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The use of benzodiazepines in depression

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1 In clinical practice the benzodiazepines are prescribed almost as frequently as the tricyclic antidepressants for the treatment of depression.
2 The therapeutic effects of the benzodiazepines and tricyclic antidepressants in depression have been compared in only 29 double-blind studies. The antidepressants proved overwhelmingly superior with only one study (alprazolam) even suggesting a possible parity of action.
3 A symptom response analysis failed to show any true antidepressant action for the benzodiazepines.
4 No clear indication for the use of a combination of drugs was revealed, although certain symptoms may show a more rapid response initially with combination therapy.

Keywords depression benzodiazepines alprazolam

Extent of use of benzodiazepines in depression

An examination of the prescribing habits of doctors clearly indicates that the benzodiazepines are regarded as a major treatment for depression.

Studies of the treatment of depression offered by general practitioners in the last decade (Johnson, 1973a: Tyrer, 1978) suggest that family doctors appear to prescribe tricyclic antidepressants and benzodiazepines almost interchangeably, with the benzodiazepines being prescribed as much for depression as anxiety. One author (Johnson, 1973c; 1981; 1983) reported that although most general practitioners may start treatment for a new episode of depression with a tricyclic antidepressant, the longer the patient remains in treatment without a resolution of his depression, the more likely the patient is to have the dose of his tricyclic drug reduced to a non-therapeutic level, or, alternatively to have his treatment changed to a benzodiazepine (Johnson, 1974). Bellantuono *et al.* (1980) concluded from analysis of market research data that some 20% of all benzodiazepine prescriptions were motivated by the treatment of depressive symptoms. Other studies carried out by the GP Research Unit of the Institute of Psychiatry in London (Clare, 1981) found this interchange in the use of tricyclics and benzodiazepines was true only for women. Approximately one half of the depressed females were prescribed a tricyclic drug compared to almost all males. However, even with this last result since twice as many women receive prescriptions for depression, this still means a third or more of the population with depression receive benzodiazepines.

This is clearly a matter of considerable importance since most general practice surveys consistently report that depression is responsible for 10–20% of consultations, and is the fourth to thirteenth most frequent diagnosis made. A recent survey (Dunn & Skuse, 1981) revealed that nearly three-quarters of women and over half of males attend their general practitioner at least once in 20 years with a psychiatric complaint. Of this latter population 70% of the women and 34% of the men had an episode of depression.

The importance of these results is underlined by the fact that Goldberg & Blackwell (1970) found that in the setting of general practice even trained research psychiatrists miss one-third of cases, so the known results are an underestimate of the true prevalence of depression, and therefore the potential for the prescription of an antidepressant drug. It is also

known that the most common form of treatment for depression, both in general practice and hospital, is the prescription of a tablet accompanied by a fairly brief form of reassurance (Shepherd *et al.* 1966; Johnson, 1973a, b, c).

The conclusion must be that over the last decade nearly half the patients under treatment for depression were prescribed benzodiazepines as an essential part of their treatment. A recent study in Manchester comparing the drug prescriptions both in patients treated wholly in the community, and those referred to the outpatient departments of hospital, suggested that habits have not changed substantially over the last decade despite the explosion in number of available antidepressants (Johnson, 1984).

The efficacy of benzodiazepines as antidepressants

The reason why tricyclic antidepressants are so unpopular is clear in the minds of most general practitioners questioned. These drugs have unpleasant side-effects which are the single largest factor in leading to a non-compliance rate of 40–60% over a relatively short period of 6 weeks. However, the question that must be answered is, 'do the benzodiazepines have any true antidepressant action?' Is it reasonable that so many depressed patients should be prescribed benzodiazepines as their primary treatment of depression?

A search of the literature for double-blind controlled studies was very disappointing for a topic of such importance to the well-being of so many patients. In 1980 Bellantuono *et al.* reviewed 21 studies, in 1981 Schatzberg & Cole found 22 studies, in 1983 Johnson reviewed 27 published studies; this later review forms the basis for the present review.

Out of these 27 double-blind studies 12 reported the tricyclic antidepressants to be clearly superior, one study identified the benzodiazepines as superior and 14 studies failed to show any statistical difference between the groups.

The single study in favour of the benzodiazepines at the final evaluation is open to other interpretations (Shammas, 1977) for three reasons: (a) the tricyclic antidepressant group had a disproportionate high drop-out rate, (b) the mean dose of tricyclic was only 94 mg and (c) the actual symptom response reported may have explanations other than a change of depression.

A closer inspection of the 14 studies which reported no difference at final outcome reveals: (a) three studies claim a trend in favour of the benzodiazepines, but in two studies this is based only on a more rapid symptom response in the first 3 weeks, which is then lost. Therefore, in reality only one study claims a trend in favour of the benzodiazepines which exists at outcome; (b) five studies claim a trend in favour of the tricyclic antidepressants based upon final outcome; (c) six studies report no trends. These reported trends clearly add support to the conclusions of the studies which demonstrated a statistical difference, emphasising the superiority of the tricyclic antidepressants.

An inspection of the methods of the trials reported makes it very surprising that the tricyclic antidepressants ever achieved superiority, or even a significant trend for advantage, since they rarely had the opportunity to demonstrate their true therapeutic potential. In only six of the 27 studies were the patients prescribed a generally accepted full therapeutic dose of 150 mg for a minimum period of 3 weeks. An analysis of these six studies reveals that in four the tricyclics were reported as superior, and in two no statistical difference was found (Rickels *et al.*, 1973; Johnson, 1979). In the three studies claiming trends in favour of benzodiazepines—although these claims have already been challenged—two of the studies involved a non-therapeutic dose of the tricyclics and the other study failed to record the dose published.

Sub-types of depressive illness

A further difficulty in reaching any firm conclusion, and certainly in trying to establish any claim for an antidepressant action by the benzodiazepines, is the operational criteria for diagnosis used. Most of the studies were on anxious, reactive or psychoneurotic depressions. Again this raises the question of the opportunity to demonstrate a true antidepressant effect for either drug.

To overcome this particular objection those studies with endogenous, or endogenous-like, depressions have been identified. This was often difficult because of the imprecise nature of the definitions used, but seven such studies were identified. Three studies show a clear superiority for the tricyclic drugs. One of these studies was a 7-month continuation study after ECT, the other two studies were short duration treatments for an acute episode. The other four studies gave no advantage to either drug group—one of these studies specifically excluded the more severely depressed patient, and two studies included only mild depressions judged by the rating scores reported. There may be a

clue here why neither drug showed a clear superiority since Paykel (1972) has demonstrated that the potential to demonstrate a difference between drugs correlates with the initial score. A low initial score reduces the probability. In the fourth of these studies a further reason why a firm conclusion is difficult is because details of the dose schedules are not clear. However, this last study is the only study that comes anywhere near establishing parity of therapeutic effect for the two drugs in endogenous-like depressions. The author (Feighner, 1982) claims a different action for the prescribed benzodiazepine (alprazolam) to other members of this group.

In my opinion, despite the obvious problems, the clinical scene is becoming more clear. The evidence for a superiority of clinical effect is substantially in favour of the tricyclic antidepressants in both mixed depressions and endogenous-like depressions. Even where only trends can be demonstrated, the results are overwhelmingly in favour of the tricyclic drugs. Only the one study with alprazolam even suggests a possible parity.

Symptom response

So far the analysis of results has been based on outcome of illness; it may be helpful to look at more specific symptom response. In 1981 Schatzberg & Cole carried out a sophisticated analysis of 22 of the 27 studies reported. They found the benzodiazepines were most effective in reducing anxiety, tension, insomnia, decreased libido and reduced interests, but that they had little effect upon retardation, anergia, diurnal variation, suicidal ideation or suicidal behaviour. In one study psychomotor retardation was increased, and in others suicidal ideation was exacerbated by benzodiazepines. In a different analysis, Cassano & Conti (1981) found the benzodiazepines most effective in relieving insomnia, anxiety and agitation, but had a lesser effect upon mood and the level of interest. They also commented that the benzodiazepines had little effect upon the traditional biological symptoms, and concluded that patients with the more endogenous-like clinical state had the highest level of residual symptoms when treated with benzodiazepines.

The problem has been examined from a different approach. Johnstone *et al.* (1980) looked at the symptom response of 240 neurotic out-patients who were experiencing anxiety and depressive symptoms, but not allocated to diagnostic categories. Over a 4 week period the outcome was found to be quite good, but they concluded drugs only made a small contribution to this outcome. Where drugs were identified as influencing outcome it was thought the tricyclic antidepressant amitriptyline was superior to the use of benzodiazepines.

An analysis of symptom response again suggests the tricyclic antidepressants are superior, and shows no evidence of a true antidepressant effect for the benzodiazepines.

Combinations of benzodiazepines and tricyclic antidepressants

The fact that the benzodiazepines have not been shown to be as efficient as the tricyclic drugs, or even that they may not have a true antidepressant effect, does not necessarily mean that they have no place in the treatment of depression. The possibility that a combination of a tricyclic and a benzodiazepine may be the most efficient treatment has to be explored. Equally, it must be pointed out that there are many good reasons why any form of combination therapy, but in particular a combination of two drugs in a fixed ratio in one tablet, should be avoided. Nevertheless an evaluation of the literature is required since combination therapy is not uncommon.

An examination of the literature is again disappointing since very little investigation under strictly controlled double-blind conditions exists. In 1978 Hollister suggested benefits from combination therapy, but in a more recent review in 1981 appears to have revised his views, saying these patients respond to non-specific treatments. Feighner *et al.* (1979) found a combination therapy beneficial at the beginning of a trial, with insomnia and anxiety selectively responding to the addition of benzodiazepines, but by the fourth week any advantage had been lost. Johnstone *et al.* (1980) found no advantage. A literature search revealed only six studies which claimed a benefit for combination therapy, but a careful study of these results shows that the antidepressant effect claimed depends upon a high initial anxiety score, which then responds more rapidly to combination therapy than a tricyclic drug alone. However, evaluation at 4 weeks demonstrates no difference on global depression scores, or endogenous depressive type symptoms. In 1977 Cassano *et al.* carried out a factor analysis of the individual items of the Hamilton Rating Scale for Depression, and a separate Self-Administered Depression Scale. They found some individual items—mostly anxiety items—did have a better response to combined therapy than to antidepressants

alone, but this analysis did not in fact show any enhanced antidepressant effect from combination therapy.

It is likely that this particular area has been inadequately researched, but at the present time there is no evidence that the antidepressant effect of the tricyclic drugs is improved by the addition of a benzodiazepine, even though individual anxiety symptoms may benefit in the first 2 or 3 weeks.

Benzodiazepines and depression

The final question to be addressed is 'do the benzodiazepines actually cause depression?' Certainly some of our most prestigious textbooks state this to be the case, e.g. Hollister (1978), and Baldessarini (1980) in Goodman & Gilman.

An analysis of the double-blind trials reviewed today has suggested that psychomotor retardation and suicidal ideation may be made worse by benzodiazepines. Weissman & Klerman (1977) have reported that the usage of benzodiazepines can be associated with a depression assuming a more chronic form. Schatzberg & Cole (1978) also reported a relatively high percentage of benzodiazepine treated depressions as failing to respond to subsequent treatments. However, a careful examination of their reports, and others, notably by Gunderlach *et al.* (1966), Ryan *et al.* (1968), Hall & Joffe (1972) and Zisook & Devaul (1977) reveals that there are no double-blind trials demonstrating to an acceptable level of significance that the taking of benzodiazepines actually induces depression. In a recent review of this literature by Hall & Zisook (1981), it was concluded that the incidence of such paradoxical effects was very low, and when they occur would appear to be an idiosyncratic response. The entire literature on this point would appear to be without firm experimental evidence.

Conclusions

My conclusions are therefore:

(1) The benzodiazepines are extensively prescribed for depression in clinical practice as the primary treatment.
(2) The research literature at the present time fails to show any clear evidence that the benzodiazepines in general have any true antidepressant effect, and they are certainly inferior to the tricyclic antidepressants in their therapeutic effect upon such patients—the exception may be alprazolam.
(3) The response of depressive type symptoms in non-specific syndromes show a better response to tricyclic drugs (amitriptyline).
(4) There are no clear indications for the use of a combination of drugs using a benzodiazepine and tricyclic antidepressant in the treatment of depression, although it is acknowledged that certain individual symptoms may have a more rapid response to a combination therapy in the first few weeks.
(5) There is no evidence that the benzodiazepines induce a depression—but the literature is neither extensive, nor conclusive in this area.

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