

9.6%, which is about 1.5% higher than the result obtained by the new method. The eclampsia perinatal mortality rate over the same period was 36%, which is about 10% higher than the figure for the new method of sedation, and this figure is statistically significant.

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TREATMENT OF SCHIZOPHRENIA "PACATAL" AND CHLORPROMAZINE COMPARED

BY

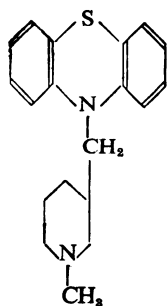
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Delay *et al.* (1952) first reported the use of chlorpromazine in psychiatry, and since then its value in the treatment of schizophrenia has become firmly established (Meyer, 1953; Labhardt, 1954; Lomas, 1955; Vaughan *et al.*, 1955; Boardman *et al.*, 1956).

The therapeutic success of chlorpromazine led to the trial of a host of new "tranquillizers," some of which were hailed with more enthusiasm than wisdom, and in particular to the more intensive investigation of the phenothiazine compounds. The need to find a substitute for chlorpromazine was increased by its potentially dangerous toxic effects, especially on the liver (Lomas *et al.*, 1955).

"Pacatal" (10-(N-methyl-3 piperidylmethyl)phenothiazine) is, like chlorpromazine, a phenothiazine derivative and has the graphic formula:



Nieschulz *et al.* (1954) published the first pharmacological study of the drug, and their work has since been further extended and confirmed by other workers (Nieschulz *et al.*, 1955; Kopf, 1955). In animals pacatal has similar effects to chlorpromazine in producing sedation without hypnosis and in potentiating the effects of other sedatives, hypnotics, and analgesics. It also has a similar though not so pronounced sympatholytic effect, but there is only slight antagonism to adrenaline, and, unlike chlorpromazine, pacatal has a marked depressive action on the parasympathetic nervous system. In consequence its hypotensive action is relatively weak.

Electroencephalograms in normal animals show that pacatal has a similar action to other phenothiazine derivatives, but experiments done in the Warner-Chilcott research laboratories showed that it does not block the arousal pattern, and Himwich *et al.* (1956) could demonstrate no blocking effect on the reticular formation.

Little has yet been published on the effects of pacatal in schizophrenia, but Werenberg (1955) reported improvement in 85% of 100 patients, most of them disturbed schizophrenics and nearly half of whom had been in hospital for over 20 years. Hiob and Hippus (1955) treated 65 female psychotic patients, nearly half of them diagnosed as suffering from schizophrenia: 65% were much improved and 20% were discharged. Most of them had shown no significant improvement with other physical methods of treatment including various "tranquillizers."

Bowes (1956) considered pacatal to be of most value in manic and schizo-affective psychoses. He found chlorpromazine more useful in acute schizophrenic disorders. In chronic schizophrenics he found pacatal controlled the grosser behaviour disturbances, but thought that a combination of pacatal and chlorpromazine was the treatment of choice in these cases. Jepsen (1955) thought that pacatal was effective in one out of three cases which had failed to respond to chlorpromazine and in which aggressive tendencies or paranoid symptoms prevailed.

It is the aim of this paper to compare the effects of pacatal and chlorpromazine in the treatment of the schizophrenic group of disorders.

Selection of Patients

All new admissions were included in the series when the diagnosis was schizophrenia, paraphrenia, or schizo-affective disorder and when the doctor in charge of the case considered that chlorpromazine was the treatment of choice. This excluded acute katatonic conditions where E.C.T. was indicated, schizo-affective cases where the affective disorder was predominant and consequently E.C.T. again the treatment of choice, and all those cases in which insulin was thought advisable. The results were based on 50 male and 50 female patients selected in this way. Once inclusion in the series had been decided on, patients were assigned to either the pacatal or the chlorpromazine group according to a prearranged code known only to the chief pharmacist. The order of assignment was decided by dealing out a well-shuffled pack of 25 red and 25 black cards for male and female patients.

The distribution of patients into the various diagnostic subgroups was comparable for the two groups. Over 60% of both pacatal- and chlorpromazine-treated patients were diagnosed as suffering from paraphrenia or paranoid schizophrenia, half the remainder were assigned to the katatonic subgroup, and the rest were evenly distributed between the simple schizophrenic, hebephrenic, and schizo-affective subgroups.

The age distribution for the two groups was also closely comparable. The mean age for the pacatal patients was 37.1 ± 1.5 years (males 33.8 ± 2 ; females 40.5 ± 2), while the chlorpromazine patients averaged 36.9 ± 1.5 years (males 33.4 ± 2 ; females 40.4 ± 2.1). The differences are entirely insignificant statistically.

The assessment of the duration of a mental illness is a notoriously difficult task, and is made even more so where, as in this case, the breakdown is not necessarily the first. The duration of the current attack is obviously unreliable, as it neglects the prognostic effect of previous illness. On the other hand, the duration since the first symptoms appeared may be equally unreliable. One patient in this series had a first attack 20 years ago and apparently remained perfectly well until the acute onset of her present symptoms; but if both the number of previous attacks and the duration of the illness since the first symptoms appeared are taken into account a fairly reliable guide to the comparability of the two groups can be obtained.

Table I shows the distribution of previous admissions. It will be seen that there is very little difference between the

TABLE I.—Number of Previous Admissions

No. of Previous Admissions	Chlorpromazine			Pacatal		
	Males	Females	Total	Males	Females	Total
0	13	5	18	10	4	14
1	6	12	18	7	13	20
2	3	5	8	4	5	9
3+	3	3	6	4	3	7

chlorpromazine and pacatal groups and that this difference is entirely insignificant statistically.

The mean duration of illness in the chlorpromazine group was 4.4 ± 0.6 (males 3.1 ± 0.7 ; females 5.7 ± 0.9), while for the pacatal group it was 4.4 ± 0.7 (males 4.6 ± 1 ; females 4.3 ± 0.9). Thus, while the male patients were more favoured prognostically in the chlorpromazine group, the female patients receiving pacatal were equally well placed, and in the patients as a whole there was no difference in duration of illness between the two groups. The differences in the male and female subgroups were not statistically significant.

Those patients receiving chlorpromazine could therefore be regarded as prognostically comparable to the pacatal group in respect of age, type of disease, and duration of illness.

Procedure

Dosage and Method of Administration.—Pacatal was supplied in tablets containing 50 mg. and chlorpromazine in tablets of either 25 mg. or 100 mg. Once included in the investigation, patients were prescribed "Tabs. P.L." in a dosage of a multiple of 50 mg. Whether they received pacatal or chlorpromazine depended on the chief pharmacist's code. The usual dosage of either was 300 mg. daily, but it might vary above or below this figure. Treatment was discontinued when the patient left hospital, if the doctor in charge of the case considered a different type of treatment desirable, if serious toxic effects supervened, or after treatment had lasted for three months. A full three-months course was always given if possible.

Assessment of Results.—The trial was only approximately a blind one. The ward medical officer did not initially know whether a patient was receiving chlorpromazine or pacatal, but as the two tablets are different the nursing staff who administered the drugs inevitably had this knowledge, and it would not always be kept from the ward doctor. The final assessment, however, was made by the physician-superintendent, who had no knowledge of the type of treatment received. The results were assessed when treatment was discontinued, for whatever reason, on the following scale: (1) Not improved=slight or no change either in symptoms or in behaviour. (2) Slightly improved=decrease in symptoms and disappearance of gross behaviour disturbance. (3) Moderately improved=improvement in adjustment at hospital level or to the outside world at a dependent level, as shown by taking an interest in environment and in ward social activities and by employability within the hospital. (4) Much improved=improvement in adjustment to the outside world at an independent level shown by increases in initiative, reliability, and responsibility. (5) Recovered=symptom-free, with insight and capacity for adjustment to the outside world at the level extant before the breakdown.

Results

The results are shown in Table II. It can be seen that chlorpromazine is much more effective than pacatal and that

TABLE II.—Results

Assessment	Chlorpromazine			Pacatal		
	Males	Females	Total	Males	Females	Total
Not improved ..	3	1	4	8	4	12
Slightly improved	6	3	9	6	3	9
Moderately improved	5	9	14	9	12	21
Much improved	9	9	18	2	4	6
Recovered ..	2	3	5	0	2	2

this difference is greater for males than for females. The difference is significant at the 1% level for the results as a whole, at the 5% level for male patients, and not statistically significant for female patients. This difference between the sexes is probably due to the variation in the duration of illness of male and female patients, and cannot therefore be regarded as reflecting any real difference of effect of the two drugs in the two sexes.

Study of Table II shows that only 8 out of the 50 patients receiving pacatal were better than moderately improved, as against 23 of those on chlorpromazine. The distribution of the pacatal patients is in fact no better than could reasonably be expected in a group of similar patients subjected to routine hospital regime without any specific treatment.

The same difference is shown if discharge rate is taken as a criterion of improvement, although this is not, of course, a very reliable guide. By the end of the investigation, defined as three months after the last patient had started treatment, 33 patients on chlorpromazine had been discharged as against 26 on pacatal. On the other hand, of those discharged the mean duration of stay in hospital was 13.2 ± 1.5 weeks for those receiving pacatal and 14.2 ± 1.5 weeks for the chlorpromazine cases. The differences are not statistically significant.

It has already been mentioned that the nursing staff invariably, and the medical staff on occasion, knew the nature of the treatment. This introduces an element of bias which might influence the results, although the final assessment was made without any knowledge of the treatment given. The staff had already accepted chlorpromazine as being a valuable method of treating schizophrenia and would therefore be inclined to suspect anything new. If treatment were therefore not immediately successful they might be inclined to abandon the newer pacatal more readily than the well-tried chlorpromazine and thus influence the results by not giving pacatal a long enough trial to produce its best effect.

The analysis of the reasons for finishing treatment shown in Table III suggests that no such bias in fact influenced the results. The two groups differ only in the numbers of patients discharged where those on chlorpromazine exceed the pacatal figure and in those patients for whom a change

TABLE III.—Reasons for Discontinuing Treatment

Reason	Chlorpromazine			Pacatal		
	Males	Females	Total	Males	Females	Total
End of course ..	12	14	26	13	13	26
Discharged ..	6	7	13	3	4	7
Discharged against advice ..	1	2	3	2	2	4
Change of treatment ..	4	1	5	4	5	9
Treatment refused ..	1	0	1	1	1	2
Toxic reaction ..	1	1	2	2	0	2

of treatment was considered necessary. Nine pacatal patients were taken off treatment for this reason, against the five in whom chlorpromazine was discontinued, but although this difference may have been due to bias it is too small to have influenced the final results.

The results of this trial therefore suggest that chlorpromazine is superior to pacatal in the treatment of a mixed group of recently admitted schizophrenic patients.

Side-effects and Toxic Reactions

The toxic reactions to chlorpromazine are now widely known and have been fully reported by Lomas *et al.* (1955). The most serious are liver damage and the much rarer agranulocytosis. Doughty (1955) from a perusal of the world's literature estimated the incidence of jaundice as 1.4% out of over 7,000 patients.

The toxicity of pacatal is less well known. Troublesome though not serious side-effects are due to the drug's parasympatholytic actions. Dryness of the mouth and difficulty in visual accommodation are frequent occurrences, and are

mentioned by most writers. Constipation, nausea, and vomiting are less common but have been mentioned in most investigations. Opinions vary about the hypotensive effects of the drug. Horatz (1954), reporting on 439 cases, thought that the danger of orthostatic collapse necessitated great caution in management, but most investigators were not seriously concerned with this complication, and the general consensus of opinion was that in this respect pacatal is safer than chlorpromazine.

Of the more serious complications following use of chlorpromazine, only Werenberg (1955) reports the incidence of epileptic fits, which occurred in 7% of 100 patients. Of these cases, four had been leucotomized, one had had fits previously, and two had had frequent electroplexy. Skin reactions and oedema are rare. Kroner (1955) reports a few cases of light sensitivity, but no mention is made of this complication anywhere else in the literature. No case of jaundice has yet been reported.

As with chlorpromazine, the blood picture varies, but a mild leucopenia is the most commonly reported finding. Three cases of agranulocytosis, however, have been recorded, two of them fatal (Wenderoth and Lennartz, 1955; Werenberg, 1955; Gore and Biezanek, 1956).

Bowes (1956) mentions one case of atonic bladder and one of paralytic ileus, while Kline and Jacob (1955) considered the drug so toxic that they abandoned it altogether. Their experience was, however, limited to seven cases.

In the present series, among the 50 patients receiving pacatal, dryness of the mouth was an almost universal complaint and in some cases was very troublesome but did not necessitate taking anyone off treatment. Cycloplegia was also common and necessitated two patients having to discontinue treatment. Physostigmine drops alleviated the complaint to some extent. Constipation was occasionally troublesome, but less so than with chlorpromazine, and neither nausea nor vomiting was noted. Twelve patients underwent extensive laboratory investigations with negative results, at periods varying from 5 to 13 weeks after treatment started. Haemoglobin levels and sedimentation rates were unchanged and the lowest recorded total white count was 4,800. Urinalyses were invariably normal, and alkaline phosphatase levels, non-protein nitrogen, and serum bilirubin were within normal limits.

In 2 of the 50 cases receiving chlorpromazine it had to be discontinued. One developed jaundice and another had an intractable dermatitis while on the drug.

Summary and Conclusions

Fifty cases falling within the schizophrenic group of disorders were treated with pacatal, while a similar number received chlorpromazine.

The method of selecting patients and the scheme of dosage are outlined. It is considered that the two groups are comparable so far as prognosis is concerned.

Assessment of results was made on a five-point scale by an independent observer who knew nothing of the type of treatment. Assessment was made either after 13 weeks or when treatment had to be discontinued for one of various reasons.

The results are significantly better in those patients receiving chlorpromazine, and there is nothing in this trial to suggest that pacatal has any value in the treatment of a mixed group of schizophrenic patients.

Both from a review of the literature and from experience in this trial pacatal would appear to be less toxic than chlorpromazine. Jaundice does not seem to be a risk in using pacatal, but agranulocytosis is a dangerous complication with both drugs.

I thank Dr. H. C. Beccle, physician-superintendent of Springfield Hospital, for his kindness in making the independent assessment of results; and Mr. Mayall, the chief pharmacist, for his

invaluable assistance in arranging the order of treatment. I am indebted to Messrs. William R. Warner and Co. Ltd. for their generous supplies of pacatal.

ADDENDUM.—Since this article was written, two reports on the use of pacatal in psychiatry have appeared in this country. J. G. Thorpe and A. A. Baker (*J. ment. Sci.*, 1956, 102, 790) agreed that pacatal was less effective but less toxic than chlorpromazine, while P. H. Mitchell, P. Sykes, and A. King (*British Medical Journal*, 1957, 1, 204) found it of some value in controlling incontinence, noisiness, and aggression in deteriorated female schizophrenics, but considered it to be much more toxic. They reported one death due to agranulocytosis and two cases of jaundice.

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ARACHNODACTYLY WITH CONGENITAL LESIONS OF THE URINARY TRACT

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A considerable number of cases of arachnodactyly have been reported since Marfan's original description of a girl aged 5 years with spider fingers (*pattes d'araignée*) and poorly developed musculature (Marfan, 1896). Although the deformities described in this case were predominantly skeletal, subsequent reports of patients with this syndrome have indicated that it may be associated with other congenital abnormalities. Salle (1912) was the first to recognize the association with patent foramen ovale, and Börger (1914) reported details of a patient who had dislocation of the lens and iridodonesis with arachnodactyly. The frequency with which congenital anomalies of the heart may occur in patients with Marfan's syndrome has been stressed by Piper and Irvine-Jones (1926). Baer, Taussig, and Oppenheimer (1943) associated arachnodactyly with developmental abnormalities of the media of the aorta, and a further case with dissecting aortic aneurysm was described by Etter