. The first step of the treatment consists of differentiating independent anxiety symptoms from symptoms that are substance-induced. Before treatment, it is necessary to screen for history of anxiety symptoms and anxiety disorders in anxious patients. Two types of anxiety states can be distinguished (Kranzler, 1996):

1. The transient anxiety state includes symptoms lasting for days, or at most, a few weeks. Although their intensity may be high, the symptoms are not sustained. Patients may also have persistent low-grade anxiety symptoms with brief periods of exacerbation. Symptoms are secondary to withdrawal or a reaction to psychosocial stressors arising from alcohol consumption. Efforts to help resolve psychosocial problems or support for continued abstinence more often result in resolution of anxiety, than the use of BZD treatment.

2. The persistent anxious state includes symptoms that may be intense and may last for periods of weeks to months. Although there may be situational effects on the severity of these symptoms, there is substantially less variability than in the transient anxious state. These cases of anxiety are much less likely to resolve spontaneously. If they persist, they may constitute an indication for BZD treatment.

For patients with anxiety disorders persisting beyond 1 month after abstinence (and resolution of acute alcohol withdrawal), adequate treatment of anxiety symptoms may contribute to the avoidance of relapse, regardless of which disorder appeared first. This position, however, has never been confirmed by a controlled study (Adès, 1989).

According to Frances and Borg (1993), treatment with BZDs may be limited to patients for whom abstinence is stable. The patient must be closely monitored in terms of anxiety and alcohol consumption and the family has to be involved in the treatment. The prescription of BZDs does not signify a specific action on alcohol consumption, as they do not possess specific effects on the reduction of craving for alcohol, as serotonin reuptake inhibitors, acamprosate or opiate antagonists do (Lejoyeux, 1996).

**UNWANTED EFFECTS OF BZD TREATMENT**

**Definition and prevalence of BZD abuse in alcohol-dependent patients**

BZD abuse and dependence as defined in DSM-IV are characterized by loss of control of drug use leading to key diagnostic criteria such as ineffec-
tive attempts to cut down drug use, increased time spent seeking the drug or recovering from its effects, curtailment of activities due to continued drug use and continued use in spite of adverse consequences.

There is disagreement about whether people with a history of alcohol dependence or abuse are at special risk of BZD dependence (Mueller et al., 1996). Estimates of the magnitude of risk vary widely (Mueller et al., 1996) according to different authors. An overestimation of this risk may cause effective and safe medication to be withheld from people who might benefit from them. Patients with anxiety disorders and a history of alcohol dependence and patients presenting with alcohol withdrawal are part of such populations.

According to Borg et al. (1993), 24 to 50% of alcohol-dependent patients take BZDs. Among these patients, the risk of BZD dependence has not been studied precisely. Isolated reports suggested that 2% of alcohol-dependent patients treated with diazepam are at risk of dual dependence.

Studies of dependence on BZDs in alcohol-dependent patients are limited by methodological difficulties. The use of terms such as abuse and dependence are not always clearly defined. Physiological BZD dependence (Ciraulo et al., 1988) cannot be equated necessarily with abuse liability. A withdrawal syndrome can occur after chronic use of BZDs at therapeutic doses. Another similar difficulty is the differentiation between physiological dependence, as demonstrated by withdrawal, and reappearance of anxiety symptoms.

Evaluation of BZD abuse or dependence among alcohol-dependent patients

One indirect measure of BZD dependence is the amount of medication used (Mueller et al., 1996). These authors assessed prospectively the consumption of BZDs in 343 subjects (99 subjects with, and 244 without, a history of alcohol abuse or dependence). They found little difference over 12 months of prospective follow-up in the mean daily dose, mean maximum daily dose, use of doses in addition to routine daily doses, and persistent drug use in these two groups. They noted that the median daily dose of BZD equivalent was slightly higher in patients with a positive alcohol-dependence history (10 mg/day of chlordiazepoxide).

Hershberg (1996) stressed that few studies demonstrate a resultant frequency of BZD dependence among alcoholics if: (1) BZDs are prescribed in reasonable doses (i.e. a maximum of 20 mg diazepam equiv/day); and (2) the treatment duration is less than 6 months. This latter author concluded that since many alcoholics replace alcohol with BZDs, alcoholism is a primary indication for the judicious use of BZDs.

Ross (1993) tried to determine the prevalence of BZD use, abuse, and dependence in 427 patients in Toronto who met lifetime DSM-III criteria for alcohol abuse or dependence. Forty per cent were recent users of BZDs and 20% had abused or been dependent upon BZDs during their lifetime. Patients with antisocial personality disorder were at higher risk for BZD abuse or dependence. Women and unemployed subjects were also at higher risk for BZD dependence. Recent users of BZDs showed more current psychological distress, depressive symptoms, and more severe substance abuse problems. They were more likely to have a lifetime DSM-III anxiety disorder. This study by Ross (1993) involved treatment-seeking alcoholic patients (427), used defined diagnostic criteria (DSM-III-R criteria of dependence) and a standardized clinical instrument (NIMH-DIS). It confirmed, for the population studied, the risk of BZD abuse or dependence. One out of every five alcoholic patients (30% of the antisocial personality patients and 10% of other patients) presented a lifetime diagnosis of BZD abuse or dependence. Two out of five alcoholics (60% of the antisocial personality patients and 20% of the other patients) admitted the non-medical use of BZDs five or more times during their lifetime. Non-medical use was defined as taking BZDs to ‘get high’ or without a prescription or in more than the prescribed doses. Ross (1993), however, failed to discuss that the results could reflect a selection bias. Treatment-seeking patients may constitute a subgroup of subjects especially exposed to BZD abuse or dependence. In order to evaluate the prevalence of BZD abuse or dependence, a study based on non-treatment seeking substance abusers might be more significant.

Risk factors for BZD dependence in alcohol-dependent patients

Impulsive patients and alcohol-dependent
patients presenting with multiple addictions appear to be especially at risk for abuse or dependence. Within the alcohol abuse populations, however, BZDs are commonly taken as part of a polysubstance pattern. The American Psychiatric Association Task Force (1990) thus recommended that 'special caution should be taken when benzodiazepines are prescribed to patients with a current or prior history of substance abuse or dependence'.

Adoption studies by Cloninger et al. (1988) defined two genetically distinct forms of alcoholism, type I and type II. Type II alcoholism affects only men. Approximately 25% of alcoholic men have the disorder. It is inherited from father to son, but not by daughters. Excessive alcohol consumption at an early age co-exists with antisocial personality and childhood history of hyperactivity. Patients with type II alcoholism are unlikely to benefit from BZDs (Nutt et al., 1989). These drugs are contraindicated for such patients, particularly if they exhibit impulsive behaviour, which may be aggravated by BZDs.

Sellers et al. (1993) published a review of the literature on this topic and noted that BZD abuse occurs in alcoholics with severe dependence and alcoholics with polydrug abuse. In less severely dependent individuals, the association of alcohol dependence with BZD abuse is unclear. In particular, the patterns of BZD use among drinking and abstinent alcoholics have not been studied carefully. Among alcohol-dependent patients presenting with co-morbid symptoms of anxiety, few data are available about the benefits or risks of prescription of BZDs.

Effects of family history of alcoholism on the risk of BZD dependence

de Witt (1990) sought to determine whether a family history of alcoholism could affect the subjective and behavioural effects of diazepam. Fourteen male light drinkers with alcoholic first-degree relatives and no personal history of alcohol problems were compared to 13 controls with no alcoholic relatives. The two groups did not differ in their satisfaction with diazepam. The tranquilizing effects of diazepam were comparable in the two groups. These results indicate that a family history of alcoholism does not necessarily influence the subjective or behavioural response to administration of diazepam, suggesting that it also does not confer a greater risk for developing excessive use or abuse with this class of drugs.

Ciraulo et al. (1996) assessed the risk of BZD dependence in 12 adult daughters of alcoholics and in 11 controls. They studied the effects of alprazolam on mood response, on the assumption that alprazolam-induced mood enhancement may indicate vulnerability to sedative/hypnotic abuse. Daughters of alcoholics had greater mood increase after a single dose of alprazolam than did women without a personal or family history of alcoholism. These results are consistent with a greater risk of alprazolam abuse in daughters of alcoholics. The relationship between the BZD-induced euphoria and the risk of abuse or dependence has never been proven. The above authors postulated that alcohol-dependent patients may self-medicate with BZDs a dysphoria that is not described by current nosology. Confirmation of this opinion requires additional study.

Memory impairment

Memory impairment is a common side-effect of BZDs. It represents more often a subjective complaint than an objective alteration of cognitive faculties. It can be induced by BZDs alone or by the interaction between ethanol and BZDs. Memory impairment may hamper efforts toward rehabilitation during the first days of hospitalization. Lorazepam (Nutt et al., 1989) produces more prolonged impairment of cognitive-psychomotor performances than other BZDs. Khajuria et al. (1995) have assessed the effects of diazepam on psychomotor function. They showed in 10 controls that diazepam induced mild impairment in simple reaction time, multiple choice reaction time and critical flicker fusion frequency. No summation of adverse effects on psychomotor performance was noted when a combination of diazepam (5 mg) plus alcohol (60 ml) was tested.

Confusion, delirium, and seizures

Confusion and delirium may be induced by BZDs, especially in older and medically ill alcoholics. Hill and Williams (1993) reported three cases of chlordiazepoxide toxicity including confusion, unsteady gait or ataxia. The three patients suffered major seizures within 24 h of completing detoxification. The above authors suggested that BZDs with short half-life may produce a paradoxical effect and initiate the seizure
activity. The authors thus recommended the use of a long-acting BZD or of carbamazepine, an anticonvulsant agent.

Other symptoms

Minor cardiovascular and respiratory depression. These symptoms only occur with high doses of BZDs, although this is unusual when BZDs are administered alone. In combination with ethanol, BZDs have an additive effect. The patient requiring treatment for ethanol withdrawal prior to the blood-alcohol level reaching zero should be given BZDs with caution. Respiratory depression and coma may be induced in patients with positive serum-ethanol levels that may act synergistically (Peppers, 1996).

Symptoms of ethanol intoxication, such as drowsiness, lethargy, ataxia, diplopia, and confusion are similar to the symptoms observed following anxiolytic overdose. Inhibition of the gag reflex has also been reported following BZD administration, increasing the risk of aspiration in nauseated patients (Nutt et al., 1989).

Behavioral dyscontrol. Bond and Silveira (1993) have studied the combined effects of an acute dose of alprazolam (1 mg) and of alcohol (0.5 g/kg) in 48 moderate social drinkers. Alprazolam tended to blunt anxiety, but not hostility. In addition, anxiety increased again 3.5 h after drug administration. The combination of alcohol and alprazolam increased behavioural aggression more than would have been predicted from the sum of the single effects. This study gives only indirect information about the effects of BZDs on behavioural dyscontrol. The study was based on a cognitive task procedure (motor reaction to a noise). A more clinically pertinent assessment could involve a systematic study of impulsiveness with standardized scales such as the Barratt Impulsiveness Scale and/or an assessment of the frequency and the severity of impulsive behaviours in alcohol-dependent patients with or without BZD treatment.

CONCLUSION AND PRACTICAL RECOMMENDATIONS

Rational BZD prescribing requires first and foremost a knowledge of what is being treated. Careful diagnostic work is critical and must answer the following questions: Is anxiety alcohol-induced, secondary to withdrawal, or an expression of an anxiety disorder? Have alternatives to drug treatment, such as psychotherapy or behavioural interventions, been considered and clearly proposed to the patient?

In cases of alcohol withdrawal, even of mild intensity, the indication for BZD treatment is justified for patients presenting with severe alcohol-withdrawal syndrome and/or history of delirium tremens or epilepsy. The BZD treatment should be instituted as soon as possible in order to prevent severe somatic and psychiatric complications of alcohol withdrawal.

During alcohol withdrawal, many protocols have been proposed. Some of them involve fixed dosages and others use a 'loading dose' technique. The current therapeutic practice involves treatment with flexible doses. In all cases (Bird and Makela, 1994), routine prescription of a BZD for treatment of withdrawal should state that doses should not be given if the patient is sedated or shows signs of BZD excess. This precaution prevents problems with oversedation.

Differences between therapeutic agents are slight. A long-life BZD like diazepam can, however, be recommended because of its greater effect on anxiety and of its smoother action. In the presence of significant impairment of respiratory or liver function, the use of a short-acting BZD to prevent drug accumulation is recommended (Shaw, 1995).

Another difficult practical question is to determine how an anxiolytic treatment may reduce alcohol consumption in patients presenting with co-morbid anxiety with alcohol dependence. No study confirmed that long-term use of BZDs has a positive effect on alcohol consumption, even among anxious alcoholics. The link between tension reduction and alcohol consumption is especially complex. Alcohol possesses anxiolytic, but also anxiogenic, properties. Even in cases of anxiety secondary to alcohol dependence, patients continue to expect to experience anxiolytic effects from their alcohol consumption. Kushner et al. (1994) showed in a population of students that the alcohol outcome expectancies and cognitive factors modulate the 'tension-reduction' effects of alcohol.

The treatment of anxiety in alcohol-dependent patients can consist of BZD prescription. This anxiolytic treatment must be associated with
cognitive therapy (Kushner et al., 1994) which aims at educating the patient about the long-term effects of alcohol of increasing stress and anxiety. In the short term, BZDs are, however, the most effective drugs available for relief of anxiety symptoms (Mueller et al., 1996). To determine continued need (Ciraulo et al., 1988), the physician should periodically taper the patient’s medication and observe if dose tapering induces a recrudescence of anxiety.

Finally, the question of the risk of abuse of, and dependence on, BZDs in alcohol dependence is crucial. The debate about the dangers of BZD dependence is especially significant for patients who have already developed BZD abuse or dependence (Mueller et al., 1996). The risk of dependence is related to the psychiatric symptoms associated with alcohol dependence. Patients presenting with a high level of impulsivity, antisocial personality or multiple drug dependence, may use BZDs as new agents of dependence. In all cases, limited amounts of medication should be prescribed, and careful follow-up should be made. The association of BZD prescription within a global treatment approach to alcohol dependence will increase the positive effects of the anxiolytic and reduce the risk of dependence.

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