agent as produces the conditions of anencephaly, etc., with which lesions malformation of the bulbus is so often associated.'

Finally one comes back to the problem of how efficient pulmonary blood flow was maintained in this case for survival during childhood and up to the age of 17 years. The following possibilities can be postulated: that the ductus arteriosus took a longer time to close during infancy, thus allowing a period of aortic pulmonary shunt. In the fetal heart there is normally a right ventricular preponderance. The progressing hypertrophy of the right ventricle must have played an important role in forcing the blood through the ostium between the right ventricle and infundibulum. One can also visualise a gradual narrowing of this ostium as the heart grew in size. The infundibulum probably acted as a special pulmonary pump, according to Keith's[4] concept of the functional significance of the bulbus cordis. These compensatory mechanisms apparently prolonged life beyond normal expectation in the light of the anatomical anomalies described.

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Evaluation of Lorazepam as an Anxiolytic Agent in Psychiatric Practice

A. J. LASICH

SUMMARY

The efficacy of lorazepam, one of the newer benzodiazepines, as an anxiolytic agent is assessed in a study involving 35 non-hospitalised patients. No serious side-effects were encountered and the drug, administered orally, was well tolerated. The patients exhibited anxiety as a primary symptom or in association with other disease entities. The drug appeared to be most effective against insomnia, tension and anxiety.

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Lorazepam or 7-chloro-5-(O-chlorophenyl)-1,3-dihydro-3 hydroxy-2H-1, 4-benzodiazepin-2-one, is one of the newer benzodiazepines, possessing in common with other members of this class, sedative, hypnotic and anxiolytic properties.

In animals lorazepam has demonstrated anxiolytic and anticonvulsant actions more potent than those of chlordiazepoxide,[1-3] and in human volunteers it has demonstrated beneficial hypnotic[4] and amnesic[5] effects. In patients with anxiety independent of, secondary to, or associated with, disorders of the psyche or other functional disorders without organic involvement, lorazepam has proved effective and was well tolerated.[6-12]

The present open study was undertaken to evaluate the anti-anxiety effects of lorazepam in non-confined patients with anxiety states of diverse origins.

PATIENTS AND METHODS

Thirty-five adult male and female outpatients were selected from private practice for a 6-week study. Their ages ranged from 19 to 68 years and 11 were males. With the exception of 2 Asiatic patients, all were White. All had

Durban
A. J. LASICH, M.B. B.CH., D.P.M., F.F. PSYCH., *Psychiatrist*

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mild to severe anxiety as a primary symptom or in association with personality disorders, depression, phobias or schizophrenia (Table I). Excluded from the study were patients with known hypersensitivity to the test drug, or with serious debilitating organic disease, and pregnant women. Generally lorazepam is not indicated in schizophrenic patients, but in 2 schizophrenic patients in this series the symptoms were of such intensity that the use of lorazepam was considered an essential therapeutic adjuvant.

TABLE I. PSYCHIATRIC DIAGNOSIS

	No. of patients
Anxiety state	18
Schizophrenia	2
Obsessional neurosis	4
Depression	
Mixed	5
Reactive	3
Agitated	2
Endogenous	1
Total	35

The average daily oral dose of lorazepam varied from 1 mg to 9 mg, depending on the response and condition of the patient. Most patients received from 1 mg to 3 mg of lorazepam daily. One patient required as much as 9,1 mg of lorazepam as an average daily dose, and 2 required as little as 1 mg daily. Where possible other psychotropic medication was discontinued 2 weeks before administration of lorazepam. Thirteen patients, however, required antidepressant medication for varying periods during the study.

Patient symptoms were evaluated and recorded on a Hamilton Anxiety Rating Scale prior to therapy and at weekly intervals thereafter for 6 weeks. Symptoms were rated on a 4-point scale: 0—absent, 1—mild, 2—moderate, and 3—severe, at the end of each week. Global evaluations were rated independently of symptoms and recorded at the end of each week using a 5-point scale: 0—worse, 1—no change, 2—slightly improved, 3—moderately improved, and 4—much improved. Side-effects and investigator's comments were also recorded. The data were then analysed with appropriate statistical methodology to determine significant pre- and post-treatment differences. A one-way analysis of variance, adjusted for pretreatment differences among patients, was performed on the individual items on the Hamilton Anxiety Rating Scale and global evaluations were chi-squared.

It should be noted that laboratory work-ups and EEGs would have been taken if required, but none were necessary.

RESULTS AND DISCUSSION

All 35 patients completed 6 weeks of the study. The anti-anxiety activity of lorazepam as reflected in the decline of Hamilton scores for each week of therapy from pretreatment scores became apparent early in the study (Table II). A one-way analysis of covariance, with pretherapy scores as the covariant, further revealed that the difference between weekly and pretherapy scores reached significance at the 0,001 level. A chi-squared analysis of the global ratings compared for changes over the 6-week period also showed significant differences at the 0,001 level. A comparison of the global ratings of worse (0) and no change (1), with those of slight (2), moderate (3) and much improvement (4), showed that the percentage of improvement for weeks 1, 2 and 3 were 43%, 83%, and 89%, respectively; for the remaining 3 weeks, collectively, it was 94%.

Lorazepam seemed most successful against insomnia, tension, anxious mood, respiratory and general somatic complaints, behaviour at interview and other tension- and anxiety-linked symptoms. A subsequent chi-square analysis of individual items on the Hamilton scale showed that

TABLE II. RESPONSE TO LORAZEPAM

		Hamilton anxiety rating scale changes*							Improvement noted at week:			
	No.	3—2	3—1	3—0	2—1	2—0	1—0	No change	1	2	3	4
Anxious mood	35	5	9	4	9	5	0	3	14	14	2	2
Tension	35	3	11	12	1	7	0	1	22	8	3	1
Fears	17	1	3	0	3	1	5	4	4	3	3	4
Insomnia	31	0	3	13	1	11	3	0	24	3	2	2
Intellectual	29	1	1	2	1	6	10	8	7	8	2	4
Depressed mood	30	2	0	2	1	8	7	10	5	5	5	5
General somatic	35	1	5	5	4	10	8	2	18	8	3	4
Cardiovascular	28	0	2	0	0	13	10	3	10	10	5	0
Respiratory	29	1	1	1	2	9	13	2	8	15	4	0
Gastro-intestinal	27	2	2	1	3	6	10	3	9	9	4	2
Genito-urinary	23	1	2	0	5	2	3	10	5	3	2	3
Behaviour at interview	34	4	5	4	5	15	1	0	14	16	1	3

*3—severe; 2—moderate; 1—mild; 0—absent.

these symptoms had improved measurably from pre-therapy ratings, reaching significance at the 0,001 level (Table III).

TABLE III. ORDER OF IMPROVEMENT

	Weeks				
	1	2	3	4	χ^2 (3)
Anxious mood	14	14	2	2	18,00*
Tension	22	8	3	1	31,65*
Fears	4	3	3	4	0,29
Insomnia	24	3	3	2	42,75*
Intellectual	7	8	2	4	4,33
Depressed mood	5	4	5	5	0,16
General somatic	18	8	3	4	17,06*
Cardiovascular	10	10	5	0	11,00†
Respiratory	8	15	4	0	17,81*
Gastro-intestinal	9	9	4	2	6,33
Genito-urinary	5	3	2	3	1,46
Behaviour at interview	14	16	1	3	20,35*

* $P<0,001$
† $P<0,01$

Lorazepam exerted its greatest effect against insomnia, tension and anxiety, in that order. Complete alleviation or reduction in severity of symptoms was noted within the first 2 weeks of treatment in approximately 80% of patients (Table II). This included 16 patients with severe, 12 with moderate, and 3 with mild degrees of insomnia; 26 patients with severe and 8 with moderate degrees of tension, and 18 with severe and 14 with moderate symptoms of anxiety.

Patients who had previously experienced difficulty in sleeping indicated that the medication had helped them and that sleep was easily induced and well-sustained. It appeared that lorazepam dispelled the anxiety and tension which were probably responsible for the insomnia, and its effect (in my opinion) exceeded all other benzodiazepines as a sleep-inducer.

Fears, intellectual, gastro-intestinal and genito-urinary symptoms as well as those relating to depressed mood, were not significantly affected by the medication (Table III).

Lorazepam exerted its least effect on depressed mood, and only in those instances where the depressive states were secondary to anxiety. In endogenous depression, lorazepam given as an adjunct to antidepressant agents appeared to lessen tension and improve the mood by virtue of its sedative effect, but did not directly affect the depression. Lorazepam was also effective in phobic states with a strong anxiety component. In most cases dosage adjustment was necessary, depending on the degree of anxiety and tension and previous habituation to similar anxiolytic and sedative-hypnotic agents. Alone or as concomitant therapy with antidepressant and other agents, the usually effective dose range for lorazepam was 1 - 3 mg and doses as high as 9 mg were without serious side-effects. None of the patients in this series showed intolerance to lorazepam.

In conclusion, findings from this study are in agreement with those of other studies[6-11] which suggest that lorazepam possesses pronounced anxiolytic and sedative-hypnotic properties, is free from serious side-effects and is a useful addition to treatment of neurotic disturbances which are accompanied by anxiety, tension and insomnia.

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