AN EVALUATION OF IPRONIAZID (MARSILID) IN THE TREATMENT OF DEPRESSION

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IPRONIAZID (1-isonicotinyl, 2-isopropyl hydrazine phosphate) was discovered by Fox and Gibas (1953) whilst working on new synthetic compounds for the treatment of tuberculosis.

Although Iproniazid was found to have therapeutically beneficial effects in tuberculosis it never achieved widespread use and eventually was virtually discontinued because of undesirable side-effects, prominent among which were symptoms due to central nervous stimulation and occasionally psychotic manifestations.

Using a smaller dosage than required for treating tuberculosis Iproniazid has recently been tried in depressed states and enthusiastic reports on its therapeutic effects have been made by Kline *et al.* (1958) and Robie (1958), the latter prophesying that it would supplant electroplexy in all but the most severe depressions.

The central nervous stimulating properties and anti-depressive effects of Iproniazid are thought to be probably related to its biochemical actions as a monoamine oxidase inhibitor (Zeller *et al.*, 1952) and to its effect in causing a rapid rise in the level of brain serotonin (Undenfreund *et al.*, 1957).

Dally (1958) found the drug most useful in mild depressive states rather than endogenous depressions. Verteuil and Lehman (1958) found that about one-third of a group of depressed and apathetic patients showed improvement with Iproniazid. The drug, was however, discontinued because of serious toxic effects which caused the death of a patient from acute toxic liver necrosis.

Further enthusiastic reports on the efficacy of Iproniazid in depression were made at a symposium held in New York in November, 1957 and reported in a special number of the *Journal of Clinical and Experimental Psychopathology* (Supplement to Vol. XIX, No. 2, April, 1958).

These reports, however, do not permit a reliable and valid assessment of the therapeutic efficacy of the drug in depression because adequate controls were not used.

In our opinion, the value as well as the limitations of any new pharmaco-therapeutic agent in psychiatric illness can only be assessed by strictly controlled clinical trials.

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The fact that many depressive states tend to run a self-limiting course in itself makes controls indispensable. Moreover, many other sources of error need to be taken into account, e.g. the multiplicity of factors relating to the individual or his environment which can influence his clinical state during the therapeutic trial, in addition and independently of the pharmacological effects of the drug.

As the complexity of psychiatric illness makes accurate matching of patients difficult, it is desirable to use the patient as a self control.

The allocation of active drug and the inert preparation used for control purposes should be carried out by a random method to avoid the possibility of bias arising from selection.

The possible therapeutic effects of receiving a course of new treatment either arising from suggestion or from the therapeutic influence of the regime of a new treatment and the associated increased medical and nursing attention.

Further possible sources of error are bias on the part of patient or observer in reporting and recording changes which would tend to occur when it is known when active and inert tablets were being given.

With these considerations in mind a controlled study of Iproniazid in depressive states was carried out using the following methods.

METHODS

1. *Triple-Blind Control*

The pharmacist was the only person who knew when active or inert tablets were being administered. They were identical in shape, size and colour and were given uncrushed to prevent the patient recognizing them by taste.

Each batch of tablets issued by the pharmacist was marked for identification by series of random numbers. Thus physicians, nurses and patients were unaware when active or inert tablets were being administered. The results were fully analysed and assessed before the code was broken, making the method a triple-blind control procedure.

2. *Multiple Recording*

Multiple recording of the patient's clinical state and progress was carried out independently by nurses and physicians.

3. *Special Record Sheets*

Nurses made daily 24-hour recordings of behavioural features. Physicians completed a form, specially designed for the investigation, containing some 18 items (*vide* Table I) relating to behaviour, clinical state and symptomatology. Each item was rated, according to severity, on a 5-point scale (ranging from 0—absent to 4—very marked). The ratings were made by the same physicians throughout the trial at weekly intervals.

4. *Sequence Control*

In view of the possibility that any clinical changes occurring during the trial period might be due to spontaneous improvement or to factors unrelated to the pharmacological actions of the drug, it was deemed essential that the active and inert preparations be given in different sequences in order to ensure that any factor which might influence the patient's clinical state would have the same chance of being coincident with inert tablets as with the active drug.

TABLE I

Mean Ratings of Clinical Features

Clinical Feature	Pre-trial	Iproniazid (I_1+I_2)	Inert Tablets (P_1+P_2)
Depressive appearance	2·9	1·5	1·58
Difficulty in occupying himself	1·5	1·4	1·18
Difficulty in making social contact	1·4	1·3	1·3
Restlessness	1·4	1·0	0·67
Retardation	1·8	0·4	0·51
Hypochondriacal complaints	1·6	0·75	0·51
Depressive speech content	2·0	1·3	1·8
Delusions	0·6	0·34	0·51
Paranoid disposition	0·6	0·33	0·29
Difficulties with eating	1·2	0·95	0·91
Difficulties with sleep	1·7	1·7	1·55
Excitement	0·01	0·01	0
Overactivity	0·12	0·17	0
Hypomania	0	0·01	0
Anxiety	1·9	1·7	1·86
Tension	2·1	1·9	1·95
Perplexity	0·85	0·34	0·48
Aggression	0	0	0·08
Total	16·9	15·4	15·3

I_1=first period of Iproniazid. P_1=first period of inert tablets.
I_2=second period of Iproniazid. P_2=second period of inert tablets.

5. *Random Allocation*

The allocation of active and inert tablets for the initial three-weekly period of the trial was effected by randomization. Half of the group received Iproniazid during the first three-week period and the other half of the group inert tablets for the same period. Thereafter, three-weekly periods of active drug and three-weekly periods of inert tablets were given alternately for the remainder of the trial. The majority of patients had four periods of three weeks giving a total trial period of twelve weeks. Periods of three weeks were chosen because the findings of a pilot trial showed that when the drug was effective, improvement was usually noticeable in the second week and was usually maximal during the third week.

6. *Statistical Methods*

The use of parametric tests, e.g. the "t" test, for assessing the significance of differences between two related samples is based on the assumption that the score differences are normally distributed and are measured on an interval scale. As we have no evidence to justify these assumptions for ratings and gradings scores as used in this study, it was considered more appropriate to use non-parametric statistics.

The following non-parametric tests were considered to be specially suitable for the investigations; the Wilcoxon matched pairs signed ranks test (Wilcoxon, 1949; Siegel, 1956) and the Signs test (Siegel, 1956).

7. *Criteria for Inclusion in the Double-Blind Trial*

All patients taking part in the double-blind trial were in-patients at the Bethlem Royal Hospital. This permitted continuous observation throughout the twenty-four hours and also a strict control over the administration of tablets, which is not usually possible in trials undertaken on out-patients.

After full investigation the patient was discussed at a conference of physicians and staff, and only patients diagnosed as suffering from depressive states were included.

The series consisted of twenty such patients successively admitted, no other criteria being used for inclusion in the trial.

8. *Assessment of Results*

In view of the findings of the pilot study that the maximal effect of Iproniazid usually occurred by the end of three weeks, it was decided to use the assessments and ratings of clinical status made at the end of the third, sixth, ninth and twelfth weeks for comparing the results with Iproniazid with those with inert tablets.

Clinical changes and therapeutic effects were assessed by two main methods. Firstly, the rating scale described above provided a standardized, detailed and quantitative presentation of the patient's clinical state and giving a measure of the patient's overall clinical status by the sum of ratings. It also enables the detection of any differential effects the drug might have on the various aspects of clinical state which is particularly important with Iproniazid which may accentuate some symptoms, e.g. anxiety and paranoid tendencies concurrently with alleviation of depression.

The second method was the grading by the physician of the patient's clinical state based on clinical examination and observation of behaviour and information contained in nurses' reports and record sheets.

A four-point scale with weights was used as follows:

		Weight
Grade I	Not improved or worse	0
Grade II	Slightly improved	1
Grade III	Moderately improved	2
Grade IV	Marked improvement with complete relief of depressive symptoms and signs	3

By weighting each grade it is possible to make allowance, in a particular patient, for any improvement which occurs with inert tablets, to provide a better measure of the effect attributed to the pharmacological actions of Iproniazid. For example, if a patient showed slight improvement (Grade II= +1) with inert tablets and marked improvement (Grade IV=+3) with Iproniazid, the degree of improvement accorded to Iproniazid would be expressed by the difference in weighting between the respective grades, viz. +2.

Results

Rating Scales

Table I lists the various clinical features rated on the five-point scale and the mean rating for each for the total group, immediately before the trial, for the two Iproniazid periods combined, and for the two inert tablet periods combined.

When compared with the pre-trial scores, both Iproniazid and inert tablets showed some improvement. But the differences were slight for either individual items considered separately or in total.

The total of all ratings gives a convenient index of the severity of illness and is useful for measuring changes in clinical state during the trial.

Comparison of sum total of ratings before the trial with that of each Iproniazid and each inert tablet period separately revealed the following statistically significant differences.

1. The first Iproniazid period showed significant improvement when compared with pre-trial scores ($P = \cdot 015$).

2. The status of the total group at the end of the first three-week period (i.e. I_1 and P_1) showed significant improvement as judged by comparison with pre-trial scores ($P = \cdot 048$).

The findings indicated that although Iproniazid had a greater degree of improvement than that associated with inert tablets, the latter ($P_1 + P_2$ combined) also was associated with improvement but the difference did not reach statistical significance ($P = \cdot 58$).

The significant degree of improvement in clinical state in the total group at the end of three weeks (i.e. with I_1 together with P_1) indicates that factors other than the pharmacological actions of Iproniazid are operating.

There were no significant differences in the total rating scores between Iproniazid and inert tablets.

Comparison of Clinical Features Separately

If we were to rely on the total ratings alone, detailed changes in the patient's clinical condition might be hidden, particularly any differential effects of the drug on various symptoms. Non-parametric tests have an advantage over the usual parametric tests by enabling comparisons to be made between each item separately. No significant differences were found in any feature between I_1 and P_1 whereas I_2 and P_2 differed significantly in depressive speech content, the difference indicating significantly greater improvement with Iproniazid ($P = \cdot 01$).

Both I_1 and I_2 showed significant improvement compared with pre-trial score in depressive speech content ($P = \cdot 01$). I_2 also showed significant improvement compared with pre-trial score in restlessness ($P = \cdot 05$).

Table II

Sum Total of Ratings of Each Patient Before and During Trial

Patients	Pre-trial	I_1	I_2	P_1	P_2
1	22	15	19	19	22
2	10	9	3	8	15
3	7	5	—	12	—
4	11	10	2	13	7
5	8	9	9	12	13
6	23	13	5	22	5
7	25	25	17	17	17
8	15	14	—	22	—
9	12	12	5	8	14
10	15	7	11	8	8
11	22	18	19	32	12
12	10	12	26	1	10
13	12	13	23	7	14
14	24	13	23	18	13
15	24	11	5	21	8
16	18	14	—	22	13
17	26	7	5	20	19
18	21	16	—	12	10
19	35	24	—	26	—
20	29	37	—	23	—
Mean of total patient ratings for group	18·45	14·7	11·45	16·15	12·5

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Thus even with such a detailed method of rating a large number of different clinical features, although revealing some statistically significant differences in favour of Iproniazid, all in all, the beneficial therapeutic effects due to Iproniazid are very modest.

Clinical Gradings

The gradings of clinical improvement associated with Iproniazid and with inert tablets are shown in Table III.

TABLE III

Clinical Gradings at End of 3-Weekly Periods with Iproniazid and Inert Tablets

Clinical Grade	Iproniazid 34 Trials		Inert Tablets 37 Trials	
	N.	Per cent.	N.	Per cent.
1. No improvement or worse ..	15	44·1	13	35·3
2. Slight improvement	12	35·4	18	48·5
3. Moderate	4	11·7	5	13·7
4. Marked	3	8·8	1	2·7
	34	100·0	37	100·0

55·9 per cent. of the group showed improvement with Iproniazid compared with 64·3 per cent. with inert tablets.

If we omit slight degrees of improvement, which are of little importance clinically, and compare moderate and marked degrees of improvement only, Iproniazid has 20·5 per cent. and inert tablets 16·4 per cent. This slight advantage to Iproniazid is not statistically significant.

The device of applying weights to grades permits a more detailed analysis of the results of paired trials with the drug and inert tablets, viz. I_1 compared with P_1, I_1 compared with P_2. There were 34 such paired trials of Iproniazid and inert tablets.

The results were:

1. In 13 trials both Iproniazid and inert tablets were identical in grade, viz. 7 showing no improvement or worse (Grade I) and 6 with slight improvement (Grade II).

2. In 11 trials Iproniazid had a higher grade of improvement than the corresponding period with inert tablets. The sum of the weight differences was +11 in favour of Iproniazid.

3. In 10 trials Iproniazid had a lower grade of improvement than the corresponding inert tablet period. The sum of the weight differences was +11 in favour of inert tablets.

This analysis again provides little evidence of efficacy of Iproniazid.

RESULTS OBTAINED FROM AN UNCONTROLLED TRIAL OF IPRONIAZID IN AN ADDITIONAL GROUP OF PATIENTS SUFFERING FROM DEPRESSIVE STATES

Advocates of Iproniazid therapy might claim that two separate three-weekly periods of drug administration was not long enough to produce optimum results and that a longer period with the drug would give much better results.

We therefore present our findings on a larger group of 60 depressed patients who received Iproniazid for periods ranging from 3 weeks to 6 months (Mean= 6 weeks of continuous treatment). This study was not controlled and we wish

to emphasize its limitation on this account for the reasons already given. The results of the double-blind trial provide a salutary check on the findings of this group.

The initial daily dose was 150 mg. in three divided doses. This was gradually reduced when clinical improvement occurred but reinstated if there was a relapse or recurrence of symptoms. The drug was immediately stopped if any toxic effects appeared or if the level of serum transaminase materially increased.

The group consisted of 32 in-patients of the Bethlem Royal Hospital and 28 out-patients attending the Maudsley Hospital.

The diagnostic categories were as follows:

Group 1—Depressive states predominantly endogenous	19
Group 2—Depressive states predominantly reactive or neurotic ..	36
Group 3—Atypical depressive states	5

The overall clinical state was graded at weekly intervals using the same methods and criteria as in the double-blind study.

The findings are shown in Table V from which it will be seen that only

TABLE IV

Grading of Clinical Status at Completion of Double-Blind Trial

Classification	1	2	3	4	Other Outcome	Totals
Endogenous	5	2	0	2	1 mania, 1 hypomania	11
Reactive or neurotic ..	0	3	1	1		5
Atypical	1	2	0	1		4
Totals	6	7	1	4	2	20

TABLE V

Results of Uncontrolled Trial of Iproniazid in 60 Depressed Patients

	Clinical Rating					
	1	2	3	4	Other Outcome	Totals
Endogenous	5	5	2	3	1—mania, 2—hypomania, 1—suicide	19
Reactive or neurotic ..	10	12	6	5	2—jaundice, 1—hypomania	36
Atypical	3	2	0	0		5
Totals	18	19	8	8	7	60
Percentage of total group	30	31·6	13·3	13·3	11·5	

16 out of the 60 patients showed either moderate or a marked improvement. Three patients showed a temporary improvement with Iproniazid but relapsed while still receiving the drug. One patient showed a marked improvement regarding retardation but became restless, agitated and later committed suicide.

Even with prolonged administration of Iproniazid, only 26·6 per cent. of the group showed moderate or marked improvement, the results being only

slightly better than those obtained with Iproniazid given for the two three-weekly periods of the double-blind trial. As shown by the latter, part of the improvement associated with the administration of Iproniazid is attributable to factors unconnected with its pharmacological properties.

Comparison of Results of Iproniazid and Electroplexy

Eighteen patients who did not benefit from Iproniazid were given electroplexy. Of these sixteen responded immediately making a complete recovery and one showing improvement but not full recovery. Thus only one patient failed to improve with electroplexy. The response to electroplexy was so striking regarding speed and in the degree and quality of recovery, that it left no room for doubt regarding the supremacy of electroplexy over Iproniazid in these patients.

Comparison of Results Obtained in Different Types of Depression

Both in the double-blind trial and in the uncontrolled trial, reactive (neurotic) depressions had somewhat better results than endogenous depressions. The group with the poorest result was atypical depression.

Taking the total 80 patients and comparing moderate and marked degrees of improvement the best results were with reactive depressions (36 per cent.) and the next endogenous depression (23 per cent.) and the worst with atypical depression (11 per cent.).

Special mention must be made of 12 patients of the total of 80 patients studied who showed consistent improvement with Iproniazid and consistently relapsed when the drug was discontinued and subsequently improving when the drug was reinstated. This sequence of events provides additional evidence that the improvement in these patients can be attributed to the pharmacological effects of the drug. These patients comprised 15 per cent. of the total and consisted of 5 with endogenous depressions, 6 with neurotic (reactive) depressions and 1 atypical depression. As a group they showed no particular features or constellations of clinical features in common which would enable them to be selected beforehand.

Complications and Side-Effects

(a) *Physical*

Two patients developed jaundice at a time when their depressive symptoms had considerably improved. A detailed description of these patients is given elsewhere (Benaim and Dixon, 1958).

One patient suffering from hypertension whilst receiving Iproniazid had an episode of cerebral thrombosis which caused a temporary hemiparesis. Iproniazid produced a considerable fall in blood pressure in this patient and the drug was immediately discontinued after the cerebral thrombosis. Such a complication of Iproniazid treatment has recently been reported by Papp and Benaim (1958).

Another patient developed an erythematous rash on the arms and body after drinking alcohol. The rash disappeared when inert tablets were substituted for Iproniazid without the patient's knowledge, but the rash recurred again when Iproniazid was re-instituted when taking alcohol.

One patient had oedema of the legs and a number of patients complained of symptoms due to hypotension, such as palpitations, giddiness and fainting with postural change.

(b) *Psychiatric*

One patient who had suffered from an attack of mania some years previously and who had been severely incapacitated by his present severe attack of depression improved with Iproniazid and was able to start work for the first time in five years, but shortly afterwards became manic even though he was on comparatively small doses of the drug, namely, 25 mg. t.d.s.

Two patients who were relieved of their depression by Iproniazid became hypomanic. Although both had suffered from lifelong mood swings, neither had previously suffered from either hypomania or mania.

Eight patients who were diagnosed as suffering from atypical depressive states derived some relief of depression, this was accompanied by the development of paranoid ideas in six of these, three also showed marked schizophrenic thought disorder. These observations are in keeping with the findings of Hoshimo and Cease (1958) who found no significant beneficial effects with Iproniazid in a group of 64 chronic schizophrenics and of Ferreira, and Freeman (1958) who observed that schizophrenics were sometimes made worse by the drug.

Discussion

During the past year reports on the use of Iproniazid for the treatment of depression have steadily appeared.

The drug was first claimed to provide fountains of energy and to achieve quasi miraculous results in depressive states.

Some early reports claimed striking results. Kline (1958) reported that three-quarters of endogenous depressions responded to Iproniazid as well, if not better than, to electroplexy.

Ayd (1958) later, although using the same dosage in similar patients, had a much lower improvement rate.

In contrast others (Dally, 1958) claim that Iproniazid is most useful for reactive depressions and is not effective in endogenous depressive states.

Such discrepancies between the conclusions made from uncontrolled studies are not surprising in view of the pitfalls already discussed.

Incorrect assessments of the value of a drug such as Iproniazid may arise from clinical heterogeneity of the group; by biased allocation of drug and control tablets; by bias on part of patient or observer in recording clinical changes; by an unequal application of criteria of improvement for active drug and for inert tablets and the manifold unseen factors which may influence the patient's clinical state during the period of the trial.

The present investigation attempted to avoid these pitfalls by using well-defined diagnostic criteria for inclusion of patients for the trial and using a random sample of such patients.

The trial was self-controlled and the allocation of the active and inert tablets for the initial periods was at random followed by alternate periods of active and inert tablets. It was sufficiently long (12 weeks) to allow spontaneous fluctuations in the clinical state to be observed and assessed. The trial was triple blind, the findings were recorded on special forms involving objective as well as subjective data and the results assessed statistically.

The findings clearly show that the improvement occurring with Iproniazid could only in part be due to its pharmacological properties and that other factors contributed, as attested by the improvement associated with inert tablets.

Some clinical features showed a statistically significantly greater improvement with Iproniazid than with inert tablets, in particular, depressive speech content, which is presumably influenced by the euphoriant effect of the drug.

In 15 per cent. of the group there was very strong evidence that relief of depression was due to the pharmacological actions of Iproniazid, as shown by relapse with inert tablets and improvement with the drug, a sequence which was further verified by repetition giving the same results.

The therapeutic effects of Iproniazid appear to be mainly symptomatic, as shown by relapse when the patient is taken off the drug. Prolonged medication was found to result in only a slightly greater incidence of improvement.

The group of patients who benefited most with Iproniazid were not clinically homogeneous, containing both endogenous and reactive depressions.

Our findings with atypical depressions are in keeping with the findings of Hoshima and Cease (1958) and Ferreira and Freeman (1958) that Iproniazid is not helpful in schizophrenics and may cause an exacerbation of the disorder.

Our findings indicate that Iproniazid is less effective than electroplexy for treating endogenous depressions and the results with all types of depressive states are such that it is extremely doubtful whether it is justifiable to continue using Iproniazid in view of its possible dangers and toxic effects.

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