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CLINICAL EVALUATION OF A TETRACYCLIC ANTIDEPRESSANT, MIANSERIN HYDROCHLORIDE

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Abstract

Org GB94, a tetracyclic antidepressant, was administered to 11 cases of involutional melancholia, 23 of MDP, depressed type, 5 of MDP, circular type, 6 of depressive neurosis and one case of reactive depressive psychosis for the total of 46 cases and the following results were obtained.

Org GB94 was very effective on 13 cases, effective on 14, slightly effective on 10 and ineffective on 7. There were no aggravated cases and two were lost for follow-up. The effective rate (very effective and effective cases) was 58.7% and when the slightly effective cases were included, the effective rate was 80.4%. The efficacy of Org GB94 based on the very effective and effective cases (plus slightly effective cases) for the different types of depression was as follows. Involutional melancholia 63.6% (90.9%); MDP, depressed type 56.5% (78.3%); MDP, circular type 40.0% (60.0%); Depressive neurosis 66.7% (83.3%).

Of the various depressive symptoms, improvement ($p < 0.01$) of insomnia (delayed) and general somatic symptoms were observed from the 4th day. During the first week a significant ($p < 0.01$) improvement was observed in depressed mood, insomnia (initial), psychomotor retardation, somatic anxiety, gastrointestinal symptoms, suicidal thoughts, work and interests, psychic anxiety and hypochondriasis. Improvement of agitation was observed after the third week. The optimal dose range of Org GB94 appears to be 30-60 mg a day. As side-effects drowsiness, dry mouth, fatigue, constipation, headache and heavy feelings in head, dizziness, and vertigo were observed, but these were mild in nature and were less frequently seen than with the tricyclic compounds.

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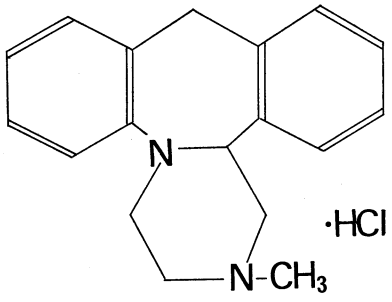
INTRODUCTION

Mianserin hydrochloride (Org GB94) is a tetracyclic compound belonging to the group of piperazino-azepines, synthesized by Organon International B.V. of the Netherlands (Fig. 1).



1, 2, 3, 4, 10, 14b-hexahydro-2-methyldibenzo [c, f] pyrazino [1, 2-a] azepine monohydrochloride

Fig. 1. Chemical Structure of Org GB94

Pharmacological studies in animals[14] revealed that Org GB94 possessed a pharmacological pattern unlike that of the tricyclic antidepressants. It did not antagonize reserpine in rats and mice; had hardly any effect on perphenzine-induced catalepsy in mice; antagonized amphetamine: but it decreased the aggressiveness of isolated mice and muricidal behavior of rats, and it had no antagonistic effect on drug-induced convulsions and slightly accelerated electro-convulsions.

In biochemical investigations Org GB94 was shown to be devoid of effects on brain monoamine oxidase in rats; reduced the serotonin turnover in mouse brain[9] but found to enhance the turnover of noradrenaline and dopamine in rat brain[7].

Itil[5,6] carried out trials with Org GB94 in normal volunteers using quantitative pharmaco-electroencephalography; thereby established that Org GB94 has an EEG profile similar to amitriptyline and predicted that Org GB94 would possess antidepressant properties.

Many open studies confirming the antidepressive effect of Org GB94 and six double-blind comparative studies[2,5,10,11,16,18] have already been published. These studies have shown that Org GB94 is a useful antidepressant with an antidepressant effect similar to that of the tricyclic compounds such as imipramine and amitriptyline but with a rapid onset of action and fewer side-effects.

In Japan results of clinical studies on Org GB94 by Onodera *et al.*[13], Shimizu *et al.*[15] and Okamoto *et al.*[12] have been reported.

We also administered Org GB94 to 46 cases of various types of depression and the evaluation of the results is reported.

PATIENTS MATERIAL AND METHODS

The patients consisted of 46 cases of various types of depression examined by the investigators of the hospitals concerned between July and December 1976. Only those patients receiving no antidepressant therapy or electroshock treatment for the present episode were included in the trial.

The background history of the patients are shown in Table 1. The patients consisted of 20 males and 26 females, ranging in age from 19 to 70 years old (average age 43.9±12.5). Based on the ICD classification there

TABLE 1. Background History of the Patients

1. No. of patients		46 case
2. Sex	Male	20 〃
	Female	26 〃
3. Status	Inpatient	12 〃
	Outpatient	30 〃
	Outpatient ⟶ Inpatient	4 〃
4. Age	Average age 43.9±12.5	
	- 19	1 〃
	20 - 29	8 〃
	30 - 39	8 〃
	40 - 49	13 〃
	50 - 59	12 〃
	60 -	4 〃
5. Type of Depression	1. Involutional melancholia	11 〃
	2. Manic-depressive psychosis, depressed type	23 〃
	3. Manic-depressive psychosis, circular type	5 〃
	4. Depressive neurosis	6 〃
	5. Reactive depressive psychosis	1 〃
6. No. of episodes (attacks)	1	20 〃
	2	6 〃
	3	10 〃
	4 - 9	4 〃
	10 -	1 〃
	Unknown	5 〃

were 11 with involutional melancholia, 23 with manic depressive psychosis, depressed type (MDP, depressed type), 5 with manic depressive psychosis, circular type (MDP, circular type), 6 with depressive neurosis and 1 with reactive depressive psychosis.

As a rule, Org GB94 was used alone starting with an initial dose of 20–30 mg a day, thereafter the dose was either increased or decreased depending on the severity of the symptoms. The maximal dose was fixed at 90mg a day. Basically the duration of treatment was fixed at four weeks; but actually 4 patients were treated for one week, 12 for two weeks, 6 for three weeks and 24 for more than four weeks, and these patients were observed for the maximum of 42 days. Concomitant use of sedatives such as nitrazepam, flurazepam and estazolam was allowed and recorded when these were used. Pregnant women, lactating women, patients with severe complications or severe depression with a high risk of suicide were excluded from the trial.

For the evaluation of the depressive symptoms the Doctor's Global Improvement Rating, Hamilton Depression Rating Scale and Beck Depression Inventory[1)] were used. For the global improvement rating the following five grades were used.

Marked improvement:	Remission of practically all symptoms
Improvement:	Remission of more than 50% of the symptoms
Slight improvement:	Remission of less than 50% of the symptoms
No change:	Practically no change in the symptoms
Aggravation:	Worsening of the symptoms

The assessment of the depressive symptoms was made with the use of the Hamilton Depression Rating Scale at 0 time and every week thereafter. The Beck Depression Inventory was also filled in at the same time. With the hospitalized patients the two rating scales were filled in on the 4th day also. To check the side-effects and treatment-emergent symptoms a side-effects battery was prepared and recorded every week. Laboratory examination consisting of blood pressure readings, pulse rate, body weight, hematology, liver function tests, urinalysis and ECG were performed as much as possible prior to treatment, and after completion of treatment.

RESULTS

[1] Global Improvement Rating (Table 2)

The global assessment of the result of treatment with Org GB94 is shown in Table 2. Of the total of 46 patients treated, Org GB94 was very effective in 13 cases (28.3%), effective in 14 cases (30.4%), slightly effective in 10 cases (21.7%) and ineffective in 7 cases (15.2%). There were no aggravation

TABLE 2. Global Improvement Rating

very effective	effective	slightly effective	ineffective	aggravation	evaluation not possible	total
13	14	10	7	0	2	46

$$\text{effective rate}: \frac{\text{very effective} + \text{effective}}{\text{total}} \times 100 = 58.7\%$$

$$\left(\frac{\text{very effective} + \text{effective} + \text{slightly effective}}{\text{total}} \times 100 = 80.4\%\right)$$

but 2 cases could not be rated. Org GB94 was effective in 27 (58.7%) out of 46 cases when the very effective and effective cases were combined. The effective rate was 80.4% (37 out of 46 cases) when the slightly effective cases were included. The 2 cases which could not be rated were patients who failed to report to treatment and therefore could not be follow-up.

[2] Global Assessment According to Type of Depression (Table 3)

The global assessment according to the type of depression is shown in Table 3. Efficacy based on the very effective and effective cases revealed that Org GB94 was effective in 63.6% (7/11) of involutional melancholia, 56.5% (13/23) of MDP, depressed type, 40% (2/5) of MDP, circular type and 66.7% (4/6) of depressive neurosis. No marked difference in efficacy was found for the different types of depression.

TABLE 3. Global Assessment According to Type of Depression

	very effective	effective	slightly effective	in-effective	aggrava-tion	evalua-tion not possible	total	effective rate
Involutional	4	3	3	1	0	0	11	63.6 (90.9)
MDP, depressed	6	7	5	3	0	2	23	56.5 (78.3)
MDP. circular	1	1	1	2	0	0	5	40.0 (60.0)
Depressive neurosis	2	2	1	1	0	0	6	66.7 (83.3)
Reactive	0	1	0	0	0	0	1	100 (100)
Total	13	14	10	7	0	2	46	

[3] Relation between Duration of Illness and Global Judgment (Table 4)

The relation between the duration of depressive illness and the results of treatment is shown in Table 4. Of the 46 patients 20 (43.5%) had been ill

for less than a year, and Org GB94 was effective in 55.0% of these cases. No correlation could be established between the duration of illness and efficacy of Org GB94. It is noteworthy that Org GB94 was almost equally effective on those patients who had been ill for more than 10 years.

TABLE 4. Relation between Duration of Illness and Global Judgement

Duration	very effective	effective	slightly effective	in-effective	aggravation	evaluation not possible	total	effective rate
less than a year	5	6	7	1	0	1	20	55.0 (90.0)
1 to 3 years	2	1	1	2	0	0	6	50.0 (66.7)
3 to 10 years	4	1	1	1	0	0	7	71.4 (85.7)
more than 10 years	1	3	1	1	0	1	7	57.1 (71.4)
unknown	1	3	0	2	0	0	6	66.7 (66.7)
total	13	14	10	7	0	2	46	

[4] Maximal Dosage and Global Assessment (Table 5)

The relation between the maximal dose and global assessment is shown in Table 5. The efficacy of Org GB94 on the 30mg, 40mg, and 60mg/day groups were 65.2%, 100% and 57.1% respectively. On the small number of patients who received 80 to 90mg/day the effective rate was low.

TABLE 5. Maximal Dosage and Global Assessment

Maximal dosage (mg/day)	very effective	effective	slightly effective	in-effective	aggravation	evaluation not possible	total	effective rate
20	1	0	0	1	0	0	2	50.0 (50.0)
30	6	9	5	1	0	2	23	65.2 (87.0)
40	1	1	0	0	0	0	2	100 (100)
60	5	3	4	2	0	0	14	57.1 (85.7)
80	0	0	0	1	0	0	1	0 (0)
90	0	1	1	2	0	0	4	25.0 (50.0)
total	13	14	10	7	0	2	46	

[5] Other Stratification Items and Global Assessment

The relation between global assessment and other stratification items, such

as the number of past episodes, the different age groups, inpatient and outpatient groups, therapy with Org GB94 alone and concomitant therapy, was accounted for in the analysis.
The difference was, however, not significant.

[6] Fluctuations in Total Scores in Hamilton Rating Scale (Fig. 2)

The total scores of the depressive symptoms recorded at the initial interview and at the end of the weekly assessment periods according to the Hamilton Rating Scale are shown in Fig. 2. The patients were divided into two groups, i. e., a group with an initial score of less than 24 (mild group) and a group with an initial score of more than 25 (moderate and severe group) respectively, and the changes in the total scores were observed. Since the number of patients varied at each assessment period, the mean scores corresponding to the number of patients at each assessment period are graphically represented.

The patients taken as a whole showed a significant ($p < 0.01$) decrease in the scores already four days after treatment. A rapid decrease in the scores was observed through the second week but leveled off thereafter. It was found that in the mild group of patients there was a significant ($p < 0.05$) decrease in the total score on the fourth day of treatment. A significant decrease in the total score at the $p < 0.01$ level at the end of the first and second week was observed but thereafter the scores leveled off. In the severe group of patients the scores continued to decrease rapidly up to the fifth week of treatment.

[7] Fluctuations in Total Scores in Beck Depression Inventory (Fig. 2)

The changes in the total scores of the patients at each weekly assessment period for the patients as a whole, for a group with an initial score of less than 24 (mild and moderate group), and for a group with an initial score of more than 25 (severe group) are shown in Fig. 2.[1)]

A significant ($p < 0.01$) decrease in the total score was observed at all assessment periods when the patients were rated as a whole. However, the decrease in the total scores was less marked after the second week of treatment. A significant decrease in total scores was observed at all assessment periods for the mild and moderate group and the severe group also. Here again the decrease in the total scores was marked after the second week.

[8] Improvement of the Separate Items on the Hamilton Rating Scale (Table 6)

Only those symptoms which showed a significant decrease in score as compared to those observed initially are shown in Table 6. After four days of treatment a significant ($p < 0.01$) improvement was observed in insomnia (delayed) and somatic symptoms general and at the level of $p < 0.05$ improve-

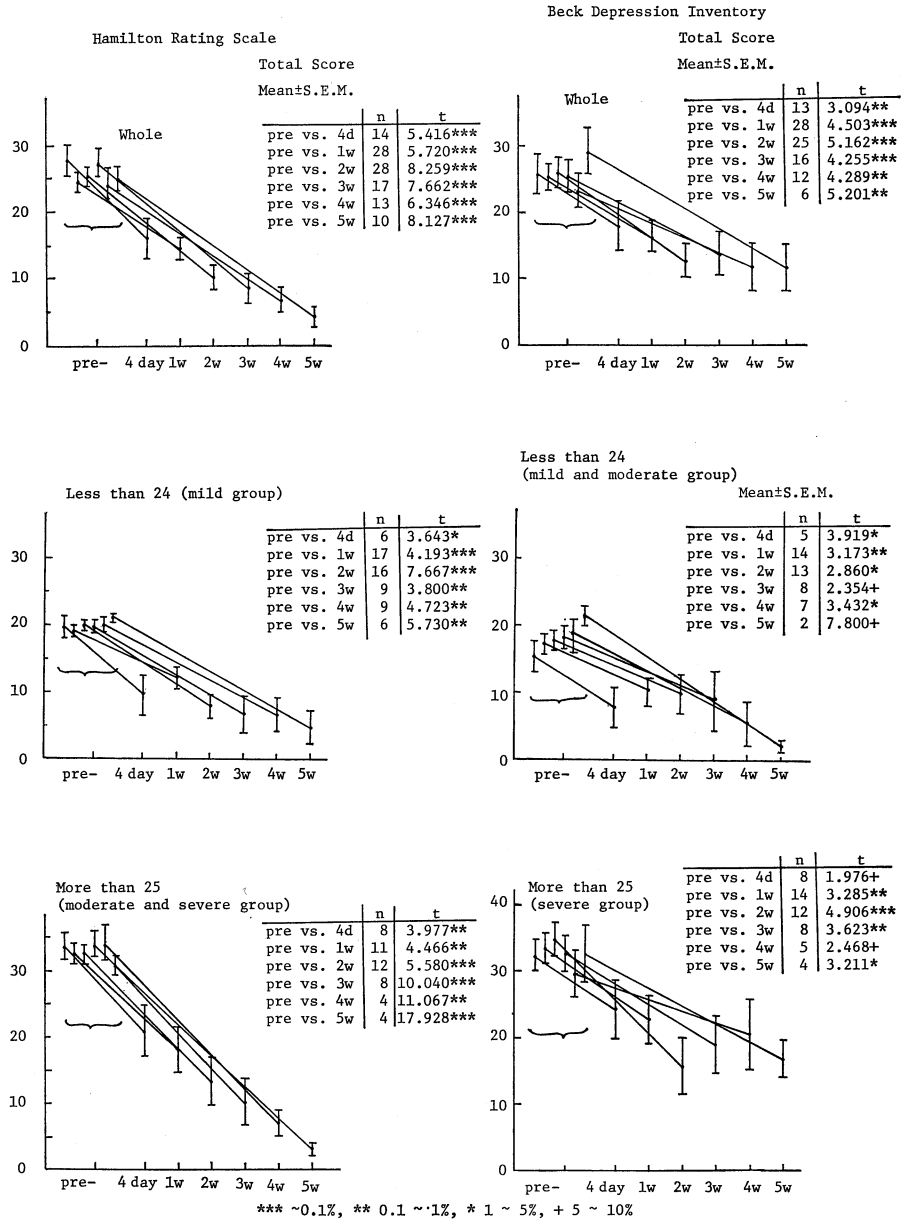


Fig. 2. Fluctuations in Total Scores in Hamilton Rating Scale and Beck Depression Inventory

TABLE 6. Improvement of the Separate Items on the Hamilton Rating Scale

Changes of mean score of each item, showing only those items which showed a significant decrease in the scores in compariosn with pretreatment scores.

	pre-treatment	day 4	1 week	2 weeks	3 weeks	4 weeks	5 weeks
1. Depressed mood	1.91	1.29	1.11***	0.71***	0.59***	0.62***	0.25***
2. Guilt	1.24	0.93	0.82*	0.52***	0.59**	0.54**	0.13***
3. Suicide	1.12	0.86	0.54**	0.39**	0.29**	0.08***	0.00***
4. Insomnia, initial	1.09	0.64	0.29***	0.25***	0.12***	0.00***	0.00***
5. Insomnia, middle	1.12	0.57*	0.57*	0.36***	0.35**	0.15***	0.38*
6. Insomnia, delayed	1.29	0.57**	0.64**	0.39***	0.18***	0.00***	0.00***
7. Work and interests	2.62	2.29	1.82**	1.50***	1.06***	1.00***	0.63***
8. Retardation	1.50	1.07	0.82***	0.68***	0.47***	0.62***	0.25*
9. Agitation	0.65	0.46	0.36	0.32	0.13*	0.15*	0.00*
10. Anxiety, psychic	1.97	1.36*	1.21**	0.82***	0.71***	0.62***	0.25***
11. Anxiety, somatic	1.94	1.29	0.96***	0.68***	0.59***	0.46***	0.13***
12. Somatic symptoms, gastro-intestinal	1.18	0.86	0.57***	0.50***	0.29***	0.23***	0.13***
13. Somatic symptoms, general	1.24	0.64**	0.82*	0.57***	0.53***	0.57**	0.25***
14. Genital symptoms	1.41	0.79*	1.18	0.79**	0.59**	0.85*	0.38**
15. Hypochondriasis	1.74	1.07*	0.96**	0.75***	0.65***	0.69**	0.50**
16. Loss of weight	0.71	0.64	0.56	0.29*	0.24*	0.15**	0.00*
17. Diurnal variation	0.94	0.43*	0.61	0.25***	0.18***	0.07***	0.00**
18. Paranoid symptoms	0.29	0.00*	0.14	0.07	0.00*	0.00	0.00

In comparison with pre-treatment score * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Wilcoxon rank test)

ment in insomnia (middle), psychic anxiety, genital symptoms, hypochondriasis, diurnal variation and paranoid symptoms was observed. At the end of one week improvement of depressed mood, insomnia (initial), retardation, somatic anxiety, somatic symptoms gastro-intestinal ($p < 0.001$), suicide, work and interests ($p < 0.01$) and guilt ($p < 0.05$) was observed. From the second week and thereafter most of the symptoms were significantly ($p < 0.001$) improved, showing complete agreement with the decrease in the total scores on the Hamilton Rating Scale after the second week as shown in Fig. 2.

[9] Side-effects (Table 7)

Of the 44 patients (excluding the two who were lost for the follow-up) 30 patients (68.2%) complained of some sort of side-effect. The remaining 14 patients (31.8%) had no complaints. Symptoms frequently observed were drowsiness (22.7%), dry mouth (20.5%), fatigue (15.9%), constipation (13.6%), headache and heavy feelings in head (11.4%) and dizziness (6.8%). These

TABLE 7. Side-effects and Treatment Emergent Symptoms

	+++	++	+	±	total
1. Drowsiness		4	6		10 (22.7%)
2. Dry mouth			8	1	9 (20.5%)
3. Fatigue	1	1	5		7 (15.9%)
4. Constipation		3	3		6 (13.6%)
5. Headache and heavy feelings in head			5		5 (11.4%)
6. Dizziness, vertigo and dysregulation		1	1	1	3 (6.8%)
7. Nausea and vomiting			1	1	2 (4.5%)
8. Edema			2		2 (〃)
9. Insomnia			2		2 (〃)
10. Disorder of vision			2		2 (〃)
11, Tremor			1		1 (2.3%)
12. Nasal obstruction			1		1 (〃)
13. Paraesthesia	1				1 (〃)
14. Rash			1		1 (〃)
15. Increased appetite			1		1 (〃)
Total	2	9	39	3	53

Having some complaints of side-effects or treatment-emergent symptoms

+: 30 (68.2%)

−: 14 (31.8%)

+++: severe, ++: moderate, +: mild, ±: slight

side-effects were observed more frequently during the first week but tended to disappear after the second week.

A patient was dosed with Org GB94 20mg a day but the treatment was discontinued on the patient's request because he complained of fatigue. Another patient was dosed with 30mg a day but the patient complained of anxiety and agitation. The treatment was discontinued on the 9th day of treatment due to aggravation of the above symptoms despite the fact that the drug was effective on depressive mood and suicidal thoughts up to the 4th day.

The frequency of occurrence of other side-effects was low, and these were observed in the patients receiving other antidepressants or psychotropics together with Org GB94. A case of rash was observed in patient who had been taking imipramine 75mg a day until a few days prior to receiving Org GB94.

[10] Laboratory Examinations

Of the total number of patients treated with Org GB94 laboratory examinations were performed on 16 patients prior to, during and after completion of the study.

Hematological examinations revealed no marked changes in RBC, WBC, Hb, Ht and platelet count.

In the liver function test some elevation of the GOT and GPT was observed in three patients. With the first patient the GOT was elevated from 16 to 34 and the GPT from 14 to 65 after the 35th day of treatment, but no other abnormal values were observed in the other laboratory tests.

With the second patient treated with a combination of Org GB94 and psychotropic drugs was found to have a slightly elevated GPT prior to treatment. On the 21st day of treatment the patient's GOT rose from 16 to 61 and GPT from 47 to 156, therefore treatment was discontinued. However the patient's GPT and GOT were down to 21 and 52 respectively on examination performed just prior to release from hospital (30 days after drug withdrawal). With the third patient functional disorders of the liver were observed prior to treatment with Org GB94. On the 6th day of treatment his GOT changed from 59 to 47 and his GPT from 117 to 199, but on the 13th day his GOT and GPT had dropped to 28 and 35 respectively.

Urinalysis revealed no abnormal values. No abnormal findings were noted in the ECG which was performed on four patients. No marked changes were observed in the blood pressure, pulse rate and body weight.

DISCUSSION

The global judgment of the antidepressant activity of Org GB94 on various types of depression showed that it was effective in 58.7% (very effective and effective) and in 80.4% inclusive of the slightly effective cases.

Onodera *et al.*[13] have reported an effective rate of Org GB94 on endogenous depression and depressive neurosis of 53.1% (26 out of 49 cases) and 67.3% (including slightly effective cases). This is in agreement with our finding, but we were not able to match the 73.3% (86.7%) and 71.4% (90.5%) effective rates achieved by Shimizu *et al.*[15] and Okamoto *et al.*[12] respectively.

The effective rate of 58.7% (80.4%) which we obtained in our present study has shown practically the same level of antidepressant activity shown by the tricyclic antidepressants in a double-blind trial[8], indicating that Org GB94 has an antidepressant activity equal to that of the tricyclic compounds.

Our results are comparable to those of Walcher[17] who reported an effective rate of 60.0% (80.0%) for Org GB94. Already six[2,5,10,11,16,18] double blind trials with Org GB94 and imipramine or amitriptyline have been reported by foreign investigators, and these are summarized in Table 8.

Murphy[11] reported an effective rate of 43.9% (68.3%) for Org GB94. Others such as Itil *et al.*[5,6], Vogel *et al.*[16], Wheatly[18], Coppen *et al.*[2,3] and

Murphy *et al.*[10] have not found any significant difference in efficacy between Org GB94 and the reference preparations.

Regarding the improvement of the depressive symptoms of Org GB94 Fleischhauer *et al.*[4] found that this drug was effective on depressed mood and had a slight sedative action and marked anxiolytic activity.

Onodera *et al.*[13] reported that Org GB94 was effective on depressed mood loss of initiative, anorexia, retardation of thought, anxiety and irritation but its anxiolytic activity was weak.

Shimizu *et al.*[15] found a marked improvement in suicidal thoughts, somatic anxiety and gastrointestinal symptoms. Okamoto *et al.*[12] also noted a marked improvement in suicidal thoughts, depressed mood, anxiety and retardation.

In a double-blind study involving Org GB94 and amitriptyline Vogel *et al.*[16] noted that Org GB94 was effective on loss of initiative, retardation of thinking, difficulty in concentration, agitation and psychomotor inhibition. On the other hand, amitriptyline was significantly effective on depressive symptoms such as suicidal tendency, diurnal variation, hopelessness, anxiety and insomnia.

Murphy[11] also noted that Org GB94 was effective on insomnia (delayed), fatigability, libido, anorexia, heaviness in head and gastrointestinal symptoms during the first week of treatment. Depressive mood, anxiety and irritation were also improved.

From the improvement of the scores on the Hamilton Rating Scale in our study a significant improvement of symptoms such as insomnia (delayed), somatic symptoms in general, insomnia (middle), psychic anxiety, genital symptoms, hypochondriasis, diurnal variation and paranoid symptoms were observed on the 4th day of treatment. In addition to the above symptoms, depressed mood, insomnia (initial), retardation, somatic anxiety, gastrointestinal symptoms suicidal thoughts, work and interests and feelings of guilt showed improvement at the end of the first week. These results indicated that Org GB94 was effective not only on depressed mood and loss of initiative but on sleep disturbances and somatic symptoms as well. After two weeks of treatment symptoms in general showed an improvement. The improvements which we described above are in agreement with those reported by Fleischhauer *et al.*[4], Onodera *et al.*[13], Shimizu *et al.*[15], Okamoto *et al.*[12], and Vogel *et al.*[16] as described earlier. Regarding the agitation a significant improvement was observed only after three to five weeks of treatment. This may have been due to the low initial score for these symptoms which made it difficult to find any significant difference in the improvement scores. Since Vogel *et al.*[16] and Murphy[11] have already called some attention to the role of Org GB94 on these symptoms, we also would

like to confirm it in double-blind comparative trials which we hope to do in the future.

The rapid onset of action of Org GB94 has been emphasized as one of the advantages of this drug. The onset of action of Org GB94 was seen on 2 to 3 days (Fleischhauer *et al.*[4]), 2.7 days in average (Okamoto *et al.*[12]), and the effect of Org GB94 was observed on 2 to 3 days in 37.5% of the cases and within 7 days in 75% (Onodera *et al.*[15]). In our study we found that in 4 patients the onset of action of Org GB94 was on the 4th day. Judging from the fact that a significant decrease in the total score was observed on the 4th day on the Hamilton Rating Scale and Beck Depression Inventory, it would be possible to say that Org GB94 had taken effect on the 4th day.

For the sake of analysis the patients were classified into groups: type of depression, age, number of attacks, duration of illness and outpatient and in-patient groups respectively. As to the efficacy of Org GB94 on the various groups of patients, it was not possible to find out to what group Org GB94 was specially effective. However, it appeared that with some of the severe cases of depression the therapeutic effect of Org GB94 may have been inadequate.

According to the Beck Depression Inventory the total scores for the patients with severe depression (total score over 25) at the end of the 4th and 5th were 20.6 ± 5.07 and 16.8 ± 2.84 respectively. On the other hand, the total scores for the patients with mild or moderate depression were less than 10 after the second week.

For an optimum dose ranges of 10-40mg/day[4], 20-100mg/day[17], and for double-blind studies dose ranges of 29-55mg/day[5,6], 10-60mg/day,[16], 30-60mg/day[11,18], 60mg/day[2,3] and 40mg/day[10] have been established. Onodera *et al.*[13] have recommended doses of 20-60mg/day and Okamoto *et al.*[12] 20-30mg/day.

In our study favorable results were obtained with doses of 30-60mg/day (Table 5) and doses in excess of this dose range have not necessarily produced good results. Therefore, a dose of 30-60mg/day appears to be the appropriate dose for the patients in Japan.

Side-effects of Org GB94 were similar to those of the tricyclic compounds (Table 7). According to Kurihara *et al.*[8], the frequency of appearance of side-effects with imipramine was dry mouth (37.0%), drowsiness (44.4%), fatigue (14.8%), constipation (18.5%), heaviness in head and headache (14.8%) and dizziness (44.4%). However, with Org GB94 the incidence of side-effects was considerably lower.

There is complete agreement among the authors that side-effects such as constipation and dry mouth which are related to the effect of drugs on the

autonomic nervous system are rare with Org GB94. Our results were also in complete agreement with those obtained by other authors. As a therapeutic agent Org GB94 may become a powerful weapon for senile patients and for those depressive patients with glaucoma for which tricyclic compounds cannot be used because of their anticholinergic side-effects. However, in one of the cases treatment with Org GB94 had to be discontinued because the patient complained of severe fatigue. Also in about 20% of the cases mild drowsines and fatigue were observed. In these cases the dose of Org GB94 was not necessarily large; in fact, the majority of the cases was observed in the early stage of treatment at dose levels of 20-30mg a day. This point should be carefully watched when Org GB94 is used in the treatment of depression. Wheatley[18] and Murphy[11] also reported that drowsiness was very frequently observed with Org GB94. These were observed frequently during the first week of treatment but tended to disappear thereafter.

The administration of Org GB94 did not cause significant changes in hematology, urinalysis, blood pressure, pulse rate and body weight. In biochemical examinations elevation of GOT and GPT was observed in three cases but two of these had abnormal values prior to treatment with Org GB94. Nevertheless, liver function tests should be performed periodically whenever, Org GB94 is to be used for treatment.

Acknowledgment

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TABLE 8. Results of Six Double-blind Comparative Studies

	Itil, T. M.[5] (U. S. A.)		Vogel, H. P. *et al.*[16] (Germany)		Murphy, J. E.[11] (U. K.)		Wheatley, M. D.[18] (U. K.)		Coppen, A. J. *et al.*[1] (U. K.)		Murphy, J. E. *et al.*[10] (U. K.)		
Drugs	GB94	ATL	GB94	ATL	GB94	IMP	GB94	ATL	GB94	ATL	GB94	IMP	Placebo
Daily dosage	1st week		1st and 2nd week		3rd day		4th day		20mg×3	150mg	10mg×4	25mg×4	
	20mg	50mg	10mg	25mg	10mg×3	25mg×3	10mg×3	25mg×3					
	2nd week		After 3rd week		After 4th day		After 5th day						
	30mg	75mg	60mg	150mg	20mg×3	50mg×3	20mg×3	50mg×3					
	3rd week												
	40mg	100mg											
Type of trial	Group comparative		Group comparative		Group comparative		Group comparative		Group comparative		Group comparative		
Rating scale	HZI Depression R. S. Hamilton Anxiety Scale		AMP system		Seventeen Symptom Depression R. S. A 10cm Line Visual Analogue Self R. S.		Hamilton R. S.		Hamilton R. S. Newcastle Diagnostic R. S.		Physician R. S. A Patient Self R. S. A Standardised Sixteen-Point Side Effect Inventory		
Assessment period	0 day, 1w, 3w		0 day, 10d, 20d, 30d		0 day, 2w, 4w, 6w		0 day, 1w, 2w, 4w		0 day, 2w, 4w, 6w		0 day, 1w, 2w, 3w, 4w, 5w, 6w		
Patient material	patients with depressive syndrome		all depressive patients who were in need of anti-depressive pharmacotherapy		depressive illness		depressive neurosis, reactive depressive psychosis, other affective psychosis, manic-depressive psychosis, depressed type		endogenous dep. reactive depression		primary diagnosis of depression		
Other drugs					nitrazepam				nitrazepam				
No. of patients	13	12	23	20	41	43	39	40	17	22	35	34	33
Results	N. S.		N. S.		++ 43.9% ++ ~ + 68.3% N. S.	++ 37.2% ++ ~ + 58.8%	N. S.		N. S.		Both GB94 and IMP were found to be significantly more effective than placebo.		
Remarks			GB94 has no anti-cholinergic side-effects		13-70 years old		18-65 years old		GB94 has a few side-effects.		18-70 years old There is no significant difference in side-effects between the three treatments.		

ALT: Amitriptyline, IMP: Imipramine N.S.: Not Significant
AMP: Arbeitsgemeinschaft fur Methodik und Dokumentation in der Psychiatrie.