A COMPARATIVE TRIAL OF FOUR MONO-AMINE OXIDASE INHIBITORS ON CHRONIC DEPRESSIVES

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DEPRESSION is a serious illness in Western Europe and the United States of America. It is estimated that in 1957 the combined total of suicides in the United States, Britain, France and Western Germany was approximately 30,000 (1). The attempted suicide rate is considered to be six or seven times as great, which could give a grand total of 200,000 suicide attempts in that year in these countries. Many of these patients are depressives, as stated in a recent *British Medical Journal* leading article (2).

While electroplexy is still the treatment of choice for depression particularly in acute and suicidal types, nevertheless, it has some limitations. It fails to benefit certain cases and it has unpleasant side-effects, especially if it has to be administered over long periods. Some of the most troublesome side-effects are amnesia, E.C.T. phobia and possible organic changes with prolonged use. Administration of it can cause considerable disruption to the lives of the patients receiving it. This would apply in particular to those chronic depressives who often receive electroplexy over a long period of time. Consequently, any valid chemotherapy in the form of tablets would have marked advantages over electroplexy. Cerletti (3) would seem to have this in mind when he expressed the opinion that electroplexy was a trying treatment. It seemed, therefore, worth while to investigate the effect of four mono-amine oxidase inhibitors on a group of chronic depressives who had failed to respond satisfactorily to electroplexy or any other treatment. Most previous publications would seem to have been carried out with individual drugs of this group and to have been conducted on cases where the illness has been present for a relatively short time. We have only been able to discover two comparative trials involving mono-amine oxidase inhibitors (4, 5). A disadvantage in using the acute type of case is that there is a natural tendency towards remission during the first year, which is less likely to occur in the chronic depressive. Zubin (6) reported that 80 per cent. of patients discharged from mental hospitals do so by the end of the first year, thus indicating that any method will be more effective when tried on patients ill less than one year. The main purpose in conducting the present investigation was (*a*) to test the comparative efficacy of four known anti-depressant drugs on chronic depressives, (*b*) to ascertain whether any particular diagnostic category, symptom complex, age group or other factors would respond more readily and finally, (*c*) to evaluate the side-effects, if any, of these drugs.

TECHNIQUE

The four mono-amine oxidase inhibitors chosen for the trial were β-phenylisopropyl hydrazine hydrochloride (Cavodil), iproniazide (Marsilid),

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phenelzine (Nardil) and nialamide (Niamid). The trial was conducted according to the "Latin-square" technique using all 24 possible arrangements of the four drugs. The actual arrangements used were reasonably balanced as replacements had to be found, which resulted in increased numbers being used. Patients were on each drug for a period of five weeks with a two-week interval between each drug in order to minimize the possibility of cumulative side-effects. The following fourteen symptoms were taken as a rating scale; depressed mood, difficulty in thinking, psychomotor retardation, early morning wakening, morning accentuation of symptoms, hypochondriasis, self-deprecation, suicidal rumination, morbidity of outlook, agitation, inability to cope with duties, loss of interest, paranoid feelings and other symptoms. The presence of any of these symptoms was indicated by means of a tick and if they were present to a more marked degree, this was scored by means of one, two or three pluses, so that we were able to get a qualitative and quantitative estimation for each patient. Immediately prior to the trial each patient was rated by the psychiatrist normally in charge. During the course of the trial patients were seen weekly for an assessment of side-effects and any adjustment of dosage considered necessary. At the end of each five-week period the psychiatrist not normally in charge assessed the patient according to the above rating scale, so that ultimately each patient had four different ratings and the original assessment. The psychiatrist who had rated each patient then assessed them for the four different drugs, the following scale being used: recovered, much improved, improved, no change and worse. When each patient had completed the trial of the four drugs they were asked for a personal assessment using the same criteria.

Case Material

A total of 63 patients took part in the trial, 38 females, 25 males. Of this total nine failed to complete the trial of which six were females. Six of these cases required emergency electroplexy. The other three developed serious side-effects necessitating immediate termination. Fifty-four patients completed the trial and of these 42·6 per cent. were out-patients. The criteria for including patients in the trial was the presence of depression and a history of being under treatment for at least one year. Duration of illness varied fron 1 to 25 years. Eight men and eight women were known to have made at least one suicidal attempt. The diagnoses and age groups were as follows:

Age (Years)	Endogenous Retarded Depression	Endogenous Agitated Depression	Neurotic Depression	Atypical Depression	Schizo-Affective
30–39	4	–	3	1	–
40–49	3	1	5	2	–
50–59	7	2	3	6	1
60–69	7	7	3	2	–
70 and over ..	2	4	–	–	–
Total ..	23	14	14	11	1

By "atypical depression" is meant those patients with a good pre-morbid personality who develop phobic anxiety symptoms with depression as described by West and Dally (7).

Dosage

This was restricted to the optimum recommended dose by the manufacturers at the time the trial commenced, viz., Cavodil 12 mg. mane, Marsilid 50 mg. t.i.d., Nardil 15 mg. t.i.d. and Niamid 50 mg. t.i.d. The dosage was never raised above the recommended level, but was reduced in some cases, either temporarily or permanently because of the presence of side-effects. The patients received no other form of therapy while undergoing the trial except amylobarbitone gr. 3 at night if insomnia was marked.

Side-Effects

These were classified into two main categories (*a*) minor and (*b*) major.

Minor Side-Effects

	Cavodil	Marsilid	Nardil	Niamid
Elation	4	2	1	3
Drowsiness	1	–	6	3
Swollen face and ankles	2	6	3	1
Dry mouth	1	1	–	–
Hypotensive attacks	1	7	3	3
Paresthesia of skin	1	–	–	–
Twitching muscles	2	–	–	–
Difficulty in starting micturition	–	2	–	–
Weight increase	–	3	1	–
Erythema of arm	–	1	–	–
Mild confusional episode	–	1	–	1
Constipation	–	1	1	1
Insomnia	–	–	1	1
Increased appetite	–	–	1	–
Ataxia	–	–	1	–
Dyspepsia	–	–	–	1
Increased tension	–	1	3	–
	12	25	20	13

The above table enumerates the minor side-effects in relation to each drug.

Minor Side-Effects

It will be noticed that Iproniazide produces the greater number of side-effects, in particular mild hypotensive attacks which occur early in treatment and oedema chiefly of the ankles which occurred late. The main side-effect of Nardil was drowsiness, which tended to occur early. There were three cases of increased tension on this drug. Many of the symptoms remitted spontaneously after the first week or did so on reducing the dosage.

Major Side-Effects

Major Side-Effects

	Cavodil	Marsilid	Nardil	Niamid
Hypomania	–	2	3	1
Acute toxic confusional state	–	–	1	–
Jaundice	–	?1	?1	?1
	–	–	–	–
Total	–	2	4	1

The above table indicates serious side-effects. It will be noted that Cavodil did not, in this series, produce any major side-effects. The possible explanation

may be that the dosage was inadequate. Nardil was the drug that produced the greater number of major side-effects in contrast to Marsilid which was responsible for most minor ones.

Acute Toxic Confusional State

A female, aged 72, became confused after two weeks on Nardil, 15 mg. t.i.d. There were course tremors of the arms, clonic movements of the right leg and food refusal. At night she became acutely apprehensive, auditorily and visually hallucinated, maintaining that bombs were being dropped through the roof and dead bodies lying about the ward. The condition persisted for two weeks after the drug was discontinued.

Hypomania

This occurred in six cases, of which three were known manic-depressives (2 male, 1 female). In these three hypomanic symptoms persisted for as long as a month in spite of treatment. The other three consisted of two females and a male. In the case of the females the hypomanic state remitted within a week of withdrawal of the drug. The male, aged 64 with a diagnosis of retarded depression of 5 years' duration and no known history of hypomania, developed this condition after two weeks on Niamid. The symptoms persisted for 8 weeks despite heavy doses of Largactil. He finally discharged himself in a state of elation.

Jaundice

Female patient, aged 59, who started on Marsilid. The five-weekly interviews showed no evidence of side-effects except for a complaint of dizziness. This was followed by Niamid, during which time she showed no side-effects at the interviews. After one week on Nardil, she developed jaundice and complained of sickness, which she stated she first noticed while she was on Niamid. Bile salts and pigments were strongly positive in her urine and urobilinogen and urobilin were present in increased amounts. Liver function tests were as follows:

Van-den-Bergh Positive direct reaction
Total bilirubin = 5·0 mg. per 100 ml.
Alkaline phosphatase = 21 units per 100 ml.
Thymol turbidity = 3 units.
Thymol flocculation, Nil.
Zinc sulphate turbidity = 1 unit.
Zinc flocculation, Nil.
Total protein = 6·2 per cent.

Three weeks later:

Van-den-Bergh = Negative direct reaction.
Total bilirubin = 1·0 mg. per 100 ml.
Alkaline phosphatase = 17·5 units per 100 ml.

She discharged herself from hospital approximately 2 months from the time the jaundice was first noticed. This had cleared completely when she left the hospital.

DATA

Comparison of Whole Group

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Nardil better than Niamid ..	24	22	8	
Nardil better than Marsilid ..	27	15	12	P<0·1
Nardil better than Cavodil ..	31	13	10	P<0·02
Niamid better than Marsilid ..	22	19	13	
Niamid better than Cavodil ..	32	15	7	P<0·02
Iproniazide better than Cavodil	27	15	12	P<0·1

Comparisons for Patients Over 50

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Nardil better than Niamid ..	20	11	6	P<0·2
Nardil better than Marsilid ..	20	8	9	P<0·05
Nardil better than Cavodil ..	24	6	7	P<0·01
Niamid better than Marsilid ..	14	16	7	
Niamid better than Cavodil ..	22	11	4	P<0·1
Iproniazide better than Cavodil	21	8	8	P<0·05

Comparisons for Patients Under 40
(7 males and 1 female)

Comparison	Number With This Preference	Number With Opposite Preference	Equal Preference	Probability
Niamid better than Nardil ..	7	1	–	P<0·1
Niamid better than Marsilid ..	5	1	2	
Niamid better than Cavodil ..	7	1	–	P<0·1

Data in Terms of Diagnosis

Diagnosis	Number	Mean Rank Preference (Lowest=Best) Cavodil	Marsilid	Nardil	Niamid
Endogenous retarded ..	18	2·9	2·6	2·1	2·3
Endogenous agitated ..	13	3·1	2·0	2·3	2·6
Neurotic depression ..	12	2·8	2·7	2·5	2·0
"Atypical depression" ..	9	2·7	2·5	2·3	2·5

Age Ranges at Which Drugs most Effective

Data divided into 30–40, 40–50, 50–60 and over 60 years ranges.

The best age range was 50–60 years.

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This was *significantly better than over 60 years, $P<0{\cdot}02$*, and the 30–40 and 40–50 year ranges when the latter are compared *en bloc* with 50–60 years, *$P<0{\cdot}05$* (when 30–40 year and 40–50 year range compared with 50–60 year range not quite significant).

Out-Patients Versus In-Patients

Out-patients did slightly better than in-patients, but the difference was not significant.

Patients' Assessment

	Cavodil	Marsilid	Nardil	Niamid
30–40 years	1·1	1·5	1·5	2·0
40–50 years	1·5	1·9	2·2	2·2
50–60 years	2·1	2·1	2·6	2·5
Over 60 years	1·2	2·4	2·5	2·2

Doctors' Assessment

	Cavodil	Marsilid	Nardil	Niamid
30–40 years	1·5	2·1	1·4	2·5
40–50 years	2·2	2·4	2·2	2·3
50–60 years	2·4	2·6	3·2	7·9
Over 60 years	1·7	2·2	2·7	2·2

The above tables show average results for different age ranges, using the following scores:

0 Worse; 1 No change; 2 Improved; 3 Much improved; 4 Recovered.

Comparison of Ten Most Successful Patients with Ten Least Successful: Notable Differences

	Number of Patients of Successful Group	Number of Patients of Unsuccessful Group
Age 50–60	6	–
Age 46–51	9	1
Depression more severe	2	6
Hypochondriasis more severe	2	4
Other symptoms: Insomnia	–	2
Hallucinated	–	1
Accentuation of symptoms A.M.	5	1

While the only difference that is significant is that with age, nevertheless "accentuation of symptoms in morning" and severity of the depressive mood could be important.

	Successful	*Unsuccessful*
Duration of illness, average	3·4 years	3·3 years

Further investigation of importance of "accentuation of symptoms in the morning" showed that this tended to be associated with the 50–60 age range, though not at a statistically significant level.

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When all patients were investigated by ranking methods, keeping 50–60 years range, other ages, males and females separate, as four groups, and later combining for an overall test of significance, it was shown that "accentuation of symptoms in the morning" was significantly associated with success of drug treatment ($P<0\cdot05$).

Comparison of Responses to Particular Drugs with Particular Symptoms

It was not possible to observe any differences. The three best responses to individual drugs as above other drugs were investigated for Nardil, Marsilid and Niamid but no particular symptoms appeared to be associated with these patients. There were relatively few patients where one drug showed superiority over other drugs from both doctors' assessment, patients' assessment and where the response to the particular drug was also rated highly.

Discussion

The present trial, in common with other reports on mono-amine oxidase inhibitors (Ayd *et al.* (8); Vaisberg *et al.* (9); Beresford Davies (10)), fails to give any clear-cut indications as to the type of depressive illness benefited by these drugs. In this trial the outstanding fact is that the 50–60 age group showed the best response. This was statistically significant for all patients both above and below this age group. This may be in agreement with Middlefell (11) who, among his best results, mentions involutional menopausal depression in women and Beresford Davies (12) associated possible improvement with the older patient who had a long history of depression. The only symptom that was associated with success of treatment on a statistically significant level was "accentuation of symptoms in the morning" and although this symptom occurred more frequently in the 50–60 age group, it was not statistically significant for it. Hutchinson and Smedberg (13) consider that early morning wakening and inability to sleep were helped, but again this was not confirmed in the present trials. The clinical impression from this investigation was that insomnia and anxiety were not only unchanged, but in some cases aggravated. The "atypical" depressive group showed the best response to treatment and most of them were in the 50–60 age limit, although this did not reach statistical significance. This trend is in keeping with the report of West and Dally (14) who found Iproniazide to be of particular value in the treatment of "atypical" depression. Factors that were not significant in this trial were sex, duration of symptoms, whether in- or out-patient or any particular diagnostic grouping with the exception, as already mentioned, of a trend towards "atypical" depression. These observations appear to be in agreement with Ayd (15) who in a comparative trial of mono-amine oxidase inhibitors could find no relation to age, sex, duration or severity of patients' illness.

The drugs responded in the following order, (1) Nardil, (2) Niamid, (3) Iproniazide, (4) Cavodil for all ages. There was a more distinct preference in the over 50 age group. For patients under 40 years, Niamid appeared to be better than each of the other drugs although these differences were not always statistically significant. Comparisons between Cavodil and the other drugs reach a statistically significant level. The only other finding of statistical significance was in the over 50 age group, where Nardil was superior to Iproniazide. While the differences between Niamid and Nardil are not statistically significant at any age level, there was, nevertheless, a statistically significant

reversal in the position of these drugs with increased age, that is to say, relative to Nardil, Niamid is more effective in the younger patient. Further trends showed that Nardil appeared to be better with retarded and "atypical" depression while Niamid appeared more beneficial with neurotic depression. Procter (16) reports a similar experience with Niamid when he considers that this drug seems most useful in the treatment of neurotic depressive reaction in patients under 50. A slender preference was shown for Iproniazide in relation to agitated depression. Cavodil in this trial showed itself to be statistically of less value than the other three drugs. A possible explanation is that the dosage of this drug used in the trial was insufficient. Ayd (17) believes that patients who fail to respond to one of these anti-depressant drugs seldom respond more than partially to another. Our findings are in disagreement with this. The clinical impression in this trial was that if patients were going to respond to the drugs favourably they did so by the end of the second week. Harrington and Imlach (18) reported a similar period of time for improvement with Nardil. A disturbing impression also noted by Ayd (19) was that patients who had made an initially good response to one of these drugs did not always continue to do so, if the drug had been withdrawn and later re-instituted.

There is no doubt that elation and even hypomania are not uncommon side-effects with these drugs, particularly in the manic depressive group. Because of this patients should be seen frequently and dosage reduced or withdrawn if elation is present. The acute toxic confusional state occurred with Nardil and as this was the first mono-amine oxidase inhibitor the patient received, there could be no possibility of cumulative side-effects. Johnson and Eilenberg (20) described a similar case with Nardil. The case of jaundice could not be attributed to any one particular drug, with the exception of Cavodil which the patient did not receive. Cumulative side-effects may have been responsible. Attention is drawn to two cases where because of markedly increased tension the trial had to be terminated. The drug in question was Nardil. Altogether four cases of increased tension were noted. From these observations it would appear that anxiety is not helped by these drugs, or that in cases where this symptom is marked, a suitable drug for anxiety should be given. No explanation can be offered why patients in the 50–60 age group did best, but it may be that an involutional factor is involved. In conclusion, from the statistical evidence it can be assumed the drugs influenced chronic depression because in the experiment there were systematic differences between the drugs—in other words the less successful drugs served as controls for the more successful.

In retrospect there were six cases (four female and two male) where some doubt could be placed on the exact diagnosis, as to whether they were neurotic depressive reactions or simply "neurotics". A study of the ten patients who showed the poorest response included this doubtful group presenting with marked tension, frequent phobic symptoms and many somatic complaints. Depression was variable and inconstant. The pre-morbid personality was hysterical and inadequate in all cases.

Summary

A comparative trial of four mono-amine oxidase inhibitors on chronic depressives resistant to other forms of treatment is described. The 50–60 age group showed the best response to treatment. The only symptom associated with success of treatment at a statistically significant level was "accentuation of symptoms in the morning". Nardil was the beneficial drug, particularly in the

over 50 age group; Niamid most effective for patients under 40 and Cavodil in the dosage used was inferior to the other drugs. The commonest major side-effect was hypomania. A case of jaundice and one of toxic confusion is also described. It is considered that the mono-amine oxidase inhibitors are of definite therapeutic value in the treatment of depression especially in chronic depressives resistant to other forms of treatment.

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