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PLACEBO-CONTROLLED TRIAL OF MIANSERIN AND MAPROTILINE IN PRIMARY DEPRESSIVE ILLNESS: A PRELIMINARY REPORT

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1 Preliminary results of a double-blind placebo-controlled trial of mianserin and maprotiline carried out in 58 outpatients with primary depressive illness are reported.

2 Patients received six weeks' treatment with 30 to 90 mg mianserin, 75 to 225 mg maprotiline or one to three capsules of placebo, all medication being taken at night.

3 There were statistically significant improvements in each treatment group and a better response to mianserin than to placebo or maprotiline on the Hamilton Rating Scale for Depression, after one week's treatment.

4 Neither mianserin nor maprotiline was superior to placebo after two or four weeks' treatment and relatively few patients completed six weeks' treatment because of a generally unsatisfactory response.

5 Unwanted effects were not particularly troublesome, though mianserin and maprotiline caused more drowsiness and blurred vision than did placebo, while maptrotiline produced more constipation than either of the other two treatments.

6 The importance of placebo-controlled trials of antidepressants is emphasized and the precautions that should be taken when they are carried out in outpatients are described.

Introduction

Numerous clinical trials of mianserin and maprotiline have been carried out but most have been based on comparisons with tricyclic antidepressants, especially imipramine and amitriptyline. Only four trials of mianserin (Murphy *et al.*, 1976; Perry *et al.*, 1978; Smith *et al.*, 1978; Stewart *et al.*, 1982) and four of maprotiline (Jukes, 1975; McCallum & Meares, 1975; Claghorn, 1977; van der Velde, 1978) have been placebo-controlled.

No trial is free from imperfection. The imperfections in the studies referred to include failure to give adequate details concerning the types of depressive illnesses treated, small sample sizes, short durations of treatment, the concomitant day-time use of a benzodiazepine, failure to use the most reliable and valid rating scales and a high drop-out rate. The results of one of the trials of mianserin and three of maprotiline are a cause for concern since they failed to show acceptable levels of statistically significant advantages over placebo, with a fourth maprotiline trial showing statistically significant advantages at three weeks that had disappeared by four weeks. Negative results of this kind necessarily cast some doubt on the efficacy of these antidepressants and highlight the need for more placebo-controlled studies.

We are currently carrying out such a study and we present here a preliminary report of our results.

Method

Patients

Outpatients of both sexes between the ages of 18 and 66 years were selected from those referred to the Psychiatric Division of the Royal South Hants Hospital, Southampton. To be included in the study patients must have had a unipolar depressive illness which had become established as an 'autonomous' process and whose course was largely independent of environmental influences even though stressful events might have been involved in its aetiology (Edwards & Ollerenshaw, 1974). Patients included met the Medical Research Council criteria for primary depressive illness (Medical Research Council, 1965) and the criteria of Feighner and his colleagues (Feighner *et al.*, 1972). They corresponded to the DSM-III category of 'major depression' and no patients had a score of less than 17 on the Hamilton Rating Scale for Depression (Hamilton, 1960).

Patients who had received treatment with a therapeutic dose of mianserin or maprotiline at any time during the course of their present illness were

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excluded. Patients were also excluded if they had a serious physical illness, organic brain syndrome, epilepsy, mental subnormality, a history of alcohol or illegal drug abuse or had been given ECT during the preceding six months. Pregnant women or women likely to become pregnant during treatment were also excluded.

Procedure

At baseline, scores for each patient were calculated from Kendall's 60 weighted items (Kendall, 1968) and on the Newcastle Scale (Carney *et al.*, 1965). Although the Kendall scores of all the patients whose results are reported in this paper were positive (mean for the mianserin group + 16.0, for the maprotiline group + 13.5 and the placebo group + 15.8) showing that their depression was towards the endogenous end of the reactive-endogenous continuum, the Newcastle scores of the majority of patients (10 each in the mianserin and maprotiline groups and 12 in the placebo group) were below six, suggesting that they had depressive neuroses. This was not in keeping with our clinical assessments or the Kendall scores and highlights the difficulty of classifying depression.

The following assessments were carried out using double-blind procedures at baseline and one, two, four and six weeks after starting treatment: the Hamilton Rating Scale for Depression, the Leeds Self-Assessment Depression Scale (Snaith *et al.*, 1976), an analogue scale measuring the three most troublesome symptoms and depression of mood, a sleep questionnaire, global assessments of severity of illness and change in condition, treatment emergent symptoms, an unwanted effects questionnaire (Edwards *et al.*, 1980), a short version of the PERI life events questionnaire (Dohrenwend *et al.*, 1978) and the Eysenck Personality Questionnaire (Eysenck & Eysenck, 1975) at baseline and after four weeks' treatment, to be reported later. Ratings were carried out blind to previous ratings. At the completion of each patient's treatment a guess was made as to which drug they had received. Prior to embarking on the study a satisfactory inter-rater reliability was reached on the use of the rating scales.

Blood was drawn for a series of biochemical investigations. Only the results of the Vickers Group Test and haematological investigations are presented here. Electrocardiographic and electroencephalographic investigations were carried out and are reported elsewhere in this workshop (Edwards & Goldie, 1983, this issue: Sedgwick & Edwards, 1983, this issue).

Treatment

Prior to starting treatment patients had a washout period of 6–8 days wherever possible. In the case of monoamine oxidase inhibitors the washout period was at least two weeks. One patient in the mianserin group (who was off drugs for five days), three in the maprotiline group (two of whom were off drugs for three days and the other for five days), and two in the placebo group (who were off drugs for four and five days) failed to complete the washout period because of the urgent need to start treatment.

Patients were then randomly allocated to treatment with blue capsules of identical appearance containing mianserin 30 mg, maprotiline 75 mg or placebo given as single night-time doses. Treatment began with one capsule at night. This could subsequently be increased to a maximum of three capsules according to a flexible schedule dependent on clinical progress and unwanted effects. No other psychotropic drugs were allowed except 5 mg nitrazepam as a hypnotic where absolutely necessary, although patients were not dropped from the study if some other physician gave them small quantities of other drugs that were unlikely to influence the outcome of antidepressant treatment. Four patients (24%) in the mianserin group, five (31%) in the maprotiline group and six (32%) in the placebo group required nitrazepam.

Results

When the code was broken it was found that 19 patients had been allocated to treatment with mianserin, 20 to treatment with maprotiline and 19 to treatment with placebo. Six patients were excluded from the analysis. Two in the mianserin group complained of side-effects and did not continue treatment, three in the maprotiline group were found to have physical abnormalities at baseline which included an atypical form of epilepsy, ventricular ectopic beats and carcinoma of the caecum. The fourth patient was excluded because another antidepressant had been inadvertently prescribed. Preliminary results are reported on 17 patients who received mianserin, 16 who had maprotiline and 19 who received placebo.

Of these patients, seven (41%) of the mianserin group, six (37%) in the maprotiline group and eight (42%) in the placebo group continued the trial for six weeks. Two of those in the mianserin group and one in the maprotiline group did not return for their six weeks appointment. Three patients in the maprotiline group did not continue treatment because of alleged unwanted effects; they were dry

mouth, stammering and ventricular ectopic beats. Two patients in the placebo group were so much improved that further treatment was not thought necessary. All others were discontinued because they made poor progress.

The number of patients remaining in the study at six weeks was too small for meaningful statistical analyses to be carried out, so the results for one, two and four weeks only will be reported in detail.

Baseline variables

The sexes and ages of these patients are shown in Table 1 while the duration of illness and previous medication are outlined in Tables 2 and 3. Matching on these variables was satisfactory.

Dosage

The mean doses of mianserin given at one, two and four weeks were 45.9, 76.9 and 81.2 mg, respectively. The corresponding doses of maprotiline were 117.2, 201.6 and 200.0 mg while the mean number of capsules of placebo were 1.7, 2.6 and 2.2.

Hamilton Rating Scale

The mean Hamilton scores for items 1–17 are shown in Table 4.

There were no statistically significant differences in baseline scores between the groups. There was a statistically significant decrease from the baseline

Table 1 Sex and age distribution

	Mianserin (*n* = 17)	*Maprotiline* (*n* = 16)	*Placebo* (*n* = 19)
Sex	11 female 6 male	10 female 6 male	12 female 7 male
Age (years)			
18–20	0	2	0
21–30	3	5	5
31–40	4	0	4
41–50	3	1	4
51–60	5	5	4
61–66	2	3	2

Table 2 Length of illness

	Mianserin		*Maprotiline*		*Placebo*	
	No.	%	*No.*	%	*No.*	%
2 weeks–3 months	5	29	3	19	4	21
3–6 months	5	29	3	19	4	21
6–12 months	5	29	4	25	6	32
More than 1 year	2	12	6	38	5	26
Total	17	100	16	100	19	100

Table 3 Previous medication

	Mianserin		*Maprotiline*		*Placebo*	
Drugs	*No.*	%	*No.*	%	*No.*	%
Tricyclic antidepressant	6	35	6	38	5	26
Monoamine oxidase inhibitor	1	6	1	6	1	5
Phenothiazine or butyrophenone	0	0	0	0	2	11
Benzodiazepine	8	47	10	63	7	37
Other psychotropic drugs	2	12	3	19	5	26
Non-psychotropic drugs	5	29	9	56	9	47
None	3	18	1	6	0	0

Table 4 Hamilton Rating Scale (mean scores)

Day	*Mianserin* (*n* = 17)	*Maprotiline* (*n* = 16)	*Placebo* (*n* = 19)
0	24.5	22.1	24.1
7	19.4	21.1	22.1
14	16.6	19.4	19.7
28	17.1	18.3	17.1

scores of each group during the treatment period. An analysis of covariance in which the baseline score was used as a covariable, showed that patients responded better to mianserin than to both placebo and maprotiline at day 7 ($P<0.05$) but this difference could not be demonstrated at days 14 and 28. No patient in any of the treatment groups had a 50% decrease in their total Hamilton scores at day 7, but seven patients (41%) in the mianserin group, two (13%) in the maprotiline group and five (26%) in the placebo group had such a decrease by day 14. The corresponding figures for day 28 were six (35%), three (19%) and eight (42%).

By means of the Yates test applied to the scores for individual items (shown in Table 5) mianserin appeared to be more effective than placebo in reducing anxiety somatic and insomnia initially at day 14 ($P<0.05$). Such a large number of statistical comparisons were carried out, however, that these significant differences could have occurred by chance.

Leeds Self-Assessment Scale

The mean self-Assessment of depression specific scores are shown in Table 6. There was a statistically significant decrease in each group during the course of the study but an analysis of covariance again with the baseline score as a covariable did not show any significant differences between the three treatment groups.

Table 6 Leeds Self-Assessment Scale (mean scores)

Day	*Mianserin* (*n* = 17)	*Maprotiline* (*n* = 16)	*Placebo* (*n* = 18)
0	13.9	13.6	14.3
7	11.9	12.4	13.1
14	9.9	11.4	10.9
28	10.3	11.6	8.9

Sleep questionnaire

The Fisher's Exact Probability Test applied to the 'yes' or 'no' responses to questions concerning the previous night's sleep failed to show any significant differences between groups during the baseline and at four weeks or any significant changes from the baseline within groups.

Table 5 Hamilton Rating Scale: individual items

	Mianserin (*n* = 17)				*Maprotiline* (*n* = 16)				*Placebo* (*n* = 18)			
	Day 0	*Day 7*	*Day 14*	*Day 28*	*Day 0*	*Day 7*	*Day 14*	*Day 28*	*Day 0*	*Day 7*	*Day 14*	*Day 28*
1. Depressed Mood	2.4	2.0	1.8	2.0	2.3	2.1	2.1	1.9	2.4	2.1	1.8	1.6
2. Guilt	1.3	1.2	1.1	1.0	1.3	1.4	1.1	1.0	1.4	1.1	0.9	0.6
3. Suicide	1.8	1.3	0.9	1.0	1.6	1.1	1.2	1.3	1.5	1.2	1.0	0.9
4. Insomnia Initial	1.2	0.7	0.5	0.7	1.3	1.3	1.2	1.1	1.2	1.2	1.1	1.1
5. Insomnia Middle	1.4	0.8	0.6	0.8	1.5	1.1	1.0	0.7	1.4	1.1	1.2	0.9
6. Insomnia Late	1.4	0.6	0.7	0.7	1.1	0.8	0.8	1.0	1.3	1.1	1.1	1.1
7. Work and Activities	3.6	3.4	2.9	2.6	3.1	3.0	2.6	2.5	3.2	3.2	2.9	2.5
8. Retardation	0.6	0.6	0.5	0.5	0.8	0.6	0.5	0.4	0.5	0.6	0.6	0.4
9. Agitation	1.2	0.9	0.8	0.9	1.3	1.2	1.0	1.0	1.1	1.0	0.8	0.6
10. Anxiety Psychic	2.4	2.1	1.6	2.0	2.4	2.4	2.3	2.4	2.4	2.3	2.1	1.8
11. Anxiety Somatic	1.8	1.5	1.2	1.2	1.4	1.6	1.2	1.2	2.1	2.0	1.7	1.5
12. Somatic Symptoms Gastrointestinal	1.1	0.9	0.9	0.8	0.9	0.9	0.9	0.6	1.4	1.3	1.0	1.1
13. Somatic Symptoms General	1.5	1.5	1.1	0.9	1.1	1.3	1.4	1.0	1.2	1.5	1.1	1.2
14. Loss of Libido	1.0	1.0	1.1	1.0	1.0	1.2	1.2	1.1	0.8	0.8	0.9	0.8
15. Hypochondriasis	0.6	0.4	0.4	0.3	0.4	0.5	0.6	0.5	0.8	0.8	0.9	0.6
16. Loss of Weight	0.9	0.2	0.2	0.3	0.6	0.4	0.3	0.2	1.1	0.5	0.4	0.4
17. Loss of Insight	0.4	0.3	0.4	0.3	0.4	0.3	0.3	0.3	0.4	0.3	0.2	0.1
Total	24.5	19.4	16.6	17.1	22.1	21.1	19.4	18.3	24.1	22.1	19.7	17.1

Table 7 Global assessment of severity of illness

Severity		*Mianserin (n = 17)*				*Maprotiline (n = 16)*				*Placebo (n = 18)*			
		Day 0	*Day 7*	*Day 14*	*Day 28*	*Day 0*	*Day 7*	*Day 14*	*Day 28*	*Day 0*	*Day 7*	*Day 14*	*Day 28*
Normal, not ill	(0)	0	0	0	0	0	0	0	0	0	0	0	0
Borderline mentally ill	(1)	0	0	0	3	0	0	1	1	0	0	1	3
Mildly ill	(2)	0	1	7	2	0	1	3	3	0	0	2	3
Moderately ill	(3)	2	6	2	4	5	6	4	4	2	3	7	5
Markedly ill	(4)	8	3	3	3	6	4	4	4	7	8	3	2
Severely ill	(5)	7	7	5	5	5	5	4	4	10	8	6	6
Extremely ill	(6)	0	0	0	0	0	0	0	0	0	0	0	0
Mean score		4.3	3.9	3.4	3.3	4.0	3.8	3.4	3.4	4.4	4.3	3.6	3.3

Table 8 Global assessment of change in condition

		Mianserin group			*Maprotiline group*			*Placebo group*		
		Day 7	*Day 14*	*Day 28*	*Day 7*	*Day 14*	*Day 28*	*Day 7*	*Day 14*	*Day 28*
Very much improved	(+3)	0	1	2	0	0	1	0	0	5
Much improved	(+2)	3	6	5	1	4	4	2	9	5
Slightly improved	(+1)	8	6	5	4	6	4	6	1	1
No change	(0)	4	1	2	6	2	3	6	5	4
Minimally worse	(−1)	2	2	2	5	4	3	5	3	2
Much worse	(−2)	0	1	1	0	0	1	0	1	2
Very much worse	(−3)	0	0	0	0	0	0	0	0	0
Mean score		0.7	1.0	1.0	0.1	0.6	0.6	0.3	0.7	1.2
Number of patients		17	17	17	16	16	16	19	19	19

Global assessments of severity of illness and change in condition

These are shown in Tables 7 and 8. The weights given to the ratings are shown in parentheses and the mean weighted scores at each treatment interval are also shown in the tables. There was a statistically significant improvement in each group but the Yates test did not reveal any significant differences between treatments. Although the decrease in mean Hamilton Scores was not marked, with means of 17.1, 18.3 and 17.1 after four weeks' treatment, the global assessments of change in condition showed that appreciable numbers of patients were much improved. These amounted to seven (41%) in the mianserin group, five (31%) in the maprotiline group and 10 (53%) in the placebo group. Not surprisingly, there was a close correlation between those who were much improved on the global scale and those who showed a 50% or more decrease in their total Hamilton scores. The global improvements are, in our opinion, clinically significant.

Unwanted effects

Mianserin and maprotiline caused significantly more drowsiness at day 7 and more blurred vision at day 28 than did placebo, and constipation was more of a problem with maprotiline than either mianserin or placebo. A 25-year-old female patient developed a widespread maculo-papular exanthematous rash on her trunk and limbs after 10 to 11 days' treatment with maprotiline. This gradually disappeared over the course of a further three weeks despite continued treatment. Overall, unwanted effects were not a major problem.

Laboratory investigations

Two patients, each with normal baseline levels, had abnormal liver function tests (LFTs) during treatment with mianserin. One of them had a serum alkaline phosphatase of 684 IU/l, a serum aspartate aminotransaminase (AST) of 142 IU/l and a serum alanine aminotransaminase (ALT) of 225 IU/l, all

of which reverted to normal after treatment was stopped. The second patient whose baseline alkaline phosphatase level at 279 IU/l was just outside the normal range, had an increase to 289 IU/l. One patient on maprotiline had a raised serum alkaline phosphatase of 322 IU/l and an increase in ALT to 46 IU/l. No abnormalities in LFTs were found in the placebo group. No other relevant values outside the normal range, including significant decreases in white blood cell counts, emerged during treatment in any of the three treatment groups.

Life events

Events involving patients, relatives and other important people in the patients' lives were recorded regardless of their presumed relationship to the illness and its course. There were no significant differences in the numbers of patients in each group who reported such events or in the total numbers of events recorded.

Guesses

The numbers of correct guesses as to which treatment the patients were receiving were not significantly higher than the numbers expected by chance, showing that our assessments remained blind throughout the study.

Responders and non-responders

Patients who were much or very much improved on the global assessments of change in condition were regarded as responders, while those who showed only slight improvement or no change or were worse were regarded as non-responders. Response so defined was assessed in relation to sex, age (40 or less versus older than 40), the use of tricyclic antidepressants or monoamine oxidase inhibitors during the month before inclusion in the study, scores on the Newcastle Scale (less than 6 versus 6 or more) and Kendall's items (less than 14 versus 14 or more) and the 10 prognostic factors studied in relation to antidepressant response by Tyrer *et al.* (1980). Patients with lack of energy were more likely to be non-responders than responders to mianserin (chi^2 5.19, 1 D.F., $P<0.05$) and patients who had been ill for five years or more were more likely to be non-responders than responders to placebo (chi^2 13.07, 1 D.F., $P<0.001$). The other factors, including type of depression and stability of previous personality, did not appear to influence the response.

Discussion

Our preliminary results suggest that mianserin and maprotiline are no more effective than placebo in the treatment of depressive illness, but they should be interpreted with caution for the following reasons.

Patients referred to a psychiatric service are not representative of the total population of patients with depressive illnesses, because most depressed patients are treated by general practitioners and there is a tendency for atypical and treatment-resistant cases to be referred. This is particularly true in areas such as Southampton where there is an extensive postgraduate educational programme in psychiatry and where the standard of general practice is high. However, treatment resistance *per se* cannot be the sole explanation for our results because in the subsequent three months, 14 out of 28 non-responders that we were able to follow-up were much improved on global assessments. In some cases this may have been due to their subsequent treatment, in others a spontaneous remission may have occurred.

It is possible that the number of patients included in the study was too small to show important differences between the treatments, although there was not a significant trend in favour of either drug. The study is still in progress and when more patients have been included we may be able to assess this possibility more definitively.

We also have to consider the possibility that our findings were due to chance. If a sufficiently large number of trials of an effective drug are carried out the laws of chance will ensure that sooner or later a negative result will be found.

Finally, it is possible that mianserin and maprotiline are not as effective as antidepressants, as the large body of published evidence suggests. Most of this evidence comes from trials showing significant improvement during treatment with the drugs and responses comparable with those of tricyclic antidepressants. However, statistically significant improvements can occur during treatment with placebo, as our study and others have shown, while many comparative studies with tricyclic antidepressants have not been shown to be superior to placebo. These are clearly not the most critical tests of a drug's antidepressant potential.

In our opinion there is no satisfactory substitute for placebo-controlled trials of antidepressants although there are major ethical and practical obstacles to carrying them out. We do not believe that these difficulties are insurmountable and in giving ethical approval neither did the Joint Ethical Committee of the Southampton and South West Hampshire Health District and University of Southampton.

Depressed patients often have to wait several weeks for an outpatient appointment. We see such patients within a few days and they have frequently completed their treatment while other patients are still waiting to be assessed. Patients give their informed consent to the investigation and they may withdraw from the study whenever they choose. They receive all the customary advice, help and supportive psychotherapy in addition to their trial medication. Patients may telephone us if they are worried about their progress and if they do not turn up to their appointments they are visited at home. Close liaison is maintained with their general practitioners, community nurses, social workers and other health care providers involved in their management. If patients have a marked worsening of their depression, particularly if accompanied by serious suicidal thoughts, they are given alternative treatment.

Many believe that it is unethical to give patients placebos as they are inactive. However, a placebo, though inactive pharmacologically, is not inactive therapeutically. In 15 studies carried out in 1082 patients with many physical and psychiatric illnesses placebos were, on average, effective in 35.2% of cases and were most therapeutic when stress was greatest (Beecher, 1955). In a Medical Research Council trial in depressive illness about a third of the patients who received placebos lost their symptoms completely or almost completely within four weeks (Medical Research Council, 1968).

Many practitioners, including those opposed to the use of placebos, practise placebo-therapy without realizing that it is placebo-therapy they are practising. They do this by prescribing drugs that are later shown to be no more effective than placebos, by prescribing active drugs in inactive doses, and by giving active drugs in conditions unresponsive to their pharmacological actions.

While appreciating arguments to the contrary it could be said that it is unethical *not* to use placebo controls in clinical trials. Without them there is the risk that new drugs that are no more effective than placebos will enter clinical practice on a wide scale and add yet more serious unwanted effects to the existing catalogue of 'diseases of medical progress'.

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Discussion

S.A. Montgomery

It seems fairly obvious that the response to placebo is not as good as we would have anticipated. All the patients were categorized as endogenous depression. If there were patients with delusions this partly explains the result. I refer to the finding that delusional depressives respond rather less well than other groups.

S.R. Hirsch

How do the authors explain the fact that they have two antidepressants which have been shown in other studies to have some antidepressant action and yet they failed to show any benefit over placebo?

J.G. Edwards

First it is possible that the drugs do not have a greater effect than placebo. It is also possible that these were chance findings. Sooner or later one is going to have negative findings if enough studies are carried out. It might have something to do with the selection of patients, yet we included all patients referred, and many of them have since responded to tricyclic antidepressants or ECT. It is also possible that there are insufficient numbers in the study.

S.R. Hirsch

Can the authors explain the subsequent response to tricyclics or ECT?

J.G. Edwards

They may have responded because of the passage of time. Many depressive illnesses are self-limiting and with time many patients will get better. Alternatively they were fairly severely depressed patients and it is possible they would only respond to ECT. On the other hand some did respond to subsequent treatment with imipramine or amitriptyline.

D. Wheatley

If you have a large number of drug trials one or two will produce aberrant results compared to the others. If we take the original trials of tricyclics compared with placebo there were a few which showed them to be quite useless. However I think the consensus is that the drugs, certainly the tricyclics, are effective. I think that would be the consensus here too. We would expect one or two adverse results and it would be surprising if the studies all came out in favour of the drug.

E.S. Paykel

How many studies are there showing maprotiline to be superior to placebo?

R.M. Pinder

I reviewed the trials with maprotiline two or three years ago and there were then two placebo-controlled trials and one has been completed since then. One has shown placebo to be better and two have shown no difference between placebo and maprotiline.

M. Hamilton

One of the problems in short-term trials is the response of symptoms of anxiety to placebo effects, suggestion, comfort, reassurance, whatever you would like to call it. In a controlled trial comparing anxiolytics with placebo I found that the placebo group continued to improve steadily for five weeks from the start of the trial. All our depressives have