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Initial study of methylclonazepam in generalized anxiety disorder

Evidence for greater power in the cross-over design

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Abstract. The anxiolytic activity of methylclonazepam was compared to lorazepam and placebo in a double-blind, randomized cross-over study, using a latin square design, in 18 inpatients meeting Research Diagnostic Criteria for Generalized Anxiety Disorders. Patients presented at least 1 year of symptomatology and had a minimum score of 20 on the Hamilton Anxiety Scale, despite chronic anxiolytic pharmacotherapy. Daily dosage was flexible, from three to six tablets of methylclonazepam 1 mg, lorazepam 2.5 mg, or placebo. Clinical evaluation included Hamilton Anxiety Scale, Clinical Global Impression (CGI), a side-effects checklist, completed every 2 days, and the global preference of the patient for one of the treatment periods.

Results showed a highly significant superiority of both benzodiazepines over placebo on the Hamilton Scale ($P<0.00001$) and CGI ($P<0.001$), and also a significant superiority of methylclonazepam over lorazepam on the Hamilton Scale ($P<0.01$), CGI-1 ($P<0.01$), and in the number of patient preferences (14 versus 1; $P<0.001$), with no significant differences in side-effects or related to position in the trial. These results support the value of the cross-over design in chronic and severe anxious inpatients for the demonstration of differences in efficacy between anxiolytic pharmacotherapies.

Key words: Benzodiazepines – Methylclonazepam – Lorazepam – Anxiety disorders

The synthesis of the benzodiazepine structure has represented a major breakthrough in the pharmacological treatment of anxiety disorders (Sternbach 1983). Following the introduction of chlordiazepoxide in 1960, numerous compounds have been marketed, differing in their potency and pharmacokinetic properties (Greenblatt et al. 1983a). Controversy still exists, however, with respect to the more subtle clinical differences which seem to exist among compounds (Baskin and Esdale 1982; Greenblatt et al. 1983b; Lapierre 1983; Chouinard et al. 1983; Straw 1983). As a group, the benzodiazepines are clearly superior in anxiolytic activity to the other classes of antianxiety agents and are much less toxic at clinically useful doses (Rickels 1983). However, the marketed compounds do not consistently provide specific or definitive therapy for the exceedingly complex and variable clinical syndrome of anxiety, suggesting the need to develop more active derivatives (Goldberg 1984). In this context, the synthesis of methylclonazepam, a new long plasma half-life (40 h) benzodiazepine (Fig. 1), could represent an improvement. Indeed, animal data showed that methylclonazepam was far more potent that diazepam in tests predictive of anxiolytic activity ($\simeq 3\times$ in the conflict test in rats), and in the in vitro as well as in vivo benzodiazepine binding assay. The in vivo potency of methylclonazepam is similar to that of flunitrazepam ($ED_{50}=0.3$ mg/kg po), the most potent benzodiazepine tested to date (Möhler and Richards 1983). Moreover, in an open trial, we found that 7 of 12 chronic anxious inpatients, who had not responded well to large doses of standard benzodiazepines (essentially lorazepam, bromazepam, or diazepam), strongly preferred methylclonazepam therapy (Ansseau et al. unpublished). The purpose of the present study was, therefore, to assess more rigourously the possible anxiolytic superiority of methylclonazepam over current benzodiazepine compounds, using a double-blind cross-over design, with randomization of three treatments: methylclonazepam, lorazepam (the current most potent anxiolytic compound), and placebo, in a selected group of chronic anxious inpatients. As will be discussed, we feel that the cross-over design offers greater power in comparative efficacy studies.

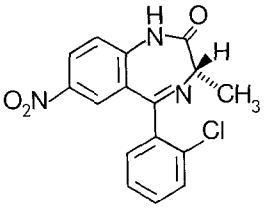

Fig. 1. Structural formula of methylclonazepam

Subjects and methods

Subjects. The study was performed in the Psychopharmacology Unit of the University Hospital of Liège, Belgium. The sample consisted of 18 newly admitted inpatients meeting Research Diagnostic Criteria (RDC) (Spitzer et al. 1978) for "Generalized Anxiety Disorder", as determined by two independent research psychiatrists using semi-standardized clinical interviews. In addition, subjects had to present: 1) chronic and steady symptomatology, with a minimum 1-year history of regular daily intake of high doses of tranquillizers (at least 30 mg diazepam or equivalent); and 2) a high level of severity (minimum of 20 on the Hamilton Anxiety Scale) (Hamilton 1959), despite their anxiolytic treatment. We excluded patients with a pre-existing or concurrent RDC diagnosis of major and minor

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Table 1. Demographical and clinical characteristics of the sample

#	Sex	Age	Illness duration (years)	Current episode duration (years)	Current anxiolytic treatment (daily dose in mg)	Concurrent Hamilton anxiety score
1	M	53	26	5	Bromazepam 36	35
2	M	46	3	3	Diazepam 60	28
3	M	48	3	3	Diazepam 40 Propanolol 60	32
4	F	51	11	2	Bromazepam 36 Lormetazepam 2	27
5	M	48	16	7	Diazepam 30 Flunitrazepam 2	35
6	F	58	10	1	Oxazepam 75 Doxepin 150	27
7	F	50	2	2	Diazepam 15 Bromazepam 15	35
8	M	66	14	14	Diazepam 20 Doxepin 75	33
9	F	35	4	4	Bromazepam 18 Mianserin 90	36
10	F	41	2	2	Bromazepam 24 Sulpiride 150	30
11	M	57	11	11	Bromazepam 36 Levomepromazine 45 Mianserin 60	31
12	F	32	3	3	Prazepam 40 Ketazolam 30 Propanolol 60	27
13	M	42	22	3	Prazepam 60 Mianserin 60	28
14	F	47	2	2	Bromazepam 24 Ketazolam 30 Propanolol 30	30
15	M	51	16	3	Diazepam 30 Levomepromazine 30 Doxepin 150	28
16	M	47	3	3	Bromazepam 18 Oxazepam 150	
17	M	39	13	2	Diazepam 30 Ketazolam 30	26
18	M	23	2	2	Prazepam 60 Propanolol 120 Doxepin 75	29
Mean (SD)		46.3 (10.1)	9.1 (7.6)	4 (3.4)		30.4 (3.3)

Sex distribution 11 M, 7 F

depressive disorders, phobic disorder, obsessive compulsive disorder, alcoholism, or drug use disorder, already treated with lorazepam, or presenting evidence of medical illness on history, physical examination, EKG, chest X-ray, EEG, and routine laboratory tests, and, prior to participation, all subjects gave informed consent.

The demographical and clinical characteristics of the sample are displayed in Table 1. All patients were hospitalized due to the high level of their anxious symptomatology, which significantly interferred with their familial, professional, and social functioning, and their poor response to previous pharmacological or psychological interventions.

Design of the study. The study compared methylclonazepam, lorazepam, and placebo according to a double-blind, cross-over design, with flexible dosage. The order of treatments was randomized according to a latin square design. Methylclonazepam (1 mg), lorazepam (2.5 mg), and placebo were presented as tablets of the same appearance, individually prepared in three different bottles (A, B, and C), according to each randomized order of treatments. The treatment was always administered in three daily intakes (7 A.M., 12 noon, and 10 P.M.), since we have previously demonstrated greater efficacy of divided doses of a long half-life benzodiazepine over a single evening intake in se-

verely anxious inpatients (Ansseau et al. 1984b). During each phase, the initial dose was three tablets daily (i.e. methylclonazepam 3 mg, lorazepam 7.5 mg, or placebo) and could be increased in increments of 1/2 tablet every other day to a daily maximum of six tablets; however, the increase could be more rapid in obvious worsening of the symptomatology. The final maintenance dosage lasted 4 days, before the beginning of the following phase or the termination of the study, but could be reduced to 2 days in complete therapeutic failure. There was no wash-out period before the beginning of the trial nor between consecutive phases. No other psychotropic medication was allowed throughout the study.

Psychometric assessment. The patients' clinical condition was assessed before treatment and every 2 days throughout the study by means of the Hamilton Anxiety Scale (Hamilton 1959), the Clinical Global Impression (CGI) (Guy 1976), and a side-effects checklist. At the end of the study, the patient was asked to select which of the three treatments he or she preferred – would like to continue – according to both efficacy and tolerance.

Data analysis. Since patients exhibited chronic and stable condition, and since no wash-out period was included between drug periods, final scores of each period (representing optimal results with the compounds) were compared using variance analysis (ANOVA) with repeated measures, first including the three periods and then comparing methylclonazepam with lorazepam. Patients were also divided into six subgroups according to their treatment sequences in order to assess a possible influence of the order of treatment on the therapeutic result (sequence effect and sequence-drug interaction). The distribution of patients' preferences was analyzed using the sign test, often referred to in this context as McNemar's test (Hills and Armitage 1979); and in order to eliminate a possible influence of the position in the trial on patients' preferences, the distribution of preferred period (A, B, or C) was analysed in the same way. Finally, the results of the study were also analyzed as a parallel group trial, using only the first treatment period, in order to compare the power of cross-over and parallel group designs in detecting differences in therapeutic efficacy.

Results

Dosages and duration of treatment phases. Mean end of period dosages (SD) were: methylclonazepam 5.1 mg (0.4), lorazepam 13.8 mg (2.0) and placebo 5.9 tablets (0.2). The mean optimal dosages (SD) corresponding to patients' preferences (including equalities of judgement) were methylclonazepam ($n=16$) 4.9 mg (0.7), and lorazepam ($n=5$) 13.2 mg (1.8).

Duration of treatment phases ranged from 8 to 18 days for methylclonazepam (mean $\pm$ SD $= 15.4 \pm 2.4$); from 4 to 18 days for lorazepam (mean $\pm$ SD $= 14.5 \pm 4.0$); and from 4 to 18 days for placebo (mean $\pm$ SD $= 8.1 \pm 4.3$), indicating a significantly shorter period on placebo than on active drugs [$F(2, 34)=17.06$; $P<0.001$], but no differences between the benzodiazepines [$F(1, 17)=2.26$; NS].

Hamilton anxiety scale. Individual final scores and changes over time on the Hamilton Anxiety Scale during each of the three treatments are displayed in Table 2 and Fig. 2. Mean scores (SD) at the end of each period were 12.3 (8.5) after methylclonazepam, 17.3 (7.8) after lorazepam, and 28.2 (9.1) after placebo. These results showed a significant superiority of both active drugs over placebo [$F(2, 24)=31.83$; $P<0.00001$] and of methylclonazepam over lorazepam [$F(1, 12)=9.93$; $P<0.01$]. The distribution of patients into six subgroups according to their treatment orders showed no sequence effect ($P=0.93$) and no sequence-drug interaction ($P=0.81$).

When analyzed as a double-blind parallel study using only the first period, mean final scores (SD) were 12.0 (9.4) for methylclonazepam, 19.5 (7.3) for lorazepam, and 29.3 (6.0) for placebo, showing a clear superiority of both benzodiazepines over placebo [$F(1, 21)=9.95$; $P<0.01$], but no difference between active drugs [$F(1, 10)=0.48$; NS].

CGI. Individual CGI scores at the end of each treatment period are presented in Table 2. Mean CGI (SD) of illness severity was 3.17 (1.29) at the end of methylclonazepam treatment, 4.17 (1.10) at the end of lorazepam treatment, and 5.61 (1.38) at the end of placebo period, indicating a significant superiority of active drugs over placebo [$F(2, 34)=15.02$; $P<0.001$] and of methylclonazepam over lorazepam [$F(1, 17)=9.00$; $P<0.01$]. Final CGI ratings of global improvement (SD) were, respectively, 1.89 (0.83), 3.06 (3.06), and 5.00 (2.03) for methylclonazepam, lorazepam, and placebo, also showing significantly better efficacy of both benzodiazepines over placebo [$F(2, 34)=14.98$; $P<0.001$] and a trend towards superiority of methylclonazepam over lorazepam [$F(1, 17)=4.14$; $P=0.06$]. Mean efficacy indexes (SD) were 3.00 (0.95) for the methylclonazepam period, 2.39 (1.00) for the lorazepam period, and 1.55 (0.86) for the placebo period, indicating a superiority of active compounds over placebo ($\chi^2=7.80$, $df=2$; $P<0.001$), without significant differences between benzodiazepines.

Patients' preferences. At the end of the study, 11 patients (61.1%) chose methylclonazepam as best treatment, one chose lorazepam, four (22.2%) preferred both active compounds without differentiating between them, one preferred both methylclonazepam and placebo over lorazepam, and one experienced a equal complete therapeutic failure with all three treatments (Table 2). These results showed a clear statistical superiority of active drugs over placebo ($P<0.0001$) and of methylclonazepam over lorazepam ($P<0.001$). The preferences in favor of methylclonazepam were based on a better activity ($n=9$) and on both greater efficacy and tolerance ($n=2$); the preference for lorazepam was based on better efficacy ($n=1$). According to the position in the trial, the 12 periods selected were five periods A (41.7%), four periods B (33.3%) and three periods C (25%), indicating absence of significant influence of position on preference.

Side-effects. Three patients experienced side-effects during methylclonazepam therapy [drowsiness ($n=1$), fatigue ($n=1$), and dry mouth ($n=1$)]; five during lorazepam therapy [drowsiness ($n=3$), ataxia ($n=2$), shaking ($n=1$), dry mouth ($n=1$), and constipation ($n=1$)]; and one during placebo period [fatigue ($n=1$)] (no significant difference). No differences in reported side-effects appeared according to the position in the trial: three during period A, five during period B, and three during period C.

Table 2. Results

Patient #	Final Hamilton			Final CGI-1			Final CGI-2			Final CGI-3			Preference
	MC	L	Pl	MC	L	Pl	MC	L	Pl	MC	L	Pl	
1	18	19	29	5	5	6	2	2	4	06	06	13	MC+L
2	18	25	41	3	4	7	1	2	6	05	05	13	MC
3	18	15	31	5	5	7	2	2	4	05	05	13	L
4	5	6	12	2	2	3	3	3	3	01	01	05	MC+L
5	10	16	28	4	5	6	2	2	3	06	06	10	MC
6	34	27	33	6	4	5	4	2	4	13	08	13	0
7	28	37	44	4	5	7	3	4	6	09	15	13	MC
8	2	11	23	1	4	5	1	2	3	01	05	09	MC
9	12	10	36	3	3	6	2	2	4	05	05	13	MC+L
10	12	17	29	3	4	6	2	2	4	05	05	13	MC
11	4	14	28	2	4	6	1	2	4	01	05	13	MC
12	15	23	32	4	6	7	2	3	4	05	09	13	MC
13	9	14	22	3	4	5	2	2	3	05	05	09	MC
14	6	11	26	2	3	5	1	2	3	01	05	09	MC
15	10	11	33	3	3	7	2	2	5	05	05	13	MC+L
16	4	26	5	2	6	2	1	4	1	01	13	01	MC+Pl
17	6	20	31	2	5	6	1	3	5	01	09	13	MC
18	11	10	24	3	3	5	2	2	3	05	05	09	MC
Mean	12.3	17.3	28.2	3.17	4.17	5.61	1.89	3.06	5.00	3.00	2.39	1.55	
SD	8.5	7.8	9.1	1.29	1.10	1.38	0.83	3.06	2.03	0.95	1.00	0.86	

MC = methylclonazepam; L = lorazepam; Pl = placebo

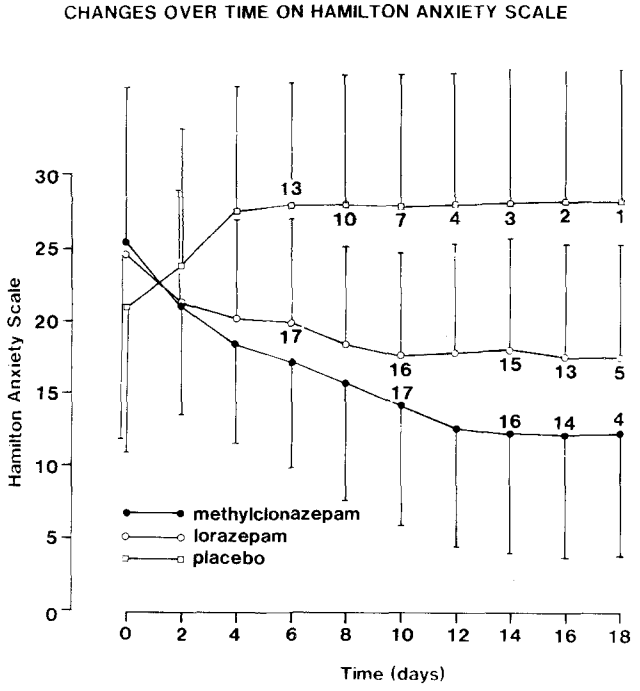

Fig. 2. Changes in Hamilton anxiety scores (mean and standard deviation) during treatment with methylclonazepam, lorazepam, and placebo, together with number of subjects in each treatment cell over time. (Endpoint scores were used for following evaluations in periods lasting less than 18 days)

Discussion

This study shows not only clear anxiolytic superiority of two benzodiazepine compounds over placebo, but also superiority of the new compound, methylclonazepam, over a standard benzodiazepine, lorazepam, as measured by the Hamilton and CGI scales, and as indicated by patient preferences.

With regard to the superiority of the benzodiazepines over placebo demonstrated in this trial, one may argue that the periods of active treatment lasted much longer than periods for which patients were taking placebo. This may give a longer period of time for the active drugs to work and therefore the difference might be due to a longer exposure to something that is actually no more powerful. However, it should be kept in mind that the discontinuation of a treatment period was decided according to the clinical evolution, and that the shorter duration of the placebo period reflects the complete ineffectiveness of placebo in this group of severe and chronically anxious inpatients.

Concerning the better anxiolytic activity of methylclonazepam compared to lorazepam in the present study, the possible superiority of any benzodiazepine over another is currently disputed. Many authors argue for a therapeutic equivalence among all compounds marketed, based upon: 1) the potency of the compound; 2) pharmacokinetics (absorption, half-life, active metabolites); and 3) the absence of demonstrated clinical differences (Kesson et al. 1976; Editorial 1977; Sellers 1978; Hollister 1978; Editorial 1978; Bellantuono et al. 1980; Lader and Petursson 1983). This state of affairs has led some cost-conscious hospital formulary committees to conclude that all needs can be adequately met if one or possibly two benzodiazepines are made available (Greenblatt et al. 1983b).

In fact, however, the lack of demonstrated clinical differences may proceed in large part from the methodology generally used in comparative drug studies. Thus, most clinical trials comparing benzodiazepines have been performed in anxious outpatients, not selected with precise criteria, and suffering from only a moderate level of anxiety. In such subjects, the placebo effects is high (Rickels et al. 1971); spontaneous remission of the clinical picture is often

present; non-pharmacological factors, which are impossible to control, play an important role; and patient compliance (i.e. treatment adherence) is problematical. Indeed, some patients will return to their former anxiolytics (sometimes without the investigator's knowledge) before an adequate trial of the prescribed treatment is completed. Moreover, these trials generally include small samples of patients, use parallel rather than cross-over designs, and last not longer than 3 or 4 weeks (Solomon and Hart 1978). Therefore, it is not surprising that the resultant coefficient of variation is very high and has led to the general conclusion of a lack of clinical differences among benzodiazepine compounds. Moreover, those studies also failed to demonstrate clinical differences between benzodiazepines and barbiturates (thus the preference for benzodiazepines over barbiturates is based essentially on a lower toxicity), and even of benzodiazepines over placebo in nearly half of the published reports (Kellner et al. 1978).

Many factors can improve the sensitivity and power of comparative studies of benzodiazepines. First, the use of strict, well-operationalized criteria (such as RDC in the present study) increases the homogeneity of the sample (Solomon and Hart 1978); secondly, the selection of patients with a sufficient duration of illness (at least 1 year in the current trial) ensures that the patients' condition is sufficiently steady that a spontaneous remission is improbable. With similar methodological refinements (i.e. the use of DSM-III criteria and a duration of illness of at least 6 months), Fontaine et al. (1983) were able to show a clear superiority of bromazepam over diazepam in two parallel groups of 24 patients suffering from generalized anxiety. However, the dosages of bromazepam (18 mg/day) and diazepam (20 mg/day) remained unchanged throughout the 4-week trial, and it can be argued that the apparent superiority of bromazepam reflects only proportionately higher dosage, as suggested by the higher rate of sedative side-effects in the bromazepam-treated group.

Another methodological refinement is to treat inpatients, with a definite level of severity (at least 20 on the Hamilton Anxiety Scale, despite anxiolytic pharmacotherapy in the current study), rather than outpatients (Ansseau et al. 1984a). An inpatient setting allows for more precise control of the non-pharmacological factors (most of them remaining constant) and facilitates treatment adherence. Moreover, the drop-out rate is generally very low in inpatient studies (none in the present study), and reasons for patient attrition can always be analyzed, whereas the drop-out rate is generally reported between 25 and 50 percent in outpatients (Blackwell 1976), for reasons that often remain unknown. With such methodology, we were able to show a clear superiority of prazepam administered in three daily divided doses over a single evening intake in inpatients with generalized anxiety (Ansseau et al. 1984b, c).

Probably the most important methodological refinement is the use of a cross-over trial design, in which the effects of different treatments are compared in the *same* subject during successive periods (Hills and Armitage 1979; Solomon and Hart 1978; Kellner et al. 1978; Ansseau et al. 1984a; Uhlenhuth et al. 1979). Such trials are particularly suitable for the evaluation of anxiolytics, which alleviate the symptoms rather than cure, so that, after the first treatment, the patient is in a position to receive a second one (Hills and Armitage 1979; Solomon and Hart 1978; Bobon et al. 1962). However, to avoid a possible influence of the sequence of different treatments, the order of the periods needs to be randomized and counterbalanced (i.e. balance between treatments and order ensured) (Kellner et al. 1978). Cross-over trials of benzodiazepines are substantially more powerful than parallel groups designs: thus, in comparison with placebo, 31 of 39 cross-over comparisons (79%) published to date have shown a significant superiority of the benzodiazepines, while only 33 of 58 parallel group studies (57%) have demonstrated significant drug-placebo difference (Kellner et al. 1978). The greater power of cross-over studies is demonstrated even in trials with fewer than 20 patients, which also have a larger proportion of positive than negative results, whereas comparable results are not reached by parallel group studies unless they include more than 60 patients (Kellner et al. 1978). A cross-over design enabled Deberdt (1974) and Sonne and Holm (1975) to show a superiority of bromazepam over diazepam with respect to patients' preferences, whereas the use of parallel groups failed to show any such difference. The same conclusion can be applied to the current study: whereas the cross-over design shows a significant superiority of methylclonazepam over lorazepam, analysis of the same data as parallel groups using the first treatment period is inconclusive.

However, many statisticians stress the pitfalls of cross-over trials: contamination of results of treatment in different periods, particularly if no wash-out period is included (as in the present trial) and the difficulty, particularly when patients are not in hospital, that any loss of information means that the entire data set may be un-analysable. It should be noted, however, that no evidence of carry-over effect has ever been demonstrated for anxiolytic agents (Kellner et al. 1978), a conclusion which is supported by the lack of sequence effect and of sequence-drug interaction in the present trial. However, the small size of the sample cannot exclude that the nonsignificant findings may be due to a lack of power of the tests rather than to the absence of true interactions.

The question may also arise of the clinical significance of a difference of five points in the final Hamilton score between two benzodiazepines, even if this difference is statistically significant. In fact, taken in isolation, these results may have few clinical implications. However, the actual clinical superiority of methylclonazepam over lorazepam is strongly suggested by the number of patients' preferences. Indeed, patients were asked to select which drug period they preferred and thus which treatment they would like to pursue and for which reason. Methylclonazepam was preferred by 11 patients (for only one preference favouring lorazepam), all of whom mentioned better anxiolytic activity of the drug (associated in two cases with a better tolerance).

With regard to tolerance, the present study shows only a low rate of side-effects, all typical of benzodiazepine therapy, without any significant difference between compounds. However, the methodology used may lack adequate sensitivity for thorough and valid assessment of side-effects. Thus, patients using chronically high doses of benzodiazepine anxiolytics develop a high tolerance to their sedative properties (Aranko et al. 1983); moreover, inpatients do not have opportunity to assess drug effects on job performance and other activities. Accordingly, the clinical tolerance of methylclonazepam and lorazepam needs to be compared in a separate study of anxious outpatients, for whom the selection criteria could be more flexible.

The final question is the extent to which the sample of subjects included in the current study is representative of the general population of anxious patients who might benefit from benzodiazepine therapy. In fact, most benzodiazepine anxiolytics are prescribed for mildly anxious outpatients over short periods. The rate of patients taking benzodiazepines for more than 1 year is low: about 15% of all anxiolytic users, according to a survey of Mellinger et al. (1984), who suggest that these patients tend to be older, mostly women, with high levels of emotional distress and chronic somatic health problems. However, in general, the most efficient way to demonstrate clinical differences in therapeutic activity is to start with the subgroup having the highest severity of illness. In an analogous fashion, clinical studies of antidepressant drugs are performed in severely depressed patients, selected by rigorous criteria (such as Research Diagnostic Criteria for primary or endogenous depression), and often in hospital settings; those patients represent a small fraction and specific subgroup of all depressed patients treated with antidepressant drugs (Miller et al. 1983). The current study supports the value of using a comparable methodology for the demonstration of clinical differences among anxiolytic agents.

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