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PARADOXICAL REACTIONS TO BENZODIAZEPINES

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1 The overall incidence of paradoxical responses to the benzodiazepines is extremely small, but a few controlled studies have been carried out which define the population at risk.

2 Such reactions tend to be idiosyncratic except possibly in patients with pre-rage personality, and do not seem to be associated with any predictable clinical indications.

Introduction

SINCE the first benzodiazepine, chlordiazepoxide, was fortuitously synthesized in 1955, these drugs have become the most widely used class of compounds in clinical medicine. They are extensively prescribed for both in- and outpatients worldwide. It has been estimated that more than $400,000,000 per year is expended on these agents. In 1973, for example, The Boston Collaborative Drug Surveillance Programme found that 30% of all medical patients hospitalized in the Boston area received diazepam, and 32% received flurazepam (Greenblatt & Shader, 1974).

As minor tranquillizers, the benzodiazepines are effective for the reduction of anxiety when compared with placebo. Their anxiolytic properties have been proven to be roughly equivalent in double-blind crossover studies and superior to most other classes of drugs used for the relief of anxiety. Their mechanism of action is thought to be stimulation of γ-aminobutyric acid (GABA) receptors in the ascending reticular activating system. As GABA is an inhibitory compound, receptor stimulation increases inhibition and blocks both cortical and limbic arousal following stimulation of the brain stem reticular formation. The benzodiazepines have been shown to depress electrical after-discharge in the septum, amygdala and hippocampus, components of the limbic system which regulate emotion (Hall & Kirkpatrick 1978).

Some effects of these agents are thought to result from other mechanisms of action. These compounds have been shown to decrease synaptosomal K+/Na+ ratios and increase membrane-associated nucleic acids (Essman, 1973). They decrease catacholamine uptake in certain regions of the brain (Taylor & Laverty, 1973), reduce the turnover to 5-hydroxytryptamine in the cortex (Lidbrink, Corrodi, Fuxe & Olsen, 1973), and increase the concentration of brain acetylcholine (Ladinsky, Consolo, Peri & Garattini 1973). As all of these substances function as neurotransmitters or modulators, slight alterations in the regulatory or modulating systems may predispose certain individuals to unusual reactions. None of the above-mentioned actions, however, truly explains the mechanisms by which a given benzodiazepine produces a paradoxical response (Taylor & Laverty, 1973).

Before proceeding with a description of the various paradoxical reactions that have been reported, one must define behavioural toxicity, paradoxical response and the dilemmas inherent in attributing such reactions to drug effect. As discussed by DiMascio & Shader (1970) one must define what one means when talking of a paradoxical effect or toxic response following administration of a drug. Both the patient's and observer's value systems become involved in defining these terms. The expression of any drug effect is determined by the patient's age and physical condition as well as the social setting in which that effect occurs. To be considered toxic, an effect must be both adverse to the health or function of the organism and undesirable relative to the use for which the drug was used. Specific problems occur when one tries to define 'behavioural side-effects' as these are most often subjective, or at best, simply inferred from the behaviour of the patient. The points at which they develop or disappear are often difficult to define, as the patient's subjective consideration is often the prime determinant. What may be considered adverse for one patient may be deemed therapeutic for another, or a particular effect may be adverse during one point of treatment, yet salutary during some other phase.

Consider for example, the effect of sedation. In a

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highly anxious sleep-deprived patient, initial sedation may be very desirable and welcomed by both the physician and the patient. After the severe anxiety is ameliorated, however, sedation may become problematic to the patient who earns his living driving a truck or erecting high steel. In addition, a particular drug may produce totally different effects in different patients which may or may not reoccur upon rechallenge. In evaluating the side-effects or toxicity of a particular drug, one would ideally like to define those reactions which result from the direct pharmacological action of the agent within the therapeutic dose range. The benzodiazepines pose several problems in working with this model of drug-related toxicity. Wide drug variations in dose and effect relationships exist, as do significant differences in the metabolism of these agents. Many of the drugs form intermediary active metabolites which may be affected by various medical conditions such as renal and hepatic disorders. In addition, the majority of patients for whom these agents are prescribed are under some form of anticipatory or immediate stress or have some sort of psychiatric symptom which may be difficult to distinguish from the behavioural side-effects often attributed to these drugs.

For the purposes of this paper, DiMascio & Shader's definition (1970) of behavioural toxicity will be used. 'Behavioural toxicity is a phrase used to denote those pharmacological reactions of a drug that, when administered within the dose range in which it has been found to possess clinical utility produce—through mechanisms not immediately specifiable—alterations in perceptual and cognitive functions, psychomotor performance, motivation, mood, interpersonal relationships or intrapsychic processes of an individual to the degree that they interfere with, or limit the capacity of the individual to function within his setting or constitute a hazard to his physical well-being.' The characteristics of the 'true' paradoxical reactions about to be described are that they usually appear insidiously or abruptly in individuals who would not otherwise be thought predisposed to such behavioural reactions. They are, in general, uncharacteristic, rare, most often idiosyncratic, and consequently extremely difficult to predict on the basis of past behaviour. They most likely occur not from some common pharmacological property of the agent, but rather from some poorly understood biochemical interaction between the drug and the human system involved. The major types of paradoxical responses that have been reported and which will be discussed include the following: depression, gross behavioural disturbances, hostility, and aggression and rage.

Depression

Some patients may be particularly susceptible to the development of depression following institution of benzodiazepine therapy. Most reports in the literature concerning this phenomenon are anecdotal and the vast majority have occurred in patients with major physical illnesses or in those taking other medications. The clinical impression that certain benzodiazepines, particularly diazepam, are associated with depressive symptoms is widespread (Rao, 1964). Gundlach, Engehardt & Hankoff (1966) found suicidal thoughts and impulses associated with therapeutic doses of diazepam in some patients but not with placebo. Ryan *et al.* (1968) reported seven patients who developed suicidal ideation after the initiation of diazepam therapy. Five of these seven patients improved within a few days after diazepam was discontinued. Two of the patients committed suicide. Hall & Joffe (1972) reported six patients with various vascular and renal diseases, all of whom were consuming more than 40 mg diazepam daily, who developed a constellation of symptoms consisting of tremulousness, apprehension, insomnia and depression, followed by severe anxiety, and ego-alien suicidal ideation. In these patients, symptom onset was abrupt, marked in severity and appeared in individuals who had previously been emotionally stable. Most of these patients evidenced some signs of organic impairment and experienced drug-induced confusion. Two of the patients were over 65 yr of age; all except one had significant vascular disease. The patient who was free of vascular disease had a history of post-meningitic convulsive disorder. In each case, the patient was taking other medication when diazepam was begun. Zisook & DeVaul (1977) reported an additional case of diazepam-induced suicidal ideation, which was also associated with mild memory and cognitive defects in a patient who was taking other medications.

In the majority of reported cases, it is extremely difficult to determine whether the depression represents a worsening of an already existing depressive process or whether it is a *de novo* condition associated with the use of benzodiazepines. Some authors have tried to explain this phenomenon (Sarwer-Foner & Ogle, 1956; Sarwer-Foner, 1960) by pointing to the relationship between personality type and drug response. McDonald (1967) and Sarwer-Foner & Ogle (1956) believe that the sedative effects of tranquillizing drugs often interfere with the customary activities used by patients as defences against conflict, thereby producing either anxiety or depressive states that seem to be paradoxical chemical effects. The fact that benzodiazepines have been shown to decrease regional brain catacholamine uptake, may be another explanation for this phenomenon in particularly sensitive individuals (Taylor & Laverty, 1973). Yet another explanation is the alteration of perceptual processes associated with decreased efficiency of memory, reasoning ability, learning, and the capacity

to abstract. Such reduced functional ability may occur and be significant in only some patients or only in patients of a particular personality type. They may occur only at specific drug dosages or only during certain critical periods of pharmacotherapy (DiMascio, Shader & Giller 1970; Bakker, 1967; Lawton & Cahn, 1963; McPeake & DiMascio, 1965; Savage & Day, 1958; Frostad, Forrest & Bakker, 1966).

It should be remembered that anxiety and depression frequently co-exist (Overall, Hollister, Johnson & Pennington 1966) and that consequently, many patients appear depressed when their anxiety is controlled by anxiolytic agents. Such depression should not be confused with a paradoxical drug reaction.

Gross behavioural disturbances

Several types of gross behavioural disturbances have been reported to be associated with benzodiazepine use. They range from agitation and Korsakoff's psychosis (Meyler, 1966) to paranoid reactions, confusional stages, hypomanic and manic responses, extreme garrulousness and states resembling alcoholic intoxication (Ayd, 1962). Hallucinations as well as vivid dreams and nightmares have been reported in association with the use of chlordiazepoxide (Greenberg, 1967); Viscott, 1968) and diazepam (Stanfield, 1973). The case reported by Viscott (1968) is impressive, as the patient, who was confined to bed for a dermatological condition, was an active individual who had received chlordiazepoxide 25 mg intramuscularly 45 min before the onset of terrifying visual hallucinations. He was rechallenged the following day with another intramuscular dose of chlordiazepoxide, whereupon similar symptoms occurred within an hour. No previous hallucinations were reported and when the benzodiazepine was discontinued no further hallucinations occurred. A diagnosis of delirium tremens was not supported by history and was further mitigated against by the fact that the patient's hallucinations ceased following environmental stimulation.

Hostility, aggression and rage

In most instances, the benzodiazepines are reported to diminish anxiety, fear and irritability. If instead of calming the patient, or diminishing his anxiety, these agents either increased anxiety or produced aggression, the response would be truly paradoxical. Such paradoxical responses do occur on rare occasions. However, studies of aggressive behaviour in man and the effects of benzodiazepines upon such behaviour are difficult to define because of the nature of the subject population, the individualization of dose-response relationships, unclear assessment criteria, a lack of double-blind studies, and the underlying psychological basis for the initiation of drug therapy. Boyle & Tobin (1961) gave chlordiazepoxide to 25 hospitalized, angry, hyperactive, aggressive, psychotic patients. Sixty per cent of these patients improved; one patient manifested increased aggressiveness when treated with 60–70 mg of the drug daily. This aggressiveness became so severe that drug treatment was discontinued.

Many subsequent studies have confirmed the fact that benzodiazepines have an anti-aggressive effect. Kalina (1964) demonstrated diazepam to reduce hostility in hostile–aggressive prison inmates. McNair, Goldstein, Lorr, Cibelli & Roth (1965) showed chlordiazepoxide to reduce aggression in outpatient veterans, whereas Glesser, Gottschalk, Fox & Lippert (1965) demonstrated similar aggression-reducing properties in juvenile delinquents. Goddard & Lokare (1970) reported excellent control of aggressive outbursts in hospitalized epileptics using diazepam. Chlordiazepoxide was reported to be effective in controlling neurotic hyperaggressivity in outpatients (Podobnikar, 1971) and in the treatment of anger-hostility among various neurotic outpatients (Rickels, 1973). In addition, diazepam has been reported to be effective in managing the hostility and anger manifested by patients with Crohn's disease (Paulley, 1974) and the explosive personality outburst of hyperactive children (Morrison & Minkoff, 1975). In short, extensive clinical evidence suggests that the benzodiazepines exert an extremely positive effect on aggressive, rageful, hostile behaviour in a variety of patients seen in different clinical settings.

Conversely, a significant literature suggests that paradoxical aggressive reactions may be produced by these drugs (Lion, Azcarate & Koepke, 1975; Lion, 1975). Ingram & Timbury (1960) reported on paradoxical aggressiveness associated with chlordiazepoxide use. Cohen's (1961) report of a similar finding occurred the following year. Increased aggressiveness associated with diazepam use was first reported as an egodystonic hatefulness followed by rage attacks (Feldman, 1962). Since these initial reports, further cases of 'drug-induced rage' have been associated with diazepam (DiMascio & Shader, 1970), chlordiazepoxide (Greenblatt & Shader, 1974) and clorazepate (Bladin, 1973). Lion (1975) has suggested that these aggressive outbursts and rage reactions result from an interaction of the pharmacology of the drug, the patient's personality and the environmental setting in which the patients finds himself.

DiMascio, Shader & Harmatz (1969), after studying this phenomenon and reviewing the literature suggested that these reactions are not paradoxical responses, but rather are predictable behaviours

which occur only in certain patients whose past history of poor impulse control interacts with the drug's pharmacological properties, thereby increasing the patient's hostility. This latter contention has been clinically demonstrated. Gardos, DiMascio, Salzman & Shader (1968) reported that chlordiazepoxide decreased patient's anxieties but increased affective hostility as measured by the Buss-Durkee Inventory. No direct behavioural hostility was demonstrated during the course of their study. Salzman *et al* (9174) replicated these findings and also demonstrated that chlordiazepoxide was capable of producing behavioural hostility when the environment was structured to produce situations of interpersonal frustration.

The relationship between other benzodiazepines and hostility has also been studied. Kochansky, Salzman, Shader, Harmatz & Ogeltree(1975), for example, compared chlordiazepoxide and oxazepam. Their findings with chlordiazepoxide supported previous work but they were unable to find an association between increased hostility and the administration of oxazepam. Diazepam has also been reported to be associated with increased anger and hostility (Feldman, 1962; DiMascio & Shader, 1970; Greenblatt & Shader, 1974; McDowall, 1966; Gundlach, 1966). Covi & Lipman (1977) presented findings that diazepam increased both mood and overt-verbal and behavioural hostility in a group of moderately depressed female outpatients. The patients most likely to demonstrate this increase in hostility were those with higher initial levels of hostile-depression.

DiMascio & Shader (1970) have suggested that benzodiazepine-induced hostility has been clinically unrecognized because it is seen as only a minor symptom, may look like a clinical improvement in a previously passive-dependent non-assertive patient, or, if recognized, may be seen as part of the patient's initial illness. Evidence is increasing that benzodiazepine-induced hostility is determined by a number of factors and that it is related to the particular benzodiazepine administered (DiMascio, Shader & Harmatz, 1969; Gardos, DiMascio, Salzman & Shader, 1968; Kochansky *et al.*, 1975; Salzman, Kochansky, Shader, Harmatz & Ogletree, 1975). It also seems related to the patient's expectations of its occurrence (Salzman, 1969), and the patient's pre-existing hostility level (Covi & Lipman, 1977).

The literature suggests, therefore, that increases in non-motoric hostility are regular, subclinical effects of the benzodiazepines which become clinically manifest in certain types of anxious individuals who are undergoing interpersonal frustration. Most of the published reports on benzodiazepine-induced hostility are based either on uncontrolled case studies or on laboratory evaluations of healthy volunteers. One study of psychoneurotic outpatients (Rickels & Downing, 1974) treated with chlordiazepoxide failed to confirm previous findings, but this study has been criticized by other investigators on the basis of inappropriate methodology (Kochansky *et al.*, 1975). Thus, the question of frequency, severity, quality and significance of benzodiazepine-induced hostility remains unsettled.

Conclusions

Depression, agitated toxic psychosis, hypomanic and manic behaviour, increased anxiety, increased hostility and 'paradoxical rage' reactions, have all been reported to be caused by the benzodiazepines. DiMascio *et al* (1969) have suggested a number of reasons why these phenomena are not more universally known and recognized. The first is that these drug-induced reactions are often not marked in intensity: second, that clinical observations are relatively insensitive when compared with the sensitivity of the hostility scales used to measure change in controlled studies; and finally, that increased hostility and aggressiveness may be seen as socially and therapeutically beneficial for certain patients when channelled appropriately. Increased assertiveness may thus be seen as part of an overall therapeutic movement rather than as some drug-induced behaviour.

Most 'paradoxical' rage reactions that have occurred have been reported either in previously violent patients or in psychotic patients, particularly those suffering from schizophrenia, in whom the benzodiazepines are reported to produce an increase in paranoid ideation and aggressive tendencies (Feldman, 1962). Confusional states, Korsakoff-like syndromes, increased anxiety, tremulousness, agitation and ego-alien suicidal ideation have been reported to occur in medically ill individuals suffering from renal or cardiovascular disease (Hall & Joffe 1972; Zisook & DeVaul, 1977). The disinhibiting effects of these agents may be most pronounced in individuals subjected to significant environmental or interpersonal frustration. Patients undergoing chronic haemodialysis have also been reported to be at higher risk for developing disinhibition syndromes (Morgan, 1975). DiMascio *et al.* (1969) have suggested that what had previously been thought to be a paradoxical response to the benxodiazepines, may in fact be a predictable response and that rage reactions should not be considered paradoxical but predictable in individuals who have a history of poor impulse control or previously aggressive and destructive behaviour. In such patients, chlordiazepoxide and diazepam may release sufficient hostility to result in a 'rage reaction'. To date, no such reaction has been reported with oxazepam, the suggested anxiolytic of choice for

these patients. Chlordiazepoxide or diazepam, on the other hand, may represent the drugs of choice for anxious patients who are inhibited. In such cases, the medication could induce appropriate amounts of hostility and produce a therapeutically beneficial effect.

In reviewing the literature, one is left with two additional impressions. First, the overall incidence of significant paradoxical responses to the benzodiazepines is extremely small; second, that few controlled studies exist which define the population at risk for these reactions. When they occur, these reactions seem to be idiosyncratic and, except for DiMascio's caution concerning the pre-rage personality patient, do not seem to be associated with any predictable clinical indicators. Further studies of the mechanism of action by which these paradoxical responses occur may provide useful insights into the understanding of human behaviour and, in particular, mental illness.

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