THE USE OF FLUPHENAZINE DECANOATE (MODECATE) DEPOT THERAPY IN OUTPATIENT SCHIZOPHRENICS — A RETROSPECTIVE STUDY

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SYNOPSIS

One hundred and twenty seven outpatient schizophrenics treated with fluphenazine decanoate (Modecate) depot therapy for a minimal period of 24 months were selected from all the psychiatric outpatient clinics in Singapore. Using a mirror image analysis in which patients act as their own controls, 105 patients showed a significant reduction of relapses requiring admissions from 139 before the institution of Modecate to 78 after its institution. The corresponding time spent in hospital also fell significantly from 4377 days to 1422 days - a saving of 2955 or 98 months. Of the remaining 22 patients, 19 showed increases in both the relapse/ readmissions rates and length of hospitalisation while 3 showed no change in the number of relapses, before and after the use of depot Modecate. The 19 who did poorly were further analysed and the findings were discussed in relation to recent literature on the use of depot fluphenazine decanoate.

INTRODUCTION

Fluphenazine decanoate (Modecate), a long acting phenothiazine with a piperazine side chain, has been found to be very useful in outpatient maintenance therapy of chronic schizophrenia. It is administered by deep intra-muscular injection in the usual dose of 12.5 to 25 mg every 2 to 4 weeks, and produces effective blood levels for up to 21 days. The drug is distributed throughout all the body tissues, the highest concentrations being in the lung, liver, adrenal gland and spleen. Within the brain there would appear to be selective distribution, highest concentrations being found in the hypothalamus, basal ganglia, thalamus and hippocampus.

Woodbridge Hospital first used the drug in January 1974. Since then, there has been increasing demand every year as more and more patients were being put on the drug. In September 1980, about 1000 patients seen at Woodbridge Hospital were receiving Modecate therapy. Most psychiatrists here and in other countries are convinced of its efficacy in preventing schizophrenic relapses and controlling psychotic symptoms provided that it is properly used and the side effects (some of which can be very severe, prolonged, and life threatening) closely monitored.

A retrospective study of selected schizophrenic outpatients on Modecate therapy in all the outpatient clinics from July to September 1979 was carried out in an attempt to evaluate the use of this drug in Singapore. A mirror image analysis method where the patients act as their own controls was used. The indices of frequency of admission and length of hospitalisation are chosen, as these are considered objective enough in a retrospective study of this nature.

MATERIALS AND METHODS

The "Modecate register" in all the psychiatric outpatient clinics (Woodbridge Hospital, Lim Ah Pin, Bukit Timah, Queenstown, Maxwell and Kallang) were screened. Altogether 127 cases were selected according to the following criteria:

1) Diagnosis of Schizophrenia
2) At least 24 months of illness prior to and following institution of Modecate treatment.
3) After institution of Modecate treatment, the oral medication should be stopped or reduced by at least an amount equivalent to the Modecate introduced.
4) Still on Modecate treatment at the time of the study.
5) Length of illness not exceeding 8 years.

Criteria number 5 is arbitarily chosen in order to exclude the more chronic schizophrenics, as the degree of chronicity of schizophrenia may be an important variable in determining the response to maintenance treatment. Some psychiatrists consider schizophrenia to be a progressive disease and treatment may be effective in the early but not the later stages of the illness.

The following items of social, therapeutic and historical data were recorded for each of the 127 patients:- age, sex, race, dose of Modecate, number of hospital admissions and length of hospitalisation (in days) 24 months prior to and after the institution of Modecate therapy, patient's and relatives' assessment of the effect of Modecate and length of illness.

Analysis revealed that 105 patients had significant reduction in relapses requiring admissions and length of hospitalisation following Modecate treatment, 3 had no significant change while 19 were worse off after Modecate. These 19 patients were compared with a control group of 19 selected from the 105 with better outcome matched for age, sex, race and length of illness. The comparison was an attempt to investigate the probable reasons for the apparent failure of Modecate therapy, and to elucidate the extent of prevalent local cultural bias in favour of a parenteral form of treatment as against oral medication.

RESULTS

1. **Age**

Table 1 shows the distribution of cases according to age. About 70% of patients are in the 20-40 age group, the range is from 15 to 65 years and the mean 32.5 ± 8.8 (S.D.).

TABLE 1: DISTRIBUTION ACCORDING TO AGE

Age (Years)	N	%
10	13	10.2
20	41	32.3
30	49	38.6
40	19	15.0
50	5	3.9
Total	127	100.0
Range 15 to 65 Mean ± S.D. 32.5 ± 8.8		

2. **Race, Sex and length of illness**

These characteristics are shown in Table 2 and Table 3. The lower limit of the length of illness is 4 years according to the study design which specifies the 2-year period before and after institution of Modecate therapy. The upper limit of 8 years is arbitarily chosen as mentioned under methods.

TABLE 2: DISTRIBUTION ACCORDING TO RACE AND SEX

Parameters		N	%
Sex :	Male	78	61.4
	Female	49	38.6
	Total	127	100.0
Race:	Chinese	104	81.9
	Malay	13	10.3
	Indian	6	4.7
	Others	4	3.1
	Total	127	100.0

3. **Outcome**

The outcome of the mirror image comparison of the total number of relapses requiring admissions and length of hospital stay 2 years before and 2 years after the institution of Modecate therapy is shown in Table 4. The outcome is categorised into 'better', 'no change' or 'worse'. In the 'better' group, 105 patients show a significant reduction of relapses from 139 to 78 while the length of

hospitalisation fell significantly from 4377 days to 1423 days (Sign Test $P<0.01$).

TABLE 3: DISTRIBUTION ACCORDING TO LENGTH OF ILLNESS

Length of Illness (in Years)	N
4	13
5	31
6	46
7 - 8	37
>8	0
Total	127

TABLE 4: OUTCOME 2 YEARS BEFORE AND 2 YEARS AFTER INSTITUTION OF MODECATE THERAPY

Outcome	N	No. of Admissions		Total Hospital Stay (Days)	
		Before	After	Before	After
1. Better*	105	139	78	4377	1422
2. No change	3	5	5	119	82
3. Worse	19	31	57	768	1029

$P<0.01$

4. **Dose of Modecate**

Table 5 shows that 122 or 96.1% of all cases received 25 mg of Modecate per month, 3 received 18.5 mg per month, 1 received 25 mg fortnightly and 1 received 37.5 mg per month.

TABLE 5: DOSE OF MODECATE

Dose	N
25 mg per month	122
25 mg fortnightly	1
18.5 mg per month	3
37.5 mg per month	1
Total	127

5. **Characteristics of 'Worse' outcome group**

Table 6 sets out the results of comparing the 19 patients with 'worse' outcome following Modecate therapy, with that of 19 selected from the 105 'better' outcome group matched for race, age, sex and length of illness.

The findings show significantly higher proportion of defaulters ($X^2 = 20.63$, $P<0.001$) and paranoid schizophrenias ($X^2 = 7.05$, $P<0.01$) among the 'worse' outcome group. Also significant were the higher number of patients in the control group who reported less aggressive/assaultive behaviour ($X^2 = 6.81$, $P<0.01$) less irrational talk ($X^2 = 5.29$, $P<0.05$) and better work records ($X^2 = 4.21$, $P<0.05$) following Modecate therapy. The higher number of control patients with less socially embarassing behaviour does not reach significant proportion.

Despite the significant differences noted above, almost all the patients (and their relatives) were of the opinion that their illness had improved with the depot injection. In other words there was no difference between the 'worse' outcome patients and the controls in the subjective opinions of the efficacy of Modecate.

6. **Frequency of default and reasons**

The frequency of default and reasons for defaulting are shown in Tables 7 and 8.

When a patient missed his Modecate for one prescribed unit of time, he is considered to have defaulted once; hence a person on monthly dose would have defaulted 4 times if he continuously or at various times failed to receive his injection for a total period of 4 months.

From Table 7, the defaulting rate is high with more than half the defaulters having defaulted at least four times. The main reasons were active resistance to treatment, troublesome side effects and interference with working hours.

TABLE 7: FREQUENCY OF DEFAULTING TREATMENT DURING 2 YEARS OF MODECATE THERAPY

Frequency	N
1. Once	1
2. Twice	1
3. Thrice	4
4. Four times	6
5. Five times	2
6. Six times	0
7. More than six	3
Total	17

See text for definition of default

TABLE 8: REASONS FOR DEFAULTING MODECATE

Reasons	N
Active refusal	8
Troublesome side effects	5
Forget appointments	1
Interfere with working hours	3
Total	17

DISCUSSION

Depot injection fluphenazine decanoate (Modecate) is evidently effective in the stabilisation and maintenance treatment of schizophrenic out-patients. Early in modern psychopharmacological era methods were devised by which urine analyses could disclose a possible failure to take oral drugs; however, such a disclosure was of little help as repeated investigations show high default rates in oral medication which psychiatrists could do little about. Hence the arrival of

long acting injection forms of neuroleptics were welcomed as another weapon in our therapeutic armamentarium.

This study shows that Modecate therapy significantly reduces the frequency of relapses requiring admissions to hospital and at the same time shortens the length of hospital stay considerably among 105 selected outpatient schizophrenics. Besides being cost effective this also relieves the acute shortage of beds in Woodbridge Hospital. Similar reduction in relapse and readmission rates have been reported by Crumpton (1), Rasmussen (2), Denham and Adamson (3), and Johnson and Freeman (4).

In 19 patients, there were apparent increases in total readmissions and periods of hospitalisation despite Modecate. Further inquiries revealed that much of the apparent increase was due to the high proportion of defaulters - 17 out of 19 or 89.5%. Only 2

TABLE 6: CHARACTERISTICS OF 19 PATIENTS WITH 'WORSE' OUTCOME COMPARED WITH CONTROLS

CHARACTERISTICS	PATIENTS N = 19	CONTROLS N = 19	STATISTICAL SIGNIFICANCE
RACE: Chinese	18	18	)
Malay	1	1	)
SEX : Male	11	12	) MATCHED
Female	8	7	) VARIABLES
MEAN AGE + S.D.	39.2 ± 6.3	37.9 ± 5.6	) P>0.05
MEAN LENGTH OF ILLNESS ± S.D.	6.7 ± 0.9	6.5 ± 0.8	)
AVERAGE DOSE OF MODECATE FOR ATTENDANCE	25 mg/mth	25 mg/mth	
PARANOID SCHIZOPHRENIA	12	3	X^2 = 7.05 P<0.01
DEFAULTERS	17	2	X^2 = 20.63 P<0.001
PATIENT'S ASSESSMENT OF MODECATE THERAPY			
a) Improved	15	19	ns
b) Worse	3	0	
c) No change	0	0	
d) Not sure	1	0	
RELATIVES' ASSESSMENT OF MODECATE THERAPY			
a) Improved	18	18	ns
b) Worse	1	0	
c) No change	0	1	
d) Not sure	0	0	
AFTER MODECATE THERAPY			
a) Less aggressive/assaultive	4	13	X^2 = 6.81 P<0.01
b) Talk less nonsense	4	12	X^2 = 5.29 P<0.05
c) Less socially embarassing behaviour	2	7	ns
d) Better work record	3	10	X^2 = 4.21 P<0.05
INJECTION SUPERIOR TO ORAL MEDICINE			
a) Agreed	19	17	
b) Disagreed	0	0	
c) Don't know	0	2	
SOME KNOWLEDGE OF MODECATE	1	0	

ns = not statistically significant
x^2 = chi² t test

defaulters or 10.5% were noted in the control group. The high default rate and a significantly high incidence of paranoid schizophrenia in the 'worse' outcome group were not unexpected. They reflect a major problem in the administration of maintenance therapy in psychiatry, that is, to ensure that patients take their medication regularly. Even among the hospitalised patients, Hare and Wilcox (5) found that about 20% did not take the tablets given by the nursing staff despite being 'supervised'. As noted in this series, Wilson and Enoch (6) found paranoid schizophrenics to be the most evasive in a group of schizophrenic drug rejectors. Woodbridge Hospital has devised a workable system of contacting defaulters since 1979; it is informative to conduct a further study to assess the effectiveness of this system.

Troublesome side effects (especially extrapyramidal) appear to be an important cause of default, apart from active refusal. Grateful enquiry into the latter group revealed that many patients dislike or fear the needle as a mean of drug administration. It is important therefore to investigate the reasons for default as the remedies are simple - either switch to oral medicine or change the dose if necessary.

We have mentioned the apparent contradiction in patients' and relatives' positive opinion of Modecate despite the 'worse' outcome following its use. Interviews revealed a culturally related bias in favour not of Modecate but the injection route of administration. Table 6 shows that in both patients and controls groups, 94% of those interviewed believed injection (not the nature of drugs injected) per se to be superior to orally administered drugs. Terms like 'more potent', 'quicker in action', 'Poh' (Chinese term meaning general tonic), 'superior quality' were commonly used to describe injection. Only 2.6% had limited knowledge of the pharmacology of Modecate. The final outcome therefore suggests that the placebos effects are insignificant in long-term maintenance treatment of schizophrenia.

Finally one should consider the cost effectiveness of depot maintenance therapy, apart from its benefits to patients. Modecate in a dose of 25 mg per month is about 7 times more costly than Trifluoperazine 15 mg per day for one month and 5 times more than Chlorpromazine 150 mg per day for one month. However, the operational expenditure in maintaining a patient in hospital per month is about 60 times higher than the cost of Modecate 25 mg per month. Therefore for outpatient defaulters and non-defaulters with frequent relapses, Modecate therapy should be considered in place of oral medication. The high wastage of oral medicine in defaulters is obvious. The defaulting rate in Modecate therapy is low, and the drug is not wasted because it cannot "be taken home and thrown away". For outpatients who are satisfactorily maintained on oral medicine, the use of Modecate is not urgently indicated.

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