

## Anxiolytic Effect of Hydroxyzine: A Double-Blind Trial Versus Placebo and Buspirone

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Benzodiazepines have major drawbacks including lessening of anxiolytic effect in long-term use, impairment of psychological functioning, problems on discontinuation, and addiction potential. Alternatives have been sought including the antihistamines such as hydroxyzine. Two studies are described, one comparing hydroxyzine 50 mg/day with placebo in GAD patients. Significant advantages were found for the active drug. The second GAD evaluation compared hydroxyzine 50 mg/day, buspirone 20 mg/day, and placebo. Hydroxyzine was significantly superior to placebo with buspirone intermediate. Adverse effects were minor and transient. It is concluded that hydroxyzine may prove a useful and safer alternative to the benzodiazepines. Copyright © 1999 John Wiley & Sons, Ltd.

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### INTRODUCTION

The benzodiazepines remain the most commonly prescribed drugs for the treatment of anxiety of various types. They are generally regarded as efficacious in assuaging anxiety and tension, and facilitating sleep. However, their unwanted effects comprise some major drawbacks which include (Lader, 1994):

- (i) Waning of effect in the long-term.
- (ii) Paradoxical release of anxiety and hostility.
- (iii) Impairment of psychomotor and cognitive functioning, particularly semantic memory.
- (iv) Severe neuropsychiatric reactions, including amnesia and depression.
- (v) Ataxia and confusion in the elderly.
- (vi) Problems on discontinuation, including a characteristic withdrawal syndrome in a minority of patients after long-term normal-dose use.
- (vii) A liability to high-dose dependence and abuse (Hallström, 1993).

Knowledge of these adverse effects has led to concern in many countries and adjurations to limit usage to a few weeks (e.g. Committee on Safety of Medicines, 1988). This has been followed by a decline in the number of anxiolytic benzodiazepine prescriptions.

As a consequence, a therapeutic need has been identified for the longer-term treatment of

anxiety disorders, specifically Generalized Anxiety Disorder (GAD; DSM-IV, APA, 1994). A switch has been made to non-drug treatments, ranging from counselling and relaxation to psychotherapies of various depths (Hackmann, 1993). Pharmaceutical alternatives have also been sought. Among the newer compounds are buspirone, a 5HT<sub>1A</sub> partial agonist (Gelenberg, 1994) and its congeners, the azapirones. Unfortunately, these compounds are gradual in onset of action and of uncertain efficacy in 'pure' GAD: they seem more efficacious in patients with an admixture of anxiety and depression.

### HYDROXYZINE

This compound is an H<sub>1</sub> antihistaminic agent with some blocking actions on cholinceptors as well. It has anxiolytic/sedative properties and was introduced in France over 40 years ago. It is licensed in most countries to treat patients with anxiety often in conjunction with bodily symptoms. Thus, an evaluation of 1600 patients by 160 physicians (Weber, 1987) confirmed its efficacy in treating anxiety (Nakache and Gueguen, 1987) associated with asthma or bronchial spasm (Ramon, 1987), dyspepsia and irritable bowel syndrome (Grimaldi, 1987), pruritus (Cambazard, 1987), and cardiac pathology (Marcadet, 1987).

Hydroxyzine has also been used with some success as a surgical premedicant, either alone (Wallace and Mindlin, 1984) or in combination with chloral hydrate (Tsinidou *et al.*, 1992) or with morphine (Schneider, 1986). One placebo-controlled trial was, however, negative (Boon and Hopkins, 1996). Some analgesic adjuvant properties have been noted (Rumor and Schlichting, 1985), but again another study was negative (Yosselson-Superstine *et al.*, 1985).

Noteworthy in all these decades of use has been the paucity of reports of memory impairments or of dependence or abuse. Discontinuation of normal-dose usage is uniformly uneventful. The only unwanted effect of note is somnolence and this is often transient, or related to higher doses (over 50 mg) only. Because of this favourable profile, it was judged opportune to re-examine the risk/benefit characteristics of hydroxyzine using modern diagnostic criteria for GAD, rigorous trial design and ratings, and up-to-date statistical analyses. To evaluate efficacy, two studies have been conducted so far.

#### THE FERRERI ET AL. (1994, 1995) STUDY

This multi-centre study (Ferreri *et al.*, 1994, 1995) involved over 100 patients suffering from GAD according to DSM-III-R criteria (APA, 1987), i.e.

with a minimum of 6 months duration of illness. All had a rating of at least 20 on the Hamilton Anxiety Rating Scale (Hamilton, 1959), and less than 10 on the 17-item Hamilton Depression Rating Scale (Hamilton, 1960). Benzodiazepines taken for more than 2 days per week in the 4 weeks preceding the study or at any time during the week before the trial precluded inclusion. Patients were allocated randomly to either 50 mg hydroxyzine daily or placebo, in divided doses. They were assessed on four occasions, at the start of the study (visit 1, week 0), after one week of therapy (visit 2, week 1), after four weeks (visit 3, week 4), and one week after stopping treatment (visit 4, week 5). A variety of rating scales was used, both observer- and self-administered.

Of the patients satisfying full criteria for inclusion into the study, 66 were female and 44 male. The mean age was  $43.7 \pm 11.9$  years. The initial HARS score was  $25.9 (\pm 4.2)$  in the hydroxyzine-treated group and  $24.1 (\pm 3.9)$  in the placebo group ( $p < 0.01$ ). The groups did not differ in any other respects. The primary outcome variable was the HARS and the total mean scores in the two groups are shown in Figure 1. Anxiety scores diminished with both treatments, but by week 4 a significant difference had emerged between active drug and placebo. Other rating scales showed similar effects (e.g. Tyrer Brief Scale;

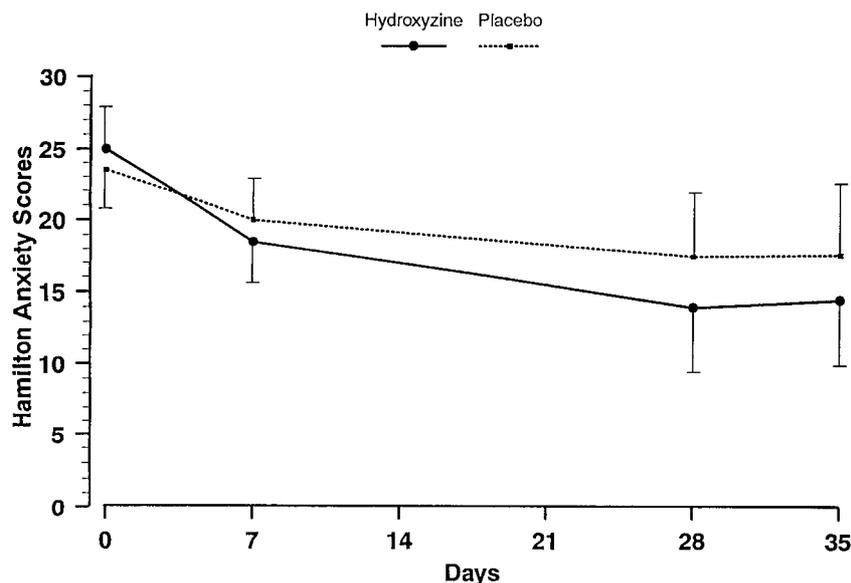


Figure 1. Mean effects of hydroxyzine and placebo on Hamilton Anxiety Rating Scale over 28 days of treatment followed by 7 days of placebo substitution (data from Ferreri *et al.*, 1995)

Tyrer *et al.*, 1984). It can also be seen that the improvements tended to persist after discontinuation of medication to week 5, and the treatment differences also persisted. No withdrawal effects were detected. Adverse effects were not usually severe: only three patients discontinued because of them — two in the hydroxyzine group (one with renal colic and infection, the other with sleepiness and vertigo) and one on placebo (nervousness, depression, vertigo and tachycardia). The most commonly reported adverse effects were sleepiness (28 per cent in hydroxyzine versus 14 per cent in placebo), dry mouth (14 per cent versus 15 per cent), weight gain (12 per cent versus 10 per cent), insomnia (9 per cent versus 6 per cent) and nervousness (7 per cent versus 5 per cent). It would seem that drowsiness is the only adverse effect of note, but even this was not significantly different between the groups ( $p = 0.114$ ). These reports tended to decrease between weeks 1 and 4.

#### THE LADER-SCOTTO *ET AL.* (1998) STUDY

Encouraged by these results, a second double-blind placebo-controlled study was conducted. This was similar in many respects to the Ferreri *et al.* (1994, 1995) study, but it also included an active comparator, namely buspirone. The criteria for GAD were DSM-IV (APA, 1994).

Patients were seen by primary care practitioners who were coordinated by several hospital-based psychiatrists. The participating doctors were trained in the use of the various rating scales including diagnostic criteria. A total of 105 centres was involved with 75 in France and 30 in the UK. The study was approved by all the local appropriate Ethics Committees and all participants gave informed consent. The study was carried out according to the GCP-ICH guidelines.

Outpatients of either sex between the ages of 18 and 65 were eligible for inclusion. Their initial Hamilton Anxiety Rating Scale score had to be 20 or more and DSM-IV criteria for GAD had to be met, including excessive anxiety and worry, occurring more days than not, *for at least 6 months*. An admixture of depression was not an exclusion criterion, but the symptoms had not to be of sufficient severity to warrant a separate diagnosis of a depressive disorder. This was checked by using the Montgomery-Asberg Depression Rating Scale (MADRS, Montgomery and Åsberg, 1979). Thus, patients could be divided into those with uncomplicated GAD and those with a primary diagnosis

of GAD together with some depressive symptoms. This reflects the symptom patterns encountered in anxious patients seen in primary care.

Exclusion criteria included pregnancy or inadequate contraceptive precautions, severe physical illness, organic or psychotic disorders, major depressive disorder or alcohol abuse, and patients undergoing or needing psychotherapy. Treatment with psychotropic agents, including hydroxyzine and buspirone, during the previous 4 weeks was also an exclusion criterion as was the continued use of a benzodiazepine for more than 2 days per week.

Patients regarded as eligible for inclusion at the screening visit were placed single-blind on placebo for a week (D-7 to D0) and reassessed. This included a urinary drug screen for opioids, amphetamines, benzodiazepines, etc. Any patient who showed an improvement of 7 points or more in the HARS was excluded as a placebo responder, as was anyone proving positive on the urinary screen. Patients were then allocated randomly to receive over 4 weeks (D0 to D-28) fixed doses of either:

- (i) Hydroxyzine 50 mg/day in divided doses — 12.5 mg morning and midday and 25 mg in the evening.
- (ii) Buspirone 20 mg/day as 5, 5, and 10 mg.
- (iii) Placebo 3 capsules as 1, 1, and 1.

The drugs were formulated as identical-looking capsules and the trial was run under double-blind conditions. Compliance was estimated by a capsule count on each attendance. No concomitant psychotropic medication was permitted and beta-adrenoceptor antagonists and clonidine were also excluded.

After 28 days of treatment, patients were replaced single-blind on placebo for 7 days (D-28 to D-35) to evaluate possible effects of discontinuing medication.

Both investigator- and self-ratings were carried out. The investigator completed the following rating scales on days 0, 7, 28 and 35:

- (i) Hamilton Anxiety Rating Scale (Hamilton, 1959). This was designated the main outcome variable.
- (ii) Montgomery-Asberg Depression Rating Scale (Montgomery and Åsberg, 1979).
- (iii) Clinical Global Impression (Ecdeu, 1976).
- (iv) Ferreri Anxiety Rating Diagram (at French centres only) (Ferreri *et al.*, 1988).

Table 1. Demographic and baseline data (ITT)

Variable	Means (SD)		
	Hydroxyzine ( <i>n</i> = 81)	Buspirone ( <i>n</i> = 82)	Placebo ( <i>n</i> = 81)
Sex F/M	56/25	62/20	51/30
Mean age	42 (11)	41 (12)	40 (11)
Number of previous episodes of anxiety	4.3 (3.6)	5.7 (11.8)	4.7 (5.0)
Prior depressive episode	28 per cent	17 per cent	10 per cent
Ham-A	26.6 (4.3)	26.7 (4.1)	26.2 (4.2)
MADRS	17.0 (7.4)	17.7 (7.1)	15.7 (7.0)
C.G.S.	4.4 (0.7)	4.4 (0.7)	4.3 (0.7)
HADS	21.9 (5.3)	21.8 (5.3)	21.0 (4.3)
EDC	35.2 (10.6) ( <i>n</i> = 53)	31.4 (10.8) ( <i>n</i> = 53)	34.2 (10.5) ( <i>n</i> = 52)
FARD	31.1 (7.8) ( <i>n</i> = 60)	30.3 (7.4) ( <i>n</i> = 59)	29.5 (7.1) ( <i>n</i> = 60)

The patients rated themselves on:

- (i) Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983).
- (ii) Echelle de dyscontrôle comportemental (EDC, Hantouche *et al.*, 1992) — in France only.

These two scales were completed weekly. The Tyrer Withdrawal Symptom Scale (Tyrer *et al.*, 1990) was filled in by the patients on days 28 and 35. Further urinary benzodiazepine screens were carried out on days 7, 18 and 35, as were brief clinical examinations. Adverse events were recorded whether or not they were attributed to the medication.

Power calculations suggested that a total of 180 evaluable patients were needed to allow the detection with a 90 per cent probability of a drug–placebo difference of 5 points on the HARS ( $p < 0.05$ ). To allow for drop-outs, the target of 228 patients was set. Statistical analyses followed recommended procedures with last observation carried forward (LOCF) data being relied upon. Parametric data were analysed using analysis of variance, non-parametric data by the Kruskal–Wallis test, and qualitative data using the chi-square statistic. The double-blind coding was broken at the end of data analysis.

Recruitment took place over 6 months and a total of 266 patients were recruited, of whom 20 failed to meet inclusion criteria after the 7 days placebo run-in period. A further two patients dropped out before taking any medication leaving 244 evaluable patients. Their baseline character-

istics are listed in Table 1. Most patients were female, the mean age in the early forties, and most had suffered previous episodes. The mean initial HARS score was about 26.5, and the MADRS depression score quite appreciable at 17. There were no significant differences between the three treatment groups at baseline.

#### EFFICACY

Data for the primary outcome variable, the HARS, are shown in Figure 2. The difference between hydroxyzine effect (12 points) and placebo effect (7.5 points) was significant ( $F = 4.29; p = 0.015$ ), but not those between hydroxyzine and buspirone, and buspirone and placebo. The psychic and somatic anxiety subscales of the HARS showed similar patterns (Figure 3), but the hydroxyzine–placebo contrast for the somatic anxiety scale did not quite reach the conventional level of significance ( $p = 0.059$ ).

Another way of evaluating treatment effects is in terms of percentage of patients who respond (halving or more of Hamilton score) or remit (final score less than 10). These histograms are depicted in Figure 4: although the data favour hydroxyzine, the trends do not quite reach significance for either parameter.

Other outcome variables are listed in Table 2. Hydroxyzine was significantly superior to placebo with respect to CGI, MADRS, HADS-depression, HADS-anxiety, EDC and Ferreri scales. Buspirone is superior to placebo for the MADRS, HADS dep and anx, EDC and FARD, i.e. the same scales.

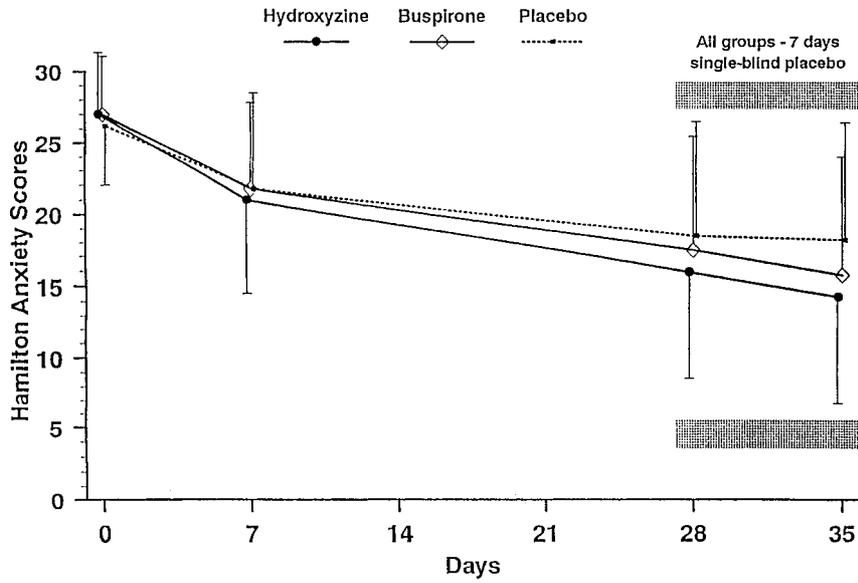


Figure 2. Mean effects ( $\pm$ SD) of hydroxyzine, buspirone and placebo on Hamilton Anxiety Rating Scale scores of 28 days of treatment followed by 7 days of placebo substitution

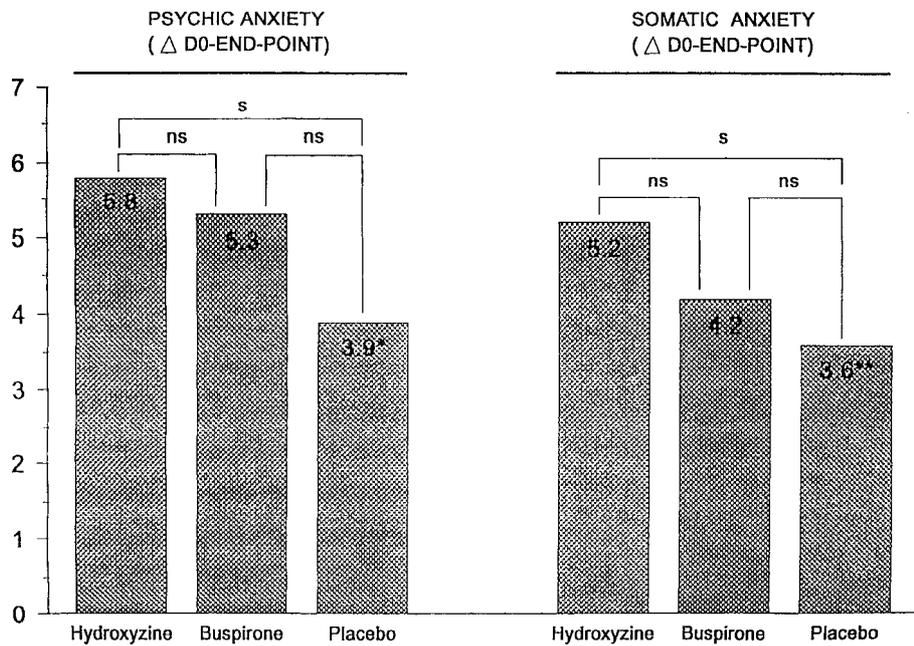


Figure 3. Mean effects of hydroxyzine, buspirone and placebo on psychic and somatic anxiety subscales

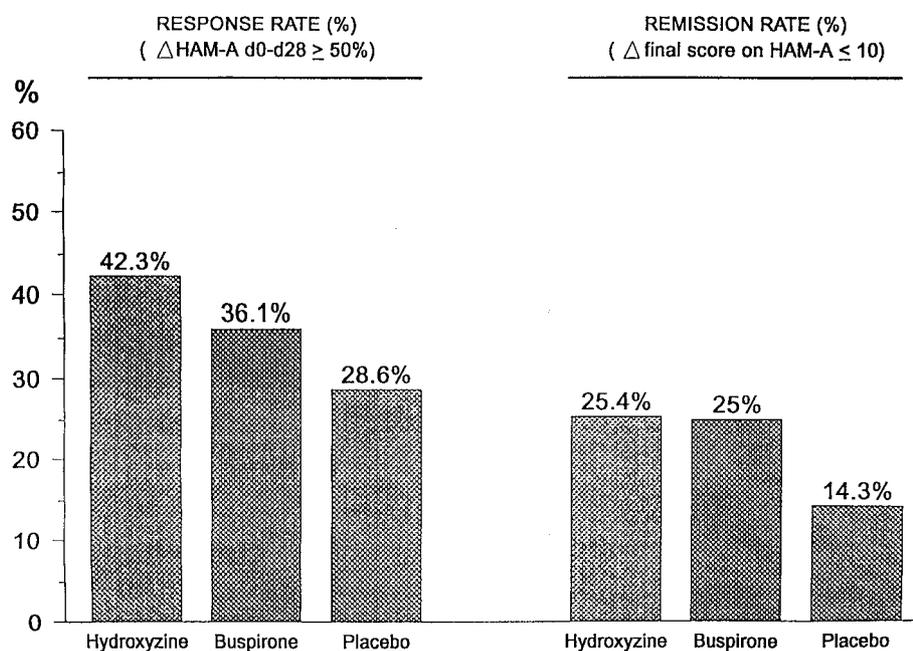


Figure 4. Response and remission rates in patients treated for 28 days with hydroxyzine, buspirone or placebo

Hydroxyzine is not significantly more effective than buspirone for any variable, although its effect size is uniformly greater.

Only one quarter of the patients were judged to have 'pure' GAD, the rest suffering an admixture of depression. This is mirrored in the appreciable initial MADRS scores. The differences between these post-hoc groups were only that the mixed

group was more anxious and impulsive than the pure group. However, some differential drug effects were detected (Figure 5): buspirone was more effective in the mixed than in the pure group, whereas hydroxyzine (HDX) tended to be equally effective in both groups.

As Figure 2 shows, no rebound was seen with respect to HARS scores when placebo was sub-

Table 2. Effects of treatments on some secondary efficacy variables — change over 28 days (D0–D28)

Variable	Means (SD)		
	Hydroxyzine	Buspirone	Placebo
CGI	1.53 (1.3)	1.27 (1.2)	0.95 (1.1)*
MADRS	6.64 (6.9)	6.35 (7.5)	2.97 (6.0)†
HADS-Dep	2.05 (3.8)	1.89 (4.2)	0.11 (3.1)‡
HADS-Anx	4.01 (3.9)	3.31 (4.0)	1.41 (3.0)§
EDC	12.8 (12.5)	10.0 (15.5)	4.0 (8.4)¶
FARD — Total	14.3 (11.5)	12.1 (11.1)	6.8 (7.7)

\*  $p < 0.02$ ; H > P.

†  $p < 0.001$ ; H + B > P.

‡  $p < 0.01$ ; H + B > P.

§  $p < 0.001$ ; H + B > P.

¶  $p < 0.02$ ; H + B > P.

||  $p < 0.001$ ; H + B > P.

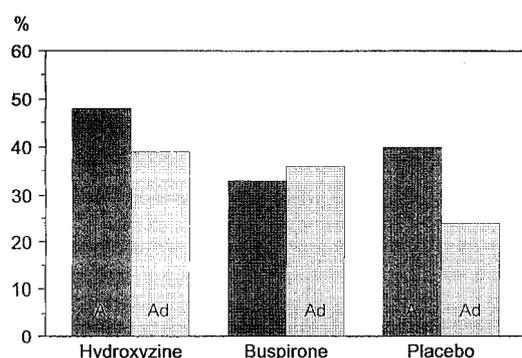
**HAM-A CHANGES AT END-POINT (50% improvement)**

Figure 5. Hamilton Anxiety Score 50 per cent improvement response rates in patients with (Ad) and without (A) depressive symptoms treated for 28 days with hydroxyzine, buspirone or placebo

stituted on day 28. In fact, both groups who had received active medication continued to improve. The other efficacy variables showed similar effects. No withdrawal symptoms were detected on the Tyrer scale.

**ADVERSE EFFECTS**

Of the 244 patients who received medication, only 10/81 in the hydroxyzine, 10/82 in the buspirone and 11/81 placebo dropped out before 28 days (an overall 12.7 per cent). The commonest reason was protocol violation, with only two per group due to lack of efficacy. No serious ADRs were reported. The main problematic side-effects complained of by more than 5 per cent of the exposed patients were:

- (i) Somnolence in the hydroxyzine group (9.9 per cent) as compared with 4.9 per cent

in the buspirone and none in the placebo group.

- (ii) Headache and migraine in the buspirone group (6.1 per cent) versus 4.9 per cent hydroxyzine and 1.2 per cent placebo.
- (iii) Dizziness in buspirone-treated (6.1 per cent) versus 0 in the hydroxyzine and 2.5 per cent in those patients given placebo.

Others, as shown in Table 3, were commoner but less troublesome. Overall, 32/81 hydroxyzine, 31/82 buspirone and 23/81 placebo-treated patients reported one or more side-effects. Many of these side-effects, such as nausea and dizziness, were transitory and drowsiness usually diminished after the first week.

**DISCUSSION**

Patients were recruited for the study quite rapidly, few responded to initial placebo, the day-to-day conduct of the study was uneventful and the drop-out rate was gratifyingly low, being less than 15 per cent. This is attributable to the experience of the investigators, and careful training by the psychiatrists of their groups of general practitioners. In addition, many of these GPs had a particular interest in psychiatric problems. In view of the consistently positive results for hydroxyzine, less so for buspirone, it can be concluded that the rating procedures were both reliable and valid.

The patients involved were fairly typical of those participating in previous GAD trials (e.g. Anseau *et al.*, 1991; Power *et al.*, 1990). Thus, the ratio of females/males was 2:1 with a mean age in the early 40s. The disorder was generally a chronic or relapsing one with about five previous episodes, during which a wide range of treatments had been employed and the typical patient had anxiety of moderate severity.

Table 3. Tolerance of hydroxyzine versus buspirone

	Hydroxyzine 50 mg (n = 81)	Buspirone 20 mg (n = 82)	Placebo (n = 81)
Side-effect	32 (39.5 per cent)	31 (37.5 per cent)	23 (28.4 per cent)
<i>Nature</i>			
Transient sleepiness	8 (9.9 per cent)	4 (4.9 per cent)	0
Anticholinergic	7 (8.6 per cent)	9 (11 per cent)	3 (3.7 per cent)
CNS stimulant*	1 (1.2 per cent)	5 (6.1 per cent)	1 (1.2 per cent)
Gastro-intestinal*	9 (11.1 per cent)	12 (14.6 per cent)	7 (8.6 per cent)

\* 5HT stimulation.

The primary efficacy variable, the Hamilton Anxiety Rating Scale Score, showed significant differences between hydroxyzine and placebo, but not between buspirone and placebo. Moreover, hydroxyzine was not significantly different from buspirone. The analyses by sub-group suggested that buspirone showed better efficacy in patients with an admixture of depression than in those with 'pure' anxiety. By contrast, hydroxyzine was equally effective in both groups. The secondary variables, including self-ratings, mostly showed both hydroxyzine and buspirone to be superior to placebo. Thus, hydroxyzine is confirmed as having efficacy in GAD, across a fairly wide spectrum of assessment instruments, both investigator- and self-rated. In terms of numbers improved (CGI rating), about 40 per cent of those treated showed major improvement as compared with less than 30 per cent on placebo. It must be remembered most of these patients had been ill for several months with anxiety.

Adverse effects were not a major problem with hydroxyzine, despite the known sedative effects of centrally-acting antihistaminic compounds. Somnolence was reported in about 10 per cent of patients, but this was a fixed dose study so that dosage adjustment might be expected to lessen this figure. The side-effect profile with buspirone was as expected, with headache and dizziness at fairly low rates.

This study was designed to confirm the results of an earlier study (Ferreri *et al.*, 1994) that hydroxyzine was an effective drug in the treatment of patients with the carefully-defined primary diagnosis of Generalized Anxiety Disorder. The main difference between the two studies was the incorporation of an active comparator, buspirone, in the present study. Comparison with the Ferreri *et al.* (1994) study shows that efficacy was a little less in the present study (Figure 6). Also, the difference in number of responders on the HAM-A on hydroxyzine (41 per cent) versus placebo (18 per cent) was significant ( $p < 0.01$ ) in the earlier study, but not the present one.

## CONCLUSIONS

One of the main reasons for re-evaluating the risk/benefits of hydroxyzine in GAD is the concern over the dependence potential of the benzodiazepines (Hallström, 1993). Although 4 weeks is a relatively short term for the induction of dependence, no discontinuation phenomena were

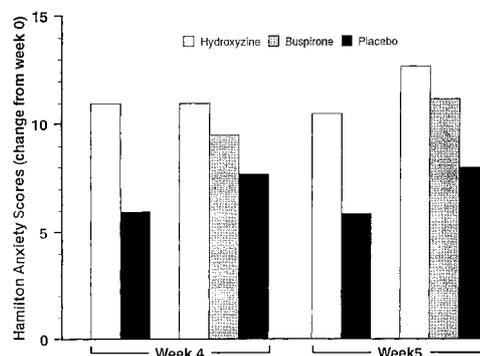


Figure 6. Comparison of drug effects in Ferreri *et al.* (1994, 1995) and Lader and Scotto (1998) studies

noted with hydroxyzine (nor with buspirone). There are no reports in the literature of any such problems with hydroxyzine, even in longer-term use (Shalowitz, 1961), and it is highly probable that this drug has a low or absent dependence potential.

This study confirms previous open-label and controlled studies (Garber, 1958; Breslow, 1968; Lipton, 1961; Goldberg and Finnerty, 1973). It also very closely replicates the data in the Ferreri *et al.* (1994) study with respect to baseline characteristics of the patients studied, improvements attained and significance levels achieved. Like them, I conclude that hydroxyzine 'offers the possibility of effective relief of generalized anxiety'. It may prove to be without doubt a useful and safer alternative to the benzodiazepines. Thus, despite its availability for 40 years or more, hydroxyzine may not have attained its appropriate place as an anxiolytic medication.

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