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Clomipramine/Bentazepam Combination in the Treatment of Major Depressive Disorders

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Eighty-three patients were recruited in a multicentre study concerning the usefulness of benzodiazepines (BZ) in major depressive disorders, diagnosed according to the DSM-III-R criteria. After 1 week wash-out, patients were randomized to clomipramine (CLMP) or CLMP plus bentazepam (BTZ) treatments (47 and 36 patients respectively). It was necessary to add hypnotics, usually a BZ, in 11 patients in the CLMP group and in one patient in the CLMP+BTZ group. The clinical improvement was faster in the group treated with CLMP+BTZ and, at the end of 6 weeks of treatment, the mean score in Hamilton Anxiety Scale (HAS) was lower than the one found in the group treated with CLMP. There were no significant differences found in Hamilton Depression Scale (HDS) between the groups. The side-effects observed were those due to CLMP, and only drowsiness was more frequent in the CLMP+BTZ group. However, the CLMP+BTZ combination was equally or better tolerated by patients than by those treated with CLMP alone. Similar results were found in hospitalized as well as in out-patients. The tricyclic antidepressant (TCA)/BZ association showed better results than TCA alone, producing a symptomatic improvement extensive to the anxious components of depression.

KEY WORDS—Bentazepam, clomipramine, antidepressant/anxiolytic combination, depression

INTRODUCTION

There is a lasting controversy on the usefulness of benzodiazepines (BZ) in depressive disorders. Some authors claim BZ useful in depressive disorders, but most of these papers deal with mixed samples, including minor depression or neurotic depression, where anxiety symptoms may be of predominance. A different situation is found when only major depressive disorders are considered, a situation in which antidepressant therapy seems to be well established. Nevertheless, as anxiety is frequently associated with depression, in 50–100 per cent of patients, depending on authors (Lehman, 1965; Hollister, 1971; Franco *et al.*, 1988), there is a place for combined therapy with antidepressant drugs and BZ. Again, most of the studies with tricyclic antidepressant (TCA)/BZ combinations deal with mixed samples, giving accuracy to the results. Moreover, authors who are against using the TCA/BZ combination maintain that anxiety symptoms will decrease under antidepressant therapy (Lauries, 1982), while the TCA/BZ association may potentiate TCA side-effects (Silverman and Braithwaite, 1972; Breckenridge, 1983).

In spite of this controversy the TCA/BZ association is prescribed frequently. Honorato *et al.* (1990) have recently reported that one of three ambulatory psychiatric patients treated with bentazepam (BTZ), a benzodiazepinic derivative, simultaneously received an antidepressant drug (TCA or not), if depressive symptoms arise. However, to date, controlled trials on the efficacy of TCA/BTZ combination in depressive disorders have not been developed.

The aim of this study is to compare the effectiveness, as well as the safety, of clomipramine (CLMP) with CLMP+BTZ combination in DSM-III-R diagnosed major depressive disorders. The trial was performed on a hospitalized and ambulatory basis, so as to establish comparisons between both types of patient sources.

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METHODS

Two hospitals (HOSP): 'Gregorio Marañón' and 'Gómez Ulla' (both located in Madrid), and two mental health centres (MHC): 'San Blas' and 'Villalba' (in the Regional Community of Madrid), were involved in the trial. A parallel, randomized, open-label (non-blind) design was used. Hospitalized and ambulatory patients fulfilling the DSM-III-R criteria for a major depressive episode (single, recurrent or bipolar) were recruited. As patients were entered, they were informed that they would receive one of two suitable antidepressant treatments, but no mention was made to the number of drugs or daily intake of pills in the other branch of the trial. Each patient knew his or her treatment, CLMP or CLMP+BTZ, but patients did not know the exact nature of the treatment in the other branch.

The exclusion criteria were: organic aetiology (causing bipolar disorder); schizophrenia, schizophreniform or paranoid disorder; uncomplicated bereavement (as a cause for the depressive episode); simultaneous treatment with other psychotic drugs or with MAOI in the preceding 15 days; recent (6 months) myocardial infarction; arrhythmias or congestive heart failure; myasthenia gravis; closed-angle glaucoma; prostatic hypertrophy; severe renal or hepatic impairment; hypersensitivity to TCA or BZ; pregnancy; age below 18 years.

After 1 week wash-out of BZ, during which the CLMP dose was titrated (100 or 150 mg/day on the basis of severity of depressive symptoms, keeping in mind DSM-III-R severity categories), patients were randomly assigned to CLMP (100 or 150 mg/day) or CLMP+BTZ (CLMP, 100 or 150 mg/day plus BTZ 75 mg/day). Treatment lasted 6 weeks, performing evaluations at baseline and at the end of the 1st, 2nd, 4th and 6th weeks. The following tests were performed at each evaluation: Hamilton Anxiety Scale (HAS) (Hamilton, 1959), 21-item Hamilton Depression Scale (HDS) (Hamilton, 1960), and one side-effects scale, which included all the most common adverse reactions compiled in a BTZ surveillance study (Honorato *et al.*, 1990), where side-effects were summarized from the patients' complaints. A baseline HAS minimum score of 14 was required to enter the study. Patients who for any reason had been under treatment for less than 4 weeks, were not considered evaluable in terms of treatment efficacy. Whenever possible, blood samples for routine analytical testing were drawn at the beginning and at the end of the treatment.

Mean values in HAS and HDS, and mean HAS and HDS increases from prior evaluation, were calculated in each evaluation time. Student's *t*-tests for matched and unmatched samples were performed for mean comparison between the same treatment group at different evaluation times, and between different treatments at the same evaluation time, respectively.

For comparison between the four subgroups formed according to patient source, HOSP or MHC and treatment, CLMP+BTZ or CLMP alone, ANOVA for two factors and Scheffe test were developed. Qualitative variables were compared by the chi-square test, and when necessary, Yates correction or Fisher exact test. The significance limit was set at $p < 0{\cdot}05$.

RESULTS

Eighty-three patients were recruited, 42 in HOSP and 41 in MHC. The randomization process assigned CLMP and CLMP+BTZ to 47 and 36 patients, respectively.

Twenty-one patients were excluded from treatment evaluation efficacy for the following reasons: need to administer hypnotics: 11 patients in CLMP and one patient in CLMP+BTZ groups ($p < 0{\cdot}05$); drop-out (unknown cause): four patients in CLMP and two patients in CLMP+BTZ groups; drop-out (side-effect): one patient in each treatment group; polarity change to maniac phase: one patient in CLMP group. Total: 17 patients in CLMP and four patients in CLMP+BTZ ($p < 0{\cdot}05$). These patients were evaluated in terms of treatment safety.

Sixty-two patients, 18 men and 44 women, with a mean age of $49{\cdot}0 \pm 13{\cdot}8$ years (range 18–75 years), all suffering major depressive disorders (22 single episode, 33 recurrent episode, seven bipolar episode) completed the study. During the CLMP titration week, 43 and 19 patients were titrated to 100 and 150 mg/day of CLMP, respectively. At randomization, 30 and 32 patients were assigned to CLMP and CLMP + BTZ combination, respectively. Thirty-six patients and 26 patients were recruited from HOSP and MHC, respectively.

The characteristics of subsamples by treatments, CLMP and CLMP+BTZ, are shown in Table 1. Both subsamples were homogeneous in relation to sex distribution, mean age, diagnoses, CLMP dose rates, and baseline HAS and HDS mean scores. The course of HAS and HDS mean scores for both

Table 1. Characteristics of the samples. Clomipramine (CLMP); CLMP plus bentazepam (CLMP + BTZ)

Group Treatment	Control CLMP	Combination CLMP + BTZ
Sample size	30	32
Sex: male/female	6/24	12/20
Age (years)	47·8 ± 14·5	50·2 ± 13·4
Hospitalized patients	19	17
Ambulatory patients	11	15
DSM-III-R diagnosis		
Single episode	10	12
Recurrent episode	15	18
Bipolar episode	5	2
CLMP dose		
100 mg/day	23	20
150 mg/day	7	12

treatment groups, CLMP and CLMP+BTZ, are shown in Figures 1a and 1b, respectively. The course of HAS and HDS mean decreases from prior evaluation time by treatments are shown in Figures 2a and 2b.

Both treatments, CLMP and CLMP+BTZ, significantly reduced HAS and HDS mean scores at consecutive evaluation times along the study, exception made for 1st week HAS mean score compared to baseline in the CLMP group. At the 2nd, 4th and 6th weeks of treatment, HAS mean scores for the CLMP+BTZ group were significantly lower than those for the CLMP monotherapy group (Figure 1a). During the 1st week, the HAS mean decrease was higher in the CLMP+BTZ group than in CLMP alone (Figure 2a). Significant differences were not found between the groups with respect to the HDS mean scores (Figure 1b), while the 1st HDS mean decrease was higher in the CLMP+BTZ group than in the CLMP group (Figure 2b).

When patient sources (HOSP or MHC) are considered, as well as treatments (CLMP or CLMP+BTZ), the four subsamples described in Table 2 are formed. The four subgroups significantly reduced HAS and HDS mean scores at consecutive evaluation times during the study, an exception being made for the 1st week HAS mean score compared to baseline in HOSP patients treated with CLMP in monotherapy.

ANOVA for two factors (treatment and patient source) was performed at every evaluation time for HAS and HDS mean scores. No interactive effect was evidenced at any time throughout the study. The HOSP group treated with CLMP+BTZ had a baseline HAS mean score higher than the other three groups ($p < 0{\cdot}05$ in each case). Nevertheless, this group reported the best evolution during treatment, showing the lowest HAS mean score at the end of the trial, significantly lower than the two groups of patients treated with CLMP alone (HOSP or MHC $p < 0{\cdot}05$ in each case). On the contrary, the MHC patients treated with CLMP in monotherapy had worse evolution than the remaining groups, showing at the end of the study higher HAS mean score than the other three groups ($p < 0{\cdot}05$ in each case). Similar evolution by subgroups was shown in HDS mean scores, but significant differences between any of the pairs of samples were not appreciated at any evaluation time.

Information concerning adverse reactions was obtained only in 77 from 83 patients, the six remaining cases having been lost. Seventy-four patients, distributed as follows, reported one or more side effects: 40 from 41 patients in CLMP group (31 and nine patients on 100 and 150mg/day of CLMP); 34 from 36 patients in CLMP+BTZ group (21 and 13 patients on 100 and 150 mg/day of CLMP). The average numbers of side-effects reported per patient were: 2·5 and 2·9 in the CLMP group (CLMP 100 and 150 mg/day, respectively) and 3·1 and 3·2 in the CLMP+BTZ group (CLMP 100 and 150 mg/day, respectively). Differences between groups were not found regarding the number of patients reporting adverse reactions and the mean number of adverse reactions reported, either when the two CLMP dose levels studied are analysed together or separately.

The number of side-effects reported in each treatment group, as well as CLMP dose level, are shown in Table 3. Two cases of sexual impotence were reported in the CLMP+BTZ group (under 'other' in Table 3). This side-effect has been reported previously for TCA and for BZ, this being the first communication for BTZ (alone or in combination). In 52 patients, blood samples were collected at the beginning and end of the treatment. No laboratory changes were found in any of the treatment groups.

DISCUSSION

Combinations of psychotropic drugs are frequently oriented towards depression (Grohmann *et al.*, 1980; Salzman, 1981), with antidepressant/BZ being a usual combination. Anxiety is, along with sadness and psychomotor retardation, one of the most constant features in depressive disorders. While antidepressants improve the two latter symp-

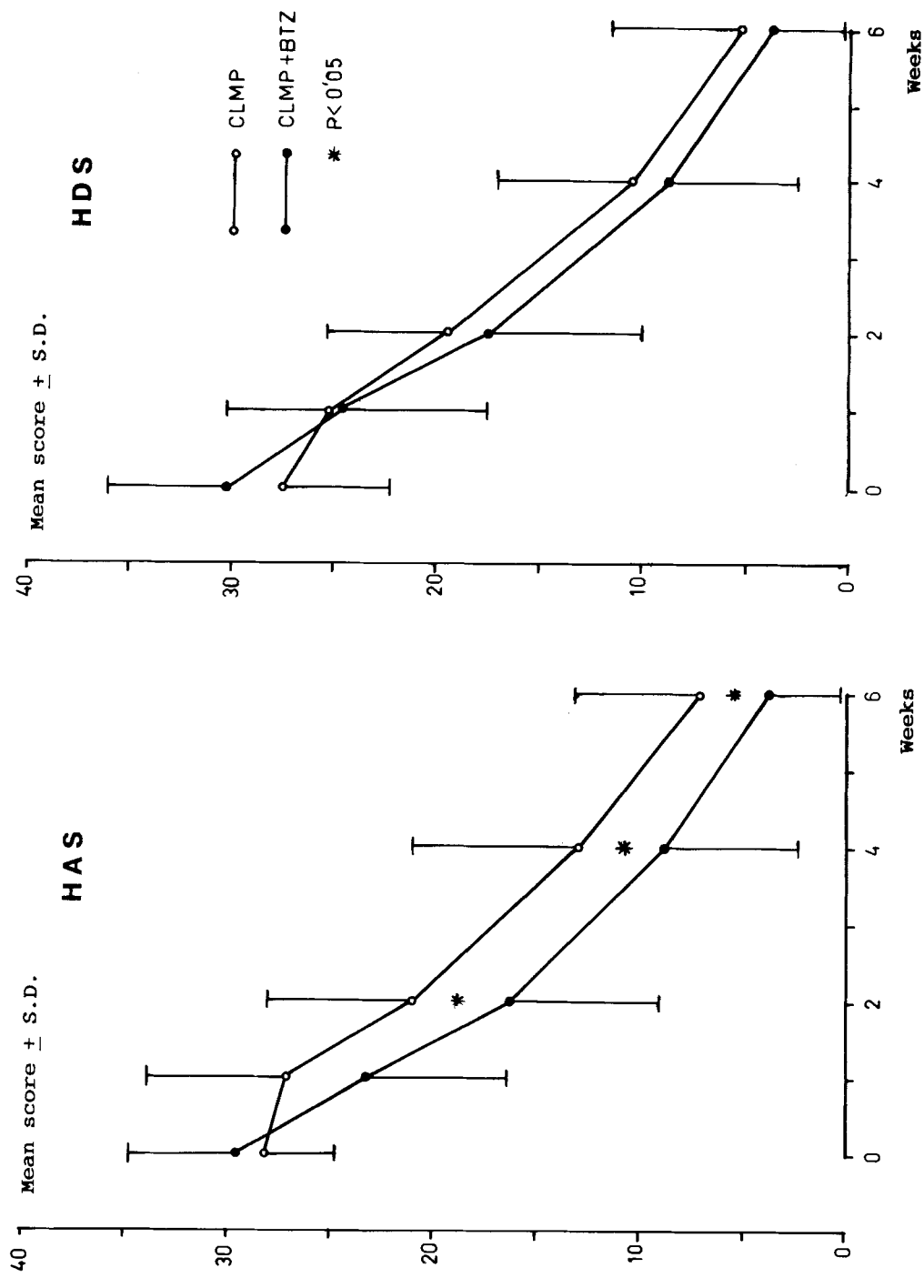

Figure 1. (a) Hamilton anxiety scale (HAS) and (b) Hamilton depression scale (HDS) mean scores in major depressive disorders through 6 weeks of treatment with clomipramine (CLMP) or CLMP plus bentazepam (CLMP + BTZ). Mean comparison for unmatched samples

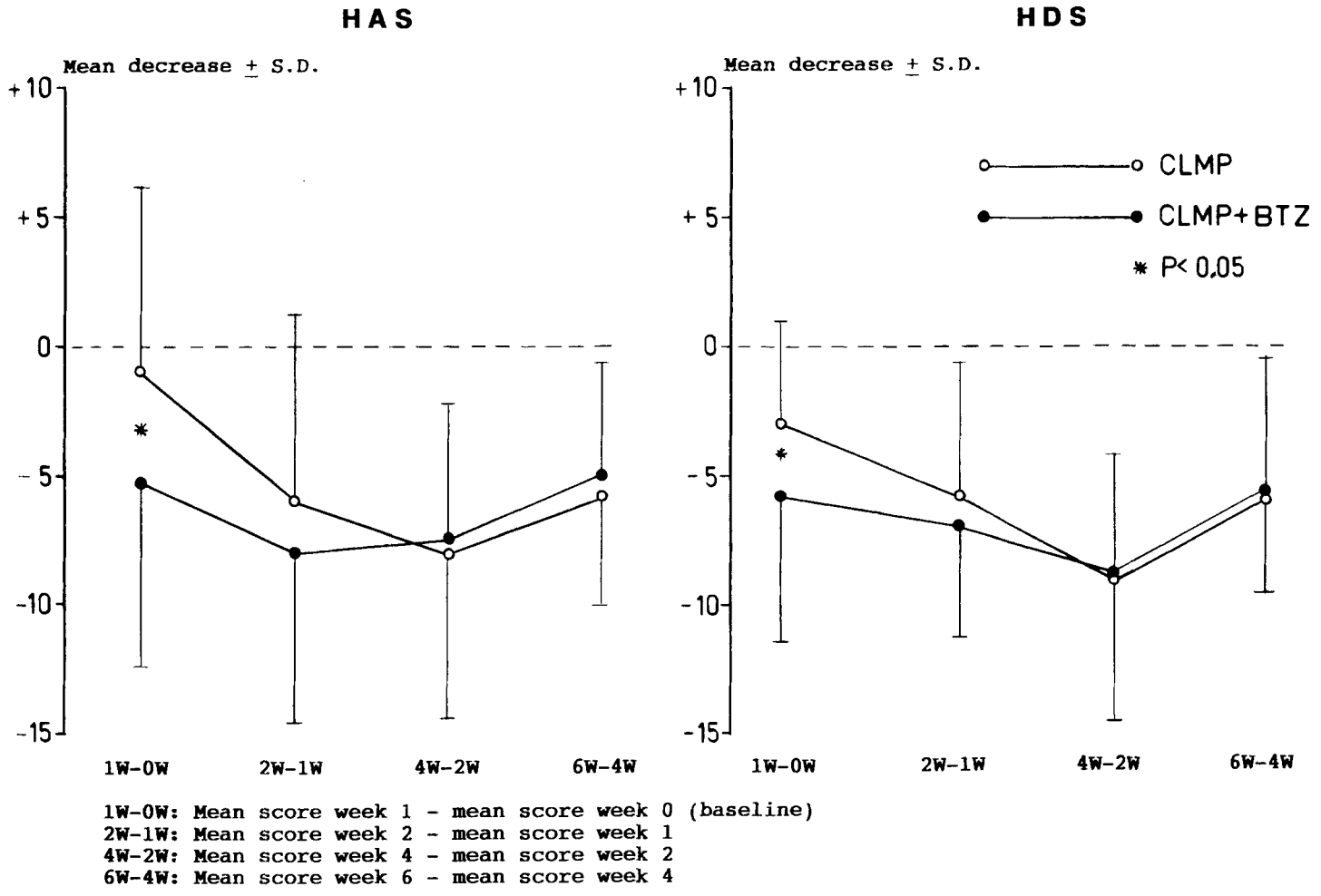

Figure 2. (a) Hamilton anxiety scale (HAS) and (b) Hamilton depression scale (HDS) mean decreases from prior evaluation time through 6 weeks of treatment with clomipramine (CLMP) or CLMP plus bentazepam (CLMP + BTZ). Mean comparison for unmatched samples

Table 2. Subdivision of sample as a function of treatment and patient source: clomipramine (CLMP); CLMP plus bentazepam (CLMP + BTZ); Hospital (HOSP); Mental Health center (MHC)

Group	Control		Combination	
Treatment	CLMP		CLMP + BTZ	
Patient source	HOSP	MHC	HOSP	MHC
Sample size	19	11	17	15
Sex: male/female	4/15	2/9	6/11	6/9
Age (years)	48·4 ± 12·8	46·8 ± 17·6	54·4 ± 13·7	45·4 ± 11·6
DSM-III-R diagnosis				
Single episode	6	4	5	7
Recurrent episode	10	5	11	7
Bipolar episode	3	2	1	1
CLMP dose				
100 mg/day	14	9	7	13
150 mg/day	5	2	10	2

Table 3. Side-effects reported during the study: clomipramine (CLMP); CLMP plus bentazepam (CLMP + BTZ)

Treatment	CLMP		CLMP + BTZ	
CLMP dose (mg/day)	100	150	100	150
Sample size	32	9	23	11
Dry mouth	24	7	18	9
Drowsiness	5	1	11	4
Asthenia	6	1	5	3
Myalgia	5	0	3	2
Heartburn	2	2	1	0
Dyspepsia	0	1	2	2
Constipation	3	1	3	1
Dizziness	6	5	7	5
Tachycardia	2	2	1	1
Blurred vision	5	2	4	5
Tremor	5	3	3	2
Others	8	1	2	1

toms, they act insufficiently or too slowly on anxiety (Cassano and Conti, 1981; Lauries *et al.*, 1982). Moreover, the anxiety and depressive states definition are not mutually exclusive (Bramley *et al.*, 1988) and DSM-III-R considers anxiety to be a symptom associated with major depressive disorders (American Psychiatric Association, 1987).

Laux *et al.* (1988) reviewed 10 controlled clinical trials in which TCA/BZ combinations were assessed versus groups treated exclusively with antidepressants in monotherapy (Haider, 1967; General Practitioner Research Group, 1969; Houck, 1970; Rickels *et al.*, 1970; Hare, 1971; Smith, 1973; Jacobson, 1978; Feighner *et al.*, 1979; Poldinger and Koeppen, 1979; Dimitriou *et al.*, 1982). In five of these studies (Haider, 1967; Rickels *et al.*, 1970; Hare, 1971; Smith, 1973; Feighner *et al.*, 1979), combined treatment yielded better results than monotherapy, and frequently combined treatment produced a more rapid commencement of clinical improvement. The critical point is that most of these studies use unclear inclusion criteria, such as 'neurotic depression', 'anxiety depression' and 'anxious-depressive reaction'. While BZ can have certain mood-elevating properties, these are probably secondary effects to their anxiolytic characteristics and cannot be regarded as true antidepressant qualities (Rickels *et al.*, 1970; Schazberg and Cole, 1978), with TCA being the first-line treatment for major mood disorders (Swinson, 1989). Imidazobenzodiazepines may be an exception, because they have shown preclinical antidepressant-like activity (Maier *et al.*, 1990) as well as clinical antidepressant activity on major depressive disorders (Rickels *et al.*, 1985; Cohn *et al.*, 1988).

In our study, comparing CLMP on monotherapy with the CLMP+BTZ combination, only major depressive disorders were included. The results showed that the response to the CLMP+BTZ combination was clearly superior to CLMP alone in the 1st week of treatment and, although at the end of the study both groups showed results with HAS and HDS mean scores below pathological breakdown, HAS mean scores in the 2nd, 4th and 6th weeks of treatment were lower in the CLMP+BTZ group than in the CLMP group. There were non-significant differences in HDS mean score. In spite of more restricted inclusion criteria, our results are compatible with those of Laux *et al.* (1988).

Some differences between inpatients and outpatients have been noted (Rickels *et al.*, 1972); thus a mixed sample, MHC and HOSP, was recruited in order to establish comparisons between the treatments in the different regimens. In both regimens the CLMP+BTZ group showed lower HAS mean scores at the end of the study than the CLMP group. No significant differences were found in HDS mean scores throughout the study. Our results show that BTZ may improve anxiety as a symptom of depressive disorders, but has little activity on other symptoms, at least in comparison with CLMP. The design of the study was open-label,

thus some biases may have been introduced. Biases related to non-blind patients were overcome by informed consent procedure (see Methods), although a possible bias related to non-blind physicians cannot be fully discarded. Some caution in interpreting results is recommended.

From the 77 patients screened for side-effects, 74 reported one or more adverse reactions. Drowsiness was more common in the CLMP+BTZ group than in the CLMP group. For the other adverse reactions, significant differences were not found between the frequencies in both treatment groups. The number of drop-outs due to side-effects was one in each group. The drop-outs due to unknown causes were four and two in the CLMP and CLMP+BTZ groups, respectively.

The addition of hypnotics to antidepressant therapy is relatively frequent. It was necessary to add hypnotics to 11 and one patients in the CLMP and CLMP+BTZ groups, respectively. Compliance with treatment could have been compromised by insomnia if hypnotics were not prescribed. Therefore, one may contemplate these patients as potential drop-outs. Considering real (any reason) and potential drop-outs, gives a total number of actual or potential drop-outs as 16/47 in the CLMP group and 4/36 in the CLMP+BTZ group. These figures suggest that combined therapy with BTZ not only does not worsen the tolerance, but it could improve it in comparison with basic treatment with CLMP.

Dimitriou *et al.* (1982) observed that many patients diagnosed as suffering from depression reported medication-related adverse effects, usually during their 1st week of treatment. Considering that most of these patients showed psychosomatic complaints before treatment, the addition of adverse reactions resembling psychosomatic troubles induced by drugs, creates problems in medical practice and, as a result, patients frequently discontinued their medication. Under these circumstances, adding a BZ acting upon somatization disorders may improve patient outcome.

In summary, since overlap of symptoms of anxiety and depression is present in practically all patients with major depressive disorders, treatment exclusively with TCA is not the optimal possible choice to cover the symptoms conforming the depressive disorder. Moreover, although monotherapy with antidepressants is a theoretically pursuable goal, in clinical practice it is frequently necessary to add a hypnotic, usually a BZ, in order to control insomnia. Addition of a BZ from the beginning of treatment may improve patient evolution, and some could benefit from the anxiolytic action of these drugs from the 1st day of treatment.

Withdrawal syndrome from BZ discontinuation could be a disadvantage of TCA/BZ combinations. Risk/benefit should be considered in relation to patient drug/alcohol addiction history or preaddictive personality, before adding BZ to antidepressant therapy. The obvious cautions, i.e. low doses, short treatments and tapering as needed, must be borne in mind.

CLMP+BTZ combination seems to be a good choice for treating major depressive disorders, being equally or better tolerated by patients than CLMP alone. This last finding requires further studies in order to obtain a thorough confirmation.

REFERENCES

American Psychiatric Association (1987). Trastornos del estado de ánimo. In: *DSM-III-R Manual diagnóstico y estadístico de los trastornos mentales*, Ediciones Masson, Barcelona, pp. 255–279.

Bramley, P. N., Easton, A. M. E., Morley, S. and Snaith, R. P. (1988). The differentiation of anxiety and depression by rating scales. *Acta Psychiatrica Scandinavica*, **77**, 133–138.

Breckinridge, A. (1983). Interactions of benzodiazepines with other substances. *The Benzodiazepines: from Molecular Biology to Clinical Practice*, Costa, E. (ed.) Raven Press, New York, pp. 237–246.

Cassano, G. B. and Conti, L. (1981). Some considerations on the role of benzodiazepines in the treatment of depression. *British Journal of Clinical Pharmacology*, **11**, 23s–29s.

Cohn, J. B., Pyke, R. E. and Wilcox, C. S. (1988). Adinazolam mesylate and placebo in depressed outpatients: a 6-week, double-blind comparison. *Journal of Clinical Psychiatry*, **49**(4), 142–147.

Dimitriou, E. U., Lagotethis, J. A. and Paschalidou, M. (1982). Antidepressant combination therapy of endogenous depressions with benzodiazepines or neuroleptics – a study comparing adjuvant treatment with oxazolam versus chlorprothixene. *Pharmacopsychiatry*, **21**, 87–92.

Feighner, J. P., Brauzer, B. and Geleberg, A. J. (1979). A placebo-controlled multicenter trial of limbitrol versus its components (amitriptyline and chlordiazepoxide) in the symptomatic treatment of depressive illness. *Psychopharmacology*, **61**, 217–225.

Franco, B., Otero, F. J. and Sicilia, L. R. (1988). Tratamiento farmacológico de la depresión en un hospital ambulatorio. (Estudio retrospectivo 1986–1987.) *Annals Psiquiatría*, **4** (Suppl. 1), 91.

General Practitioner Research Group (1969). Chlordiazepoxide with amitriptyline in neurotic depression. *Practitioner*, **202**, 437–440.

Grohmann, R., Strauss, A., Gehr, Ch., Rüther, E. and Hippius, H. (1980). Zur Praxis der Klinischen Therapie mit Psychopharmaka. *Phamacopsychiatry*, **13**, 1–19.

Haider, I. (1967). Combination of amitriptyline and chlordiazepoxide in depressive states. *British Journal of Clinical Practice*, **21**, 39–40.

Hamilton, M. (1959). The assessment of anxiety states by rating. *British Journal of Medical Psychology*, **32**, 50–55.

Hamilton, M. (1960). A rating scale depression. *Journal of Neurology, Neurosurgery and Psychiatry*, **23**, 56–62.

Hare, H. P. (1971). Comparison of chlordiazepoxide-amitriptyline combination with amitriptyline alone in anxiety-depressive states. *Journal of Clinical Pharmacology*, **11**, 456–460.

Hollister, L. E. (1971). Anxiety, depression and psychotropic drugs. *Drug*, **1**, 189–193.

Honorato, J., Rubio, A., Tristan, C., Otero, F. J. and Garrido, J. (1990). Estudios de farmacovigilancia con bentazepam en una muestra de 1046 pacientes psiquiátricos ambulatorios. *Rev. Med. Univ. Navarra*, **34**(2), 80–7.

Houck, J. E. (1970). Combined therapy in anxiety–depressive syndromes. *Diseases of the Nervous System*, **31**, 269–273.

Jacobson, A. F. (1978). Doctor–patient concordance in a placebo controlled trial of limbitrol versus components. *Psychopharmacology Bulletin*, **14**, 61–63.

Laux, G., Koenig, W. and Pfapp, G. (1988). Antidepressant combination therapy of endogenous depressions with benzodiazepines or neuroleptics – A study comparing adjuvant treatment with oxazolam versus chlorprothixene. *Pharmacopsychiatry*, **21**, 87–92.

Lauries, A., Puech, A. and Allilaire, J. F. (1982). Des associations mèdicamentouses dans le traitment des dépressions. *Semaine des Hôpitaux, Paris*, **58**(42), 2432–2439.

Lehman, H. E. (1965). Problems of differential diagnosis and choice of therapy in depressive states. *Psychosomatics*, **6**, 266–272.

Maier, S. F., Silbert, L. H., Woodmansee, W. W. and Desan, P. H. (1990). Adinazolam both prevents and reverses the long-term reduction of daily activity produced by inescapable shock. *Pharmacology, Biochemistry and Behavior*, **36**(4), 767–773.

Poldinger, W. and Koeppen, D. (1979). Treatment of anxious-depressed outpatient with a fixed combination (nomifensine/clobazan) in comparison to a monosubstance (dozepine). In: *Biological Psychiatry Today*, Obiols, J. *et al.* (eds) Elsevier, Amsterdam, pp. 111–123.

Rickels, K., Gordon, P. E., Jenkins, B. W., Perloff, M., Sachs, T. and Sepansky, W. (1970). Drug treatment in depressive illness. *Diseases of the Nervous System*, **31**, 30–42.

Rickels, K., Hesbacher, P. and Downing, R. W. (1970). Differential drug effects in neurotic depression. *Diseases of the Nervous System*, **31**, 468–475.

Rickels, K., Hutchinson, J. C. and Weise, C. C. (1972). Doxepin and amitriptiline-perphenazine in mixed anxious-depressed neurotic outpatients: a collaborative controlled study. *Psychopharmacologie (Berlin)*, **23**, 305–318.

Rickels, K., Feighner, J. P. and Smith, W. T. (1985). Alprazolam, amitriptiline, doxepin, and placebo in the treatment of depression. *Archives of General Psychiatry*, **42**, 134–141.

Salzman, C. (1981). Psychotropic drug use and polypharmacy in a general hospital. *General Hospital Psychiatry*, **3**, 1–9.

Silverman, G. and Braithwaite, R. (1972). Interaction of benzodiazepines with tricyclic antidepressant. *British Medical Journal*, **4**, 111.

Smith, M. (1973). Clinical response to amitriptyline and chlordiazepoxide–amitriptyline (Limbritol) in anxiety-depressive states. *Psychosomatics*, **14**, 168–175.

Swinson, R. P. (1989). The acute treatment of anxiety and depression. *Psychiatry Journal of the University of Ottawa*, **14**(2), 375–378.