SOME CONSIDERATIONS ON THE ROLE OF BENZODIAZEPINES IN THE TREATMENT OF DEPRESSION

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1 Benzodiazepines are regarded as pure anxiolytics, and their value in the treatment of depression is controversial. Nevertheless, symptoms of anxiety and depression coexist in patients with endogenous or neurotic depression, and clinical trials indicate that depressed patients respond better to a benzodiazepine-tricyclic antidepressant combination than to either drug alone.

2 Benzodiazepines may extend tricyclic antidepressant efficacy by rapidly relieving anxiety and insomnia. Factor analysis of scores obtained using the Hamilton Depression and Self-Administered Depression Rating Scales confirm the clinical findings by revealing that a close correlation exists among anxiety, insomnia and endogenous depression. The factor analysis data seem to support the wide use of benzodiazepine-tricyclic combinations to treat depressed patients.

Introduction

THE pharmacological treatment of depressive disorders is a problem with many possible solutions, but no definitive one will be established until standards for classifying the aetiology of depressive disorders become available. The current use of many different classification systems reflects the lack of agreement in assigning depressive disorders to diagnostic and therapeutic categories. The present categories provide neither unequivocal diagnostic criteria nor specific treatment guidelines.

Effective treatments are available, however, and their use has improved our knowledge of depressive disorders by encouraging early recognition and diagnosis of these conditions and stimulating development of new treatment methods. This paper will focus on the role of the benzodiazepines in treating depression.

Benzodiazepines in the treatment of depressive disorders

No clear-cut boundary exists between anxiety and depression. There is generally a large overlap: the syndromes in 50% of the inpatients and 90% of the outpatients receiving psychopharmacological treatment are characterized by symptoms of both anxiety and depression, with the symptoms of anxiety predominating (Lehmann, 1965; Hollister, 1971). In depressive disorders, symptoms cannot always be exclusively categorized as anxiety—or depression—related. Similarly, the practice of defining a psychotropic drug according to its anti-anxiety or antidepressant action may have simplified the nomen-

clature, but it has blurred the differences between properties of individual drugs and their effects on various kinds of patients (Claghorn & Kellner, 1971). Benzodiazepines have been regarded as anxiolytics rather than antidepressants, and opinions vary on their value in treating various depressive disorders. The key question in this controversial issue is: Should benzodiazepine treatment be restricted to anxiety states in neurotic patients or extended to endogenous depression?

Some investigators have claimed that benzodiazepines have antidepressant properties (Hollister & Overall, 1965; Claghorn & Kellner, 1971; Hollister, Overall, Pokorny & Shelton, 1971; Kellner, 1973; Woodward, Henry & Overall, 1975). However, no general consensus exists. Other investigators have reported benzodiazepine antidepressant efficacy independent of any specific antidepressant properties (Gold & Dribben, 1964; Svenson & Gordon, 1965; Swenson, Hachett & Kline, 1966; Frommer, 1967; Haider, 1967; Houck, 1970a,b; Hare, 1971; Raskin, Schulerbrandt, Reatig, Crook & Odle, 1974; Swanson, 1975; Bowen, 1978; Schatzberg, 1978), but these reports have been strongly challenged (Rao, 1964; McDowall, Owen & Robin, 1966; Ryan, Merrill, Scott, Krebs & Thompson, 1968; Hollister, 1976; Kleber, 1977; Bowen, 1978; Ives, Robinson, Nies, Ravaris, Korson & Lamborn, 1978).

Schatzberg & Cole (1978) have reviewed the literature on the use of benzodiazepines in the treatment of depressive disorders and concluded that benzodiazepines are less effective than standard tricyclic antidepressants in treating these disorders. According to

these authors, benzodiazepines display definite anxiolytic properties and are primarily anxiolytic rather than antidepressant. They may improve depressed mood, but their effect on the core symptoms of endogenous depression is limited. The findings that they may have positive effects in treating anxious depression would not require a change in labelling (Schatzberg & Cole, 1978).

Schatzberg & Cole have also reported that the tendency in clinical practice is to prescribe a benzodiazepine alone when anxiety symptoms predominate, or a tricyclic antidepressant alone when the core symptoms of depression predominate. It is often difficult to separate pure anxiety states from depression, and the treatment of patients with anxious neurotic states with a benzodiazepine alone is questionable. Also, the effects of the tricyclic antidepressants are not exclusively antidepressant, and such drugs as amitriptyline (Burton, Gordon & Holt, 1962; Ayd, 1965; Kielholz, 1965; Kielholz & Poeldinger, 1967; Poeldinger, 1967; Hollister, 1976) and doxepin (Johnstone & Claghorn, 1968; Krakowski, 1968; Castrogiovanni, Biagini, Conti, Riccioni, Maggini & Cassano, 1969; Montgomery, Cullinan & Bayley, 1970; Sim, Bindman, Conochie & Sandilands, 1971; Butterworth & Watts, 1971; Sterlin, Ban & Jarrold, 1972; Hollister, 1976) have widely recognized anxiolytic effects. According to Weissman & Klerman (1977), most anxious neurotic patients are actually suffering from depression, and the chronicity of their conditions can be correlated with their treatment with a benzodiazepine alone. Thus, if the use of a benzodiazepine to treat depressed patients involves a risk, it arises mainly when such a drug is given alone.

Scientific and empirical grounds for discouraging the use of a benzodiazepine-tricyclic antidepressant combination to treat depression are insufficient. In clinical trials the tricyclic antidepressants alone often failed to reduce insomnia, and patients receiving a tricyclic alone often required another drug, usually a hypnotic benzodiazepine, to relieve their insomnia. In clinical practice a benzodiazepine-tricyclic antidepressant combination is used quite commonly, but the benzodiazepine is prescribed for its hypnotic effects, and its anxiolytic properties are often overlooked.

The use of a benzodiazepine-tricyclic antidepressant combination has been further justified by clinical trial findings indicating that: (1) anxiety and depression coexist in some patients (Lehmann, 1965; Hollister, 1971; Sarteschi, Cassano, Castrogiovanni & Conti, 1973; Cassano, Castrogiovanni & Conti, 1973, 1977); (2) the combination relieves symptoms of anxiety and depression better than either treatment alone (Cassano, Castrogiovanni, Gallevi & Riccioni, 1968; Browne, 1969); (3) the activity spectra of the benzodiazepines and the tricyclic anti-

depressants differ (Cassano *et al.*, 1973, 1977). The anxiolytic and hypnotic effects of the benzodiazepines occur rapidly and mostly extend the spectrum of activity of the tricyclics.

Clinical data analysed

We have used factor analysis (Veldman, 1967) to analyse scores obtained using Hamilton Depression (HAM-D) and Self-Administered Depression (SAD; Cassano, Castrogiovanni, Ghiozzi & Principe, 1977) Rating Scales and collected during clinical trials in patients suffering from endogenous or neurotic depression. Four of the analyses reported here were carried out for this study, of which three focus on pretreatment HAM-D scores and one focuses on pretreatment SAD scores. The fifth analysis was a previous study (Cassano, Castrogiovanni, Conti & Maggini, 1976) and focuses on the differences in HAM-D scores before and after benzodiazepine or tricyclic antidepressant treatment. The scores analysed were stored in the Psychopharmacological Data Bank of the Institute of Clinical Psychiatry at the University of Pisa. Through this data bank we can store, retrieve and analyse individual patient information.

Results of factor analyses

Analyses of pretreatment HAM-D scores

In our first analysis we isolated three factors from 497 depressed patients' HAM-D scores (Table 1). The first factor included both anxiety and the core symptoms of depression (depressed mood, suicide, work and activities, retardation, feelings of guilt) with no distinction between anxious and retarded depression. The second factor included anxiety and insomnia and the third factor included somatization and hypochondriasis (Sarteschi *et al.*, 1973).

In our second analysis we isolated one factor from 1057 depressed inpatients' HAM-D scores (Table 2). This factor included anxiety, insomnia and the core symptoms of depression. The increased number of patients allowed a sharper definition of the depressive disorder by isolation of a few closely related items.

In our third analysis we used a procedure that allowed us to isolate as many factors as we wanted from the same 1057 depressed patients' HAM-D scores. We chose to isolate two factors to separate the symptoms of anxiety and depression. The first factor included anxiety and insomnia, and the second included the core symptoms of depression (Table 3). Figure 1 shows patient distribution according to

Table 1 Items included in three factors isolated by factor analysis of 497 depressed patients' HAM-D scores*

Item	Factor loading
First factor	
Depressed mood	0.73
Suicide	0.62
Work and activities	0.62
Retardation	0.52
Feelings of Guilt	0.49
Anxiety (psychic)	0.48
Depersonalization-derealization	0.43
Paranoid symptoms	0.40
Agitation	0.36
Total score	0.64
Second factor	
Insomnia (middle)	0.81
Insomnia (early)	0.77
Insomnia (late)	0.72
Anxiety (psychic)	0.37
Somatic symptoms (gastrointestinal)	0.37
Anxiety (somatic)	0.36
Agitation	0.34
Total score	0.44
Third factor	
Hypochondriasis	0.59
Anxiety (somatic)	0.50
Somatic symptoms (gastrointestinal)	0.43
Somatic symptoms (general)	0.30
Total score	0.35

*Rotated factor matrix (Kaiser, 1962). Eigen value >1.0. Items with factor loading >0.30 are reported.

Table 2 Items included in one factor isolated by factor analysis of HAM-D scores from 1057 depressed patients (816 with endogenous depression and 241 with neurotic depression)*

Item	Factor loading
Depressed mood	0.60
Work and activities	0.57
Suicide	0.46
Insomnia (late)	0.45
Anxiety (psychic)	0.45
Insomnia (early)	0.45
Insomnia (middle)	0.44
Retardation	0.44
Agitation	0.41
Somatic symptoms (gastrointestinal)	0.37
Feelings of Guilt	0.37
Somatic symptoms (general)	0.32
Depersonalization-derealization	0.26
Anxiety (somatic)	0.25
Hypochondriasis	0.23
Loss of insight	0.22
Paranoid symptoms	0.18
Loss of weight	0.14
Loss of libido	0.10
Obsessional symptoms	0.10
Diurnal variation	0.02

*Rotated factor matrix (Kaiser, 1962). Eigen value >1.0. Items underscored have factor loading >0.40.

Figure 1 Patient distribution (%) according to the higher loading of two factors, representing anxiety (first) and depression (second), isolated by factor analysis of 1057 depressed patients' HAM-D scores. Table 3 lists the items included in each factor. Solid columns, Endogenous depression ($n = 816$); hatched, neurotic depression ($n = 241$).

Table 3 Items included in two factors isolated by factor analysis of HAM-D scores from 1057 depressed patients (816 with endogenous depression and 241 with neurotic depression)

Item*	Factor loading
First factor	
Insomnia (early)	0.56
Insomnia (middle)	0.55
Insomnia (late)	0.53
Anxiety (psychic)	0.39
Agitation	0.39
Anxiety (somatic)	0.38
Somatic symptoms (gastrointestinal)	0.37
Somatic symptoms (general)	0.33

Second factor	
Depressed mood	0.59
Work and activities	0.55
Suicide	0.49
Retardation	0.49
Feelings of guilt	0.45

*Items with factor loading >0.30 are reported.

which of the two factors had the higher loading. In 28.2% of the patients with endogenous depression and 29% of those with neurotic depression, the loading in the two factors was equivalent. In 33.2% of the patients with endogenous depression and 47.3% of those with neurotic depression, the loading was higher in anxiety than in depression. In 38.6% of those with endogenous depression and 23.7% of those with neurotic depression, the loading was lower in anxiety than in depression.

Thus, in this group of 1057 depressed inpatients the loading in the anxiety factor seemed to equal or exceed that in the depression factor in 61.4% of the patients with endogenous depression and 76.3% of those with neurotic depression. We would expect that this clear numerical superiority of anxiety over depression as factors in depressive disorders would be even greater in an outpatient population.

Analysis of pretreatment SAD scores.

We used a procedure that allowed us to isolate factors with an eigen value >1.0. Two factors were isolated from the SAD scores of 648 patients with endogenous

depression and 565 with neurotic depression. Among 17 items the first factor included the core symptoms of depression, anxiety and insomnia. The second factor was very selective and included items reflecting somatic anxiety. In 26.1% of the patients with endogenous depression and 31.1% of those with neurotic depression, the loading in the two factors was equivalent. In 44.4% of the patients with endogenous depression and 22.7% of those with neurotic depression, the loading in the first factor was higher. In 29.5% of the patients with endogenous depression and 46.2% of those with neurotic depression, the loading in the second factor was higher.

Analysis of HAM-D scores after benzodiazepine or tricyclic antidepressant treatment

We isolated two factors from HAM-D score differences before and after benzodiazepine or tricyclic antidepressant treatment in 507 patients with endogenous depression (Table 4) and 214 patients with neurotic depression (Table 5). Data in both tables are categorized by patient age. In endogenously depressed patients 60 yr old or less, the first factor

Table 4 Items included in the first two factors isolated by factor analysis of HAM-D score differences before and after treatment with a benzodiazepine or a tricyclic antidepressant in 507 patients with endogenous depression*

<i>Patients ≤ 60 yr of age</i>		<i>Patients > 60 yr of age</i>	
<i>First factor items</i>	<i>Factor loading</i>	<i>First factor items</i>	<i>Factor loading</i>
Benzodiazepine patients (126)		Benzodiazepine patients (73)	
Retardation	0.48	Insomnia (middle)	0.69
Somatic symptoms (general)	0.40	Insomnia (early)	0.66
Depressed mood	0.31	Insomnia (late)	0.63
Tricyclic patients (179)		Somatic symptoms (general)	0.34
Work and activities	0.66	Anxiety (psychic)	0.32
Depressed mood	0.59	Tricyclic patients (129)	
Anxiety (somatic)	0.54	Depersonalization—derealization	0.52
Anxiety (psychic)	0.52	Feelings of guilt	0.52
Somatic symptoms (general)	0.47	Anxiety (psychic)	0.50
Retardation	0.43	Depressed mood	0.48
Agitation	0.42	Work and activities	0.44
Diurnal variation	0.40	Suicide	0.40
Somatic symptoms (gastrointestinal)	0.33	Agitation	0.32
Second factor items		Second factor items	
Benzodiazepine patients		Benzodiazepine patients	
Insomnia (middle)	-0.66	Somatic symptoms (general)	0.69
Insomnia (late)	-0.65	Work and activities	0.56
Insomnia (early)	-0.60	Depressed mood	0.52
Anxiety (psychic)	-0.40	Anxiety (somatic)	0.50
Somatic symptoms (general)	-0.30	Tricyclic patients	
Tricyclic patients		Insomnia (middle)	0.68
Insomnia (middle)	-0.71	Insomnia (late)	0.64
Insomnia (late)	-0.70	Insomnia (early)	0.63
Insomnia (early)	-0.68	Depressed mood	0.38
Depressed mood	-0.38		
Anxiety (psychic)	-0.34		

*Rotated factor matrix (Kaiser, 1962). Eigen value >1.0. Items with factor loading >0.30 are reported.

Table 5 Items included in the first two factors isolated by factor analysis of HAM-D score differences before and after treatment with a benzodiazepine or a tricyclic antidepressant in 214 patients with neurotic depression*

<i>Patients ≤ 60 yr of age</i>	
<i>First factor items</i>	<i>Factor loading</i>
Benzodiazepine patients (135)	
Insomnia (early)	0.63
Insomnia (middle)	0.63
Insomnia (late)	0.61
Anxiety (psychic)	0.60
Anxiety (somatic)	0.47
Somatic symptoms (general)	0.40
Agitation	0.34
Depressed mood	0.33
Tricyclic patients (79)	
Anxiety (somatic)	0.70
Hypochondriasis	0.44
Somatic symptoms (general)	0.34
Work and activities	0.31
Second factor items	
Benzodiazepine patients	
Depersonalization-derealization	0.49
Suicide	0.43
Tricyclic patients	
Libido	0.51
Paranoid symptoms	0.47

*Rotated factor matrix (Kaiser, 1962). Eigen value >1.0. Items with factor loading >0.30 are reported.

showed that the tricyclic antidepressant was more effective than the benzodiazepine against the core symptoms of depression, whereas the second factor showed the effect of both drug types on insomnia and anxiety (Table 4). In endogenously depressed patients more than 60 yr old, the first factor showed that the benzodiazepine primarily affected insomnia and anxiety, and the tricyclic antidepressant primarily affected the core symptoms of depression (Table 4).

In neurotically depressed patients 60 yr old or less, the first factor showed a wide benzodiazepine spectrum of activity, ranging from insomnia to anxiety to depressed mood, whereas the tricyclic primarily affected the somatic symptoms of anxiety (Table 5). Data for neurotically depressed patients more than 60 yr old were not analysed due to the limited number.

Discussion

Most of our factor analyses of HAM-D and SAD scores from patients with endogenous or neurotic depression enabled the anxiety and depression factors to be isolated. The prevalence of anxiety or depression in a given patient could be determined

even though pure anxiety or pure depression could not be distinguished.

The items included in the first factor in Table 1 and the underscored items in Table 2 reflect a correlation between anxiety and the core symptoms of depression. This correlation seems to indicate that patients suffering from endogenous depression may require a drug that is anxiolytic as well as antidepressant. In Table 1 the prominence of anxiety in the first factor, insomnia in the second factor and somatization and hypochondriasis in the third factor implies that most of these depressed patients require treatment focusing on three sets of symptoms: depression-retardation, anxiety-somatization, and insomnia. Are these sets of symptoms best treated with individual drugs or drug combinations? Are the spectrum of activity and onset of action of the tricyclic antidepressants complete and rapid enough for these symptoms? According to Johnson (1979), tricyclic antidepressants such as nortriptyline do not relieve anxiety until depression has improved. Hypnotic effects and effects on the somatization of anxiety with benzodiazepines would be useful in treating these symptom sets.

The data in Table 4 reveal that in patients 60 yr old or less the tricyclic antidepressant relieved more of the core symptoms of depression than did the benzodiazepine. The tricyclic and the benzodiazepine affected anxiety and insomnia equally (Cassano *et al.*, 1976). In patients more than 60 yr old, the tricyclic spectrum of activity was comparable with that of the younger group, whereas the benzodiazepine primarily affected anxiety and insomnia.

The data in Tables 4 and 5 reveal a correlation between the effect of tricyclic antidepressants on insomnia and their effect on depression. These data also reveal a correlation between the effect of benzodiazepines on insomnia and their effect on anxiety. Particularly in patients with neurotic depression, relief of insomnia symptoms following benzodiazepine treatment correlated closely with relief of a wide range of anxiety symptoms.

Conclusions

The use of benzodiazepines in most endogenous or neurotic forms of depression is justified by their selective action on anxiety and insomnia—an action that may be considered complementary to that of the tricyclic antidepressants on the same symptoms. We base this conclusion on: (1) clinical trials which showed the coexistence of anxiety and depression in depressed patients and the effective treatment of their symptoms with a benzodiazepine-tricyclic antidepressant combination; and (2) factor analysis which supported the clinical findings.

The value of using a benzodiazepine in combination with a tricyclic antidepressant in treating depressed patients is further supported by these additional findings from earlier clinical trials: (1) the therapeutic effects of various benzodiazepines differ only slightly and their spectrum of activity involves insomnia, psychic and somatic anxiety, agitation and somatic gastrointestinal symptoms; (2) the onset of the therapeutic effects is rapid; (3) benzodiazepines differ from tricyclic antidepressants because they do not affect motor retardation and they very moderately relieve the core symptoms of depression; and (4) benzodiazepines seem to exert their therapeutic effect constantly and independently of patient's age in patients suffering from endogenous or neurotic depression (Cassano *et al.*, 1973).

In depressive disorders requiring long-term treatment, such as chronic depression or partial remission of a limited set of symptoms, a tricyclic antidepressant alone seems to be the preferable treatment. Additional clinical trials are needed to confirm this view.

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