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The benzodiazepine withdrawal syndrome

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Abstract

Physiological dependence on benzodiazepines is accompanied by a withdrawal syndrome which is typically characterized by sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty in concentration, dry wretching and nausea, some weight loss, palpitations, headache, muscular pain and stiffness and a host of perceptual changes. Instances are also reported within the high-dosage category of more serious developments such as seizures and psychotic reactions. Withdrawal from normal dosage benzodiazepine treatment can result in a number of symptomatic patterns. The most common is a short-lived "rebound" anxiety and insomnia, coming on within 1–4 days of discontinuation, depending on the half-life of the particular drug. The second pattern is the full-blown withdrawal syndrome, usually lasting 10–14 days; finally, a third pattern may represent the return of anxiety symptoms which then persist until some form of treatment is instituted. Physiological dependence on benzodiazepines can occur following prolonged treatment with therapeutic doses, but it is not clear what proportion of patients are likely to experience a withdrawal syndrome. It is also unknown to what extent the risk of physiological dependence is dependent upon a minimum duration of exposure or dosage of these drugs. Withdrawal phenomena appear to be more severe following withdrawal from high doses or short-acting benzodiazepines. Dependence on alcohol or other sedatives may increase the risk of benzodiazepine dependence, but it has proved difficult to demonstrate unequivocally differences in the relative abuse potential of individual benzodiazepines.

Introduction

Benzodiazepine dependence within the clinical as well as non-medical context has given cause for concern for some years now. This area has often been characterized by confusion and lack of reliable information, but the definition and demonstration of withdrawal symptoms has played a pivotal role in attempts to clarify the situation (Pétursson & Lader, 1984; Pétursson, 1993). It is not within the scope of this paper to go into detailed and complex definitions of the various aspects of drug dependence and abuse, but suffice it to say that the withdrawal syndrome usually involves both physical and psychological manifestations, the nature of which varies with the drug on which dependence exists. Woods *et al.* (1987) noted the importance of defining the benzodiazepine withdrawal syndrome as time-limited. In treatment of disorders such as anxiety and sleep disturbances, discontinuation of chronic benzodiazepine administration may lead to reappearance of those symptoms that originally indicated the need for treatment. It follows that such symptoms could go on for a long time, or perhaps indefinitely, following discontinuation of drug treatment and should therefore not be listed as part of the withdrawal syndrome.

The different aspects of the development of drug dependence are all germane to the study of benzodiazepine dependence. Thus different classes of drugs have their own characteristic set of withdrawal symptoms and pharmacokinetic aspects, such as dosage and duration of exposure, may affect the severity of a withdrawal reaction. Not only does the duration of action determine the frequency of exposure needed to produce dependence, but may also to some ex-

tent determine the time course of the withdrawal syndrome. The precipitation of withdrawal signs by a drug antagonist can circumvent some problems related to the pharmacokinetic differences between individual drugs and can thus provide valuable information, for example in the study of abuse liability.

The ability of one drug to suppress the manifestations of physiological dependence produced by another and to maintain the physiological dependence state is termed cross-dependence (Jaffe, 1980). Such a drug is therefore likely to produce a similar type of dependence. The benzodiazepines can reverse withdrawal from alchol and barbiturates and could thus be expected to produce a similar withdrawal syndrome. In fact, Jaffe (1980) has suggested that the term "general depressant withdrawal syndrome" refers to the manifestations of withdrawal from sedatives and alcohol. In its mildest form the syndrome may consist of only anxiety, insomnia, REM rebound or paroxysmal EEG abnormalities. Tremulousness and weakness imply somewhat greater degrees of physiological dependence, and seizures and delirium may develop in its most severe form.

Physiological dependence is associated with withdrawal signs mainly characterized by rebound effects or overshoot phenomena in the same physiological systems that were initially modified by the respective drugs (rebound hyperexcitability). Although such effects are customarily included among withdrawal phenomena, some investigators have excluded rebound effects from benzodiazepine withdrawal symptoms. It has been pointed out that the earliest signs of rebound excitability can, for example, be detected after brief periods of CNS depression, but it may require weeks or months of moderate doses of sedatives to produce clinically significant physiological dependence. Although rebound effects imply an altered physiological state, the definition of physiological dependence also requires a manifestation of a characteristic illness, the withdrawal syndrome, which is of much more clinical significance than mild rebound effects.

Benzodiazepine dependence

In their authoritative review of the abuse liability of benzodiazepines, Woods *et al.* (1987) have concluded that studies in animals have shown that at high doses all benzodiazepines studied are capable of producing physiological dependence. Furthermore, there are some suggestions that the physiological benzodiazepine dependence is different from the physiological dependence of other classes of drugs. However, it has proved difficult to determine whether individual benzodiazepines vary qualitatively with respect to their potential to produce physiological dependence. Few animal studies have been conducted with doses analogous to those used in the clinical context, but these have demonstrated some degree of withdrawal from prolonged exposure to such doses.

The benzodiazepine withdrawal syndrome

In the late 1970s a number of systematic studies of benzodiazepine dependence within the clinical context were mounted. The benzodiazepine withdrawal syndrome was found most typically to comprise severe sleep disturbance, irritability, increased tension and anxiety, panic attacks, hand tremor, sweating, difficulty in concentration, dry wretching and nausea, some weight loss, palpitations, headache, muscular pain and stiffness, and a host of perceptual changes (e.g. Hallstrom & Lader, 1981; Pétursson & Lader, 1981; Rickels, 1981; Shöpf, 1981; Tyrer, Rutherford & Huggett, 1981). Instances are also reported within the high-dosage category of more serious developments, such as seizures and psychotic reactions (for review see Pétursson & Lader, 1984).

More recent studies have revealed similar findings (e.g. Tyrer, Owen & Dawling, 1983; Rickels *et al.*, 1983; Winokur & Rickels, 1984; Busto *et al.*, 1986). Some investigations have compared short-and long-acting benzodiazepines and have found that withdrawal symptoms occurred either earlier or were more severe following withdrawal from short-acting benzodiazepines (Busto *et al.*, 1986; Rickels *et al.*, 1990; Noyes *et al.*, 1991). Power *et al.* (1985) have found that withdrawal of diazepam after as little as 6 weeks may be accompanied by withdrawal symptoms and rebound anxiety. Tyrer *et al.* (1983) reported a pseudo-withdrawal syndrome in a substantial number of patients and also found personality factors to be among clinically important predictors of withdrawal, a finding which has also been reported by Rickels *et al.* (1991).

Abrupt withdrawal of normal dose benzodiazepine therapy can result in a number of symptomatic patterns. The most common is a short-lived, perhaps 2–3 days, "rebound" anxiety and insomnia coming on within 1–4 days of discontinuation, depending on the half-life of the particular drug. This phenomenon resembles the transient rebound symptoms when many other types of drugs are stopped abruptly. The second pattern is the full-blown withdrawal syndrome, usually lasting between 10–14 days. Finally, a third pattern may represent the return of anxiety symptoms which then persist until therapy, pharmacological or non-pharmacological, is instituted.

Rebound effects

Rebound insomnia may frequently develop after discontinuation of hypnotic treatment with benzodiazepines (Kales *et al.*, 1986; 1991). There is some disagreement as to whether rebound insomnia should be regarded as a part of a withdrawal syndrome. This phenomenon is more frequently seen following withdrawal from shorter-acting than the longer-acting benzodiazepines.

Considering the studies of benzodiazepine withdrawal and tolerance, many of the withdrawal symptoms probably reflect an underlying state of over-arousal. This is to be expected in view of the fact that the benzodiazepines are sedative drugs and known to cause perceptual impairment and a lowering in the overall state of arousal (e.g. Bond & Lader, 1981). The development of tolerance to these effects probably leads to a state of latent "hyperexcitability" which in turn results in a rebound in arousal levels during the withdrawal reaction. However, withdrawal of effective drugs may well be associated with transient rebound phenomena without causing problems of dependence. Furthermore, it is sometimes difficult to determine whether post-withdrawal insomnia or anxiety are actual rebound effects and not simply a recurrence of previous symptoms. Nevertheless, if definite, time-limited rebound effects are demonstrated these should be considered genuine withdrawal signs, indicating a specific pathophysiological state.

Dependence-inducing factors

It has been suggested that dependence on drugs (e.g. Plant, 1981), including benzodiazepines (e.g. Marks, 1983), is primarily limited to patients with "dependence-prone" personalities. It is difficult to define such a term and generally the psychosocial characteristics of benzodiazepine-dependent patients appear not to fit into any one category. However, some studies in recent years have suggested that personality factors may be important predictors of withdrawal phenomena and later relapse. There is also some evidence from both animal and human studies indicating that concomitant or prior use of alcohol or other central nervous system (CNS) depressants may augment or predispose to the development of physiological dependence on benzodiazepines.

Treatment of withdrawal symptoms

Various techniques of withdrawal from benzodiazepine dependence have been advocated (e.g. Marks, 1988). Pharmacotherapy of benzodiazepine withdrawal symptoms, for example with oxypertine (Pétursson & Lader, 1984) or propranolol (Tyrer *et al.*, 1981), has been tried during the withdrawal period, but usually with minimal efficacy. Gradual withdrawal is probably the best approach, and there may be merits in using a benzodiazepine with a long half-life for effecting withdrawal in order to achieve a smoother fall in plasma drug levels. However, although some drugs have not proved helpful in this respect, alternative drugs such as carbamazepine (Schweitzer *et al.*, 1991) could be of therapeutic value in the benzodiazepine withdrawal syndrome. Finally, behavioural approaches and other non-pharmacological methods should also be pursued.

Further research required

Systematic studies of the potential of the many benzodiazepines to produce physiological dependence in humans are few and far between. It is not known whether the risk of physiological dependence is dependent upon a minimum dosage or exposure to the drugs, nor is it known what proportion of patients receiving normal dose benzodiazepine are likely to experience a withdrawal syndrome.

It has proved difficult to demonstrate unequivocally quantitative differences in the relative potential of benzodiazepines to produce physiolgical dependence. Griffiths & Wolfe

(1990) have, however, pointed out the apparent differences in abuse liability of different benzodiazepines. Studies of this nature are hampered by a number of pharmacological considerations; for example, pharmacokinetic differences between individual drugs. Differences in frequency and duration of administration must be taken into account when comparing various benzodiazepines. As indicated previously, longer-acting benzodiazepines may produce less intense withdrawal symptoms. One way to ensure proper comparison is to substitute a short-acting for a long-acting benzodiazepine before drug withdrawal. Another possibility would be to administer a benzodiazepine antagonist, thus precipitating an immediate withdrawal syndrome. However, it should not be forgotten that the antagonist itself may in fact produce its own signs and thus distort the withdrawal syndrome.

Because of problems with dependence and withdrawal, a number of alternative pharmacotherapies to reduce anxiety and insomnia are being developed. Partial benzodiazepine agonists are related to conventional substances, but may have less reinforcing activity and lower abuse liability (Sellers, Busto & Kaplan, 1991) while retaining the desired effects of conventional benzodiazepines. Partial benzodiazepine agonists may cause less CNS depression and perhaps also less risk of tolerance, physiological dependence and reinforcement (Haefely, 1991). Non-benzodiazepine anxiolytics and hypnotics are being extensively investigated, and some appear to have a low dependence potential during initial clinical studies (Garreau *et al.* 1991). While preclinical and clinical studies are useful predictors of dependence and abuse, the relative risk of abuse and dependence of newer anxiolytics will only become known after extensive experience with the new medications.

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