

MELLERIL AND PLACEBO IN THE TREATMENT OF SEVERELY SUBNORMAL PATIENTS

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The aim of this controlled blind clinical trial which lasted five months was twofold:—

- a) to evaluate the effects and side-effects of Melleril in the treatment of behaviour disorders in severely subnormal patients, and,
- b) to find what psychological effect the placebo tablets had on the patients.

Melleril (Thioridazine) is a new phenothiazine derivative. Although the basic pharmacological actions of Melleril are similar to those of the phenothiazines generally, certain properties have been described which support the clinical observation that Melleril has a more specific "psycho-sedative" action than other tranquillisers.

Selection of patients: In view of the above claim, 40 severely subnormal patients were selected, of mental ages ranging from 1.2—7.0 years and average chronological age 38.11 years, from Hanham Hall Hospital, which is part of the Stoke Park Hospital Group and houses 220 severely subnormal patients. All the selected patients had suffered in the past from one or other type of behaviour disorder and all had been treated with tranquillisers or sedatives.

Included in the trial were four patients with superimposed psychotic trends, two epileptics, one phenylketonuric and one patient suffering from postencephalitic Parkinsonism.

Patients were divided at random into two groups of 20, labelled Group A, the placebo group, and Group B, the Melleril group. The nursing staff were told that after two months the drug in the two groups would be changed. Change of drugs did not, in fact, take place—only labels were changed. The identity of the tablets was known only to the Dispenser and the Author.

Examinations before the trial: All selected patients were weighed, had blood and urine examined, liver function tested, and blood pressure recorded. Nursing staff and occupational therapy staff made notes on patients' behaviour disorders and medical staff noted their mental and physical condition. All other tranquillisers and sedatives were discontinued from the first day of the trial, except for anti-convulsant and anti-Parkinsonism drugs, which were retained throughout the trial.

Dosages: The dosage was unchanged during the five months of the trial. Group A (placebo) received 1 tab. t.d.s., and Group B received 25 mg. of Melleril t.d.s.

Examinations during the trial: Any changes in each patient's behaviour were immediately reported by heads of departments and nursing staff and recorded by senior nursing staff.

Blood and liver function were examined twice monthly, urine tested and patients weighed monthly and blood pressure recorded fortnightly.

Results of the Trial:

a) **Behaviour.** Records of the patients were classified in four categories. The following is a table showing the results in the two groups:—

	(Melleril) No. of patients	(Placebo) No. of patients
1) Much improved	1	1
2) Improved	14	13
3) Unchanged	3	1
4) Getting worse	1	4
Excluded	1*	1**
Total	20	20

* Excluded from trial after two months—becoming worse mentally and developed oculogyric crises with pseudocatatonia.

** Excluded from trial after one month—deteriorating mentally.

b) **Weight.** It was noticed that there was a considerable **increase** in weight during the trial in the Melleril and a marked **loss** of weight in the placebo group as shown in the next table:—

	(Melleril) No. of patients	(Placebo) No. of patients
1) Increase in weight	16	4
2) Loss of weight	3	14
3) No change in weight	—	1
Excluded	1 (losing weight)	1 (losing weight)
Total	20	20

EFFECTS ON PARTICULAR FEATURES OF SEVERE SUBNORMALITY

1) Superimposed psychotic trends

There were two patients on Melleril and two on placebo tablets. After 54 days of treatment, one patient on Melleril developed oculogyric crises with pseudocatatonia and deteriorated mentally. Treatment was discontinued at two months and Dartalan was substituted instead which intensified the side-effects (Heaton-Ward, Carpenter, Jancar, 1959). After the withdrawal of Dartalan, these side-effects cleared. E.E.G. showed no abnormality. The second patient on Melleril improved in his behaviour but lost 4lbs. in weight during the trial.

One patient on the placebo rapidly deteriorated mentally and had to be excluded from the trial after one month and was given other drugs. The other patient was kept on placebo until the end of the trial, but was getting worse mentally and lost 9lbs. in weight.

2) Epilepsy

The two epileptics were in the Melleril Group. Both improved in their behaviour and gained 8lbs. and 5lbs. in weight respectively. There was not an appreciable change in the number of epileptic fits.

3) Phenylketonuria

The only phenylketonuric patient was in the placebo group. He improved mentally but lost 10lbs. in weight.

4) Postencephalitic Parkinsonism

One patient who was receiving Disipal 1 tab. t.d.s. as treatment for his Parkinsonism, was given placebo tablets. He lost 8lbs. in weight but improved mentally.

Side-effects. No patients suffered serious toxic reactions during the trial. There was one patient who was temporarily disabled by oculo-gyric crises and pseudo-catatonias and one who suffered from transient drowsiness which necessitated stoppage of the drug for one week. After that, treatment was resumed without any side-effects. Blood pressure, blood, urine and liver function reports were all within normal limits. There were no cases of dermatitis, photosensitivity, gastro-intestinal disturbances, oedema or seizures.

Statistical Analysis of the Trial. The statistical methods used to analyse the raw data were: 1, The method of Product Moment Correlation. 2, The difference between Means. 3, The use of Arithmetical Means. 4, Graphical presentation. Significance tests were used to evaluate the results of these tests where appropriate. The raw data itself was a record of 40 subjects, of whom 20 were subjected to the Melleril treatment and 20 to the placebo treatment. These two groups are roughly matched for mental and chronological age, neither of which, in any event, was significantly correlated with the assessment of their change of condition.

The following general conclusions can be stated with some measure of confidence:

1. That Melleril is shown to be effective in improving the general mental state of these patients. This major result requires some explanation. It is quite clear that the difference between the means of the Melleril and placebo groups is **not** statistically significant, although **there is a difference**. However, if we now compare the Melleril group with a control group that has not significantly changed over the same period, then the Melleril group shows a marked **statistically significant difference**. The point here is that the placebo group is not a control group relative to the Melleril group and the fact must be born in mind that the Melleril group is highly correlated with a positive change of weight whereas the placebo is not. It is for this reason that irrespective of the placebo group, the Melleril group is undoubtedly effective in bringing about a change.

2. That placebo tablets were also effective in improving the state of the patients, although to a slightly lesser extent (the differences are not in fact statistically significant) **and it is effective in a different way**. It is important to note that if the Melleril group and the placebo group are independently compared with a group (acting as a control) who have not changed at all during the same period, then the Melleril group is **significantly** different while the placebo group is not significantly different.

Once more the reader is reminded that the placebo group should not primarily be thought of as a control group relative to the Melleril group, although even if it is the important differences in weight are of the utmost relevance.

3. The difference in the effect of the Melleril and of placebo tablets seems to be reflected most markedly in the patients change of weight (Fig. 1) and it is

CHRONOLOGICAL AGE AND CHANGE IN WEIGHT

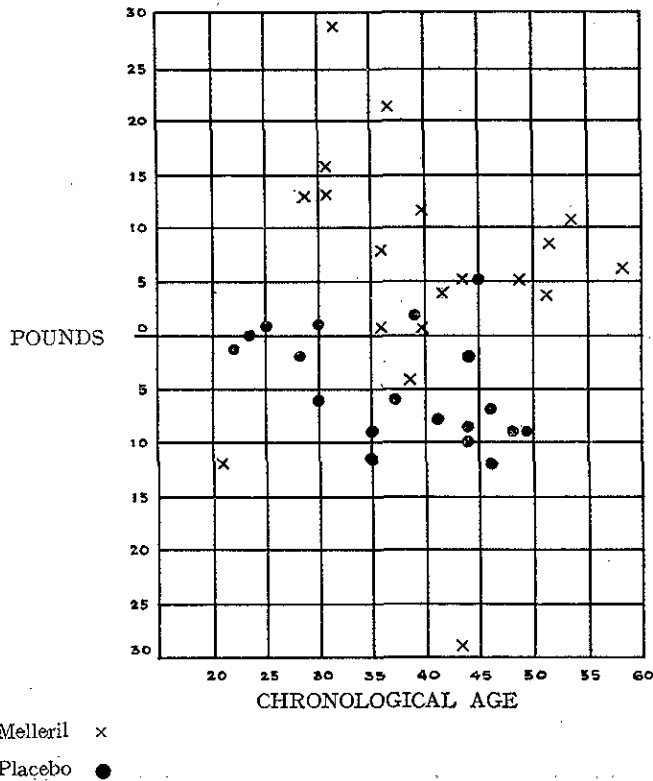


Fig. 1

hypothesized that this difference may reflect the difference between lasting and temporary improvement. The Melleril group shows a significant correlation between change of weight and improvement whereas the placebo group showed no such thing.

4. It seems unlikely that the mental age of the patient, or even his chronological age, was a factor of great importance in the experiment.

The direct comparison between the Melleril and the placebo group shows that there is no significant difference between their respective degrees of improvement as a result of the experiment, although an inspection of the raw scores—admittedly, possibly only a chance factor—suggests that the Melleril group is in fact slightly better. But it must be stated again that the most significant result in comparing the Melleril group with the placebo group is the fact that the Melleril group has its improvement highly correlated with its change of weight, whereas the placebo group has not. This may be a matter of great psychological and biological significance, and may possibly distinguish as we have already suggested a permanent from a temporary improvement, although nothing definite can yet be said about this hypothesis on the basis of these results.

Summary

Forty severely subnormal male patients were selected for blind controlled clinical trial on Melleril. Mean chronological age of the patients was 38.11 years

and mean mental age 4.3. Four patients with superimposed psychotic trends, two epileptics, one suffering from phenylketonuria and one from postencephalitic Parkinsonism were included.

From the trial the following general conclusions were drawn:—

a) that Melleril (25 mg. t.d.s.) is effective in the treatment of milder types of behaviour disorder and comparatively free of side-effects (one patient developed oculogyric-crises and pseudocatatonia and another transient drowsiness).

b) that placebo tablets have a great psychological effect on patients and were also effective in the treatment of milder behaviour disorders.

c) that the only significant result in comparing the Melleril group with the placebo group is the correlation between improvement in behaviour and increase in weight in the Melleril group. This psychosomatic improvement needs further study to establish in particular whether there is any significant difference in its duration between the Melleril and placebo groups.

Acknowledgements

I should like to express my thanks to Dr. W. A. Heaton-Ward, Medical Superintendent, Stoke Park Hospital Group, for his advice and help with the paper; to Dr. S. Brown, Medical Officer, for the clinical observations during the trial; and to the nursing and occupational therapy staff at Hanham Hall Hospital for their ready co-operation, careful observation of the patients and collection of the data throughout the trial. I am also indebted to Dr. R. A. Ellis from the research department of Sandoz Products Limited for arranging the supply of Melleril and placebo tablets without charge, to Dr. F. H. George, Bristol University, for the statistical analysis of the trial, and to Miss June Millard for the secretarial work.

Reference.

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