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Low Dose Fluphenazine Decanoate in Maintenance Treatment of Schizophrenia

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Abstract. To test the clinical efficacy of low dose fluphenazine decanoate (1.25 mg to 5.0 mg biweekly), we carried out two separate experiments: (1) an open trial in 57 schizophrenic outpatients, lasting 6 months; (2) a double-blind, placebo-controlled discontinuation study in a subgroup of patients who maintained good remission throughout the entire 6-month open trial. The results suggest that lower doses of fluphenazine decanoate than those usually used may be effective in preventing psychotic relapse while keeping total cumulative dosage to a minimum.

Key Words. Fluphenazine, decanoate, minimal dosage, outcome, schizophrenia.

Numerous drug discontinuation studies have demonstrated the enormous value of maintenance antipsychotic drug treatment in the prevention of psychotic relapse among schizophrenic patients (Davis, 1975). Studies focusing on schizophrenic outpatients in stable remission have also demonstrated the value of continued medication (Hogarty et al., 1977; Leff and Wing, 1971; Rifkin et al., 1977). There is considerable evidence that the majority of patients require maintenance treatment for at least 2 years (Hogarty et al., 1974), and there is growing evidence (Hogarty et al., 1977) that the need for such treatment may be indefinite. Given those findings, attention must now be directed toward developing strategies to maximize the benefit and minimize the risk of long-term drug treatment (Gardos and Cole, 1976). Short- and long-term side effects remain a significant problem, and attempts to reduce toxicity by establishing minimum dose requirements are necessary. One of the major causes of unsuccessful outpatient treatment is noncompliance in medication taking (Renton et al., 1963; Riley et al., 1965; Wilcox et al., 1965), and a frequent reason for noncompliance is adverse reactions (Van Putten, 1974).

A previous investigation (Rifkin et al., 1978) demonstrated the occurrence of clinically significant extrapyramidal signs in over 50% of patients participating in a double-blind, placebo-controlled study of procyclidine withdrawal. Since these

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patients had been on antipsychotic medication for at least 3 months before procyclidine withdrawal, significant extrapyramidal side effects evidently continue to be a problem even in long-term maintenance treatment. The difficulty of differentiating akinesia from postpsychotic depression, demoralization, or residual schizophrenic defects has been recognized by several authors (Rifkin et al., 1978; Siris et al., 1978; Van Putten and May, 1978).

The most important impetus, however, for establishing minimum effective dosage is tardive dyskinesia. At present, there is no established treatment for tardive dyskinesia, and considerable confusion remains as to incidence, prevalence, course, risk factors, and etiology (Baldessarini and Tarsy, 1976; Degwitz, 1969; Jus et al., 1976; Klawans, 1973; Marsden et al., 1975; Tarsy and Baldessarini, 1977). Although there are no solid data to suggest that lower cumulative dosage will reduce the incidence of tardive dyskinesia, the logic of this strategy is too compelling to resist. Despite this, to our knowledge, no systematic dose-response studies of maintenance medication in remitted schizophrenics have been undertaken. Existing dose-response studies have been based largely on chronic schizophrenic inpatients (Gardos and Cole, 1973). It is among drug responsive outpatients, in relative remission, that the issue of risk-benefit ratios and minimal dose requirements would seem most critical.

We are reporting the results of a pilot study to test the efficacy of fluphenazine decanoate (FD) in a dose range of 1.25 mg to 5.0 mg biweekly. This represents one-tenth the standard 12.5 to 50.0 mg biweekly dose used in our previous maintenance medication studies (Quitkin et al., 1978; Rifkin et al., 1977).

To test the clinical efficacy of low dose FD, we carried out two separate experiments: (1) an open trial in 57 patients, lasting 6 months; (2) a double-blind, placebo-controlled discontinuation study in a subgroup of patients who maintained good remission throughout the entire 6-month open trial.

Methods

Study I—Open Low Dose. The sample consisted of 57 patients attending the Aftercare Clinic of the Long Island Jewish-Hillside Medical Center. The Aftercare Clinic provides long-term treatment using modalities such as psychotherapy (individual, group, family, multiple family), social groups, recreational activities, vocational counseling, a hospital-based vocational rehabilitation program, and an apartment program in which the hospital sublets apartments to patients. In addition to these psychosocial approaches, medication is used when appropriate. All of these services were available to study patients.

Participants were selected for the study on the basis of the following criteria: (1) probable or definite schizophrenia, any subtype (except acute first episode), according to the Research Diagnostic Criteria of Spitzer et al. (1977); (2) in remission for at least 4 weeks, or at a stable clinical plateau despite vigorous chemotherapy; (3) not requiring adjunctive pharmacotherapy other than antiparkinsonian agents or minor tranquilizers; (4) free of clinically significant side effects; (5) receiving standard doses of FD, and (6) signed informed consent.

The demographic characteristics of the study patients are given in Table 1.

Table 1. Characteristics of the sample[1]

Characteristics	Mean	SD
Mean age	27.2	6.4
No. of previous episodes	2.4	1.3
No. of months in remission	12.5	12.3
Age at illness onset	21.4	4.7
Prestudy fluphenazine decanoate dosage in mg every 2 weeks	22.5	10.0

1. Study $n = 57$; 39 males, 18 females.

Twenty-five patients were considered to be in good remission with no evidence of significant psychopathology and with reasonably good social and vocational functioning. Twenty-seven patients were free of psychotic signs or symptoms, but manifested some psychopathology or residual social or vocational impairment. Five patients were considered to still manifest some significant symptoms (e.g., delusions, hallucinations, or thought disorder), but these symptoms were at a stable plateau despite previous vigorous pharmacotherapy. All patients were being successfully maintained in the community.

Patients were openly switched to a dilute preparation of fluphenazine decanoate (2.5 mg/ml) specially prepared for use in this project. Starting dose of the dilute preparation was determined by baseline dosage of standard fluphenazine. For example, 1.0 ml of dilute fluphenazine (2.5 mg/ml) would be given in place of 1.0 ml of standard fluphenazine (25 mg/ml). Dosage could be adjusted by the treating psychiatrist within the range of 1.25 mg to 5.0 mg biweekly. At any early sign of clinical deterioration, an attempt was made to increase the dose up to a maximum of 5.0 mg biweekly before considering the patient relapsed. Dosage of procyclidine was reduced gradually, if patients had been receiving it at baseline. (Eleven patients were not receiving procyclidine at the start of the study, and of the 46 who were, 30 had the dosage reduced or discontinued without significant extrapyramidal side effects. There was no relationship between procyclidine discontinuation and study outcome.) No other adjunctive medication besides minor tranquilizers could be prescribed, and very few patients received them. The duration of the study was 6 months. A patient's participation was terminated for relapse, toxicity, or dropout.

Relapse was defined as any increase in, or reemergence of significant symptoms, suggesting imminent psychotic relapse. We did not wait for the appearance of symptoms so severe that they necessarily interfered with social or vocational functioning or suggested the need for imminent hospitalization. In other words, due to the pilot nature of this investigation, we were quick to consider patients as relapsing so as not to expose them to the further potential risk of low dose medication. We did not, however, consider patients relapsed if they experienced an increase in anxiety or depression without other signs indicative of psychotic relapse.

Patients were seen at least biweekly by treating clinicians. No attempt was made to control for frequency of visits or use of psychosocial services.

Study II—Double-Blind Discontinuation. As a further test of the efficacy of low dose maintenance treatment, 16 patients who had maintained good remission for 6 months on open, low dose treatment entered a double-blind, placebo-controlled discontinuation study.

Patients were matched for age, sex, age of onset of illness, and length of remission (see Table 2). One member of each pair was randomly assigned to placebo and the other to continue on active fluphenazine decanoate 1.25 to 5.0 mg i.m. every 2 weeks. This design allowed for sequential analysis so that if significance were reached, no new patients would enter the study. This was done in order to avoid unnecessary exposure to placebo medication.

Table 2. Baseline characteristics of patients entering discontinuation study[1]

	Active low dose		Placebo	
Characteristics	**Mean**	**SD**	**Mean**	**SD**
Age	26.5	5.8	26.9	5.1
No. of previous episodes	2.8	2.2	2.4	1.5
No. of months in remission	26.0	15.8	19.7	14.0
Age at illness onset	20.1	3.8	21.1	3.6
Prestudy fluphenazine decanoate dose in mg every 2 weeks	3.3	1.2	4.3	1.3

1. The *n*'s for both the active low dose and the placebo groups were eight patients (seven males and one female in each group).

Results

Study I—Open Low Dose. Eight patients dropped out of the study with no evidence of clinical deterioration. Dropouts occurred at a mean of 9.6 weeks (SD 7.0; range 2-26). One patient manifested abnormal involuntary movements following the reduction in dosage of FD and was dropped from the study so that neuroleptics could be withdrawn entirely. Fifteen patients were considered relapsed. Relapses occurred at a mean of 16.7 weeks (SD 6.2; range 6-26).

To explore possible relationships between patient characteristics and outcome, the sample was divided into three outcome groups: relapsers, dropouts, and completers. These groups were then compared on the following baseline variables: age, sex, number of previous episodes, age at illness onset, prestudy dose of FD, length of remission, and level of remission. The only statistically significant findings involved length of remission at study entry. Those patients who dropped out of the study had been in remission a shorter length of time (mean = 5 months) than either those patients who relapsed (mean length of remission = 15 months, $t = 2.94$; $df = 16$, $p < 0.01$) or those patients who completed the trial (mean length of remission = 13 months, $t = 3.44$; $df = 39$, $p < 0.01$; separate variance estimate t tests, Welch, 1947).

In addition, there was a trend for those patients in good remission at baseline to have a better outcome (see Table 3); however, this failed to reach statistical significance using the life table method or a Cochran χ^2 for regression. (The failure to find a significant relationship between level of remission and outcome may be a function of the relatively small sample size for this type of analysis.)

Table 3. Level of remission and outcome ($n = 56$)[1]

Level of remission	Relapsers		Dropouts		Completers	
	No.	Percent	No.	Percent	No.	Percent
Complete remission ($n = 25$)	6	24	1	4	18	72
Fair remission ($n = 26$)	7	27	5	19	14	54
Symptomatic stable plateau ($n = 5$)	2	40	2	40	1	20

1. The patient who developed tardive dyskinesia is not included.

The mean dosage of FD for those completing the study was 3.69 mg (SD = 1.27) and the range was 1.25 to 5.0 mg every 2 weeks. Those patients who relapsed were treated with standard doses of FD. Only one patient required rehospitalization. Of the 15 relapsing patients, 12 recovered within 1 month of returning to standard dose FD, one patient required 2 months of increased dosage to return to baseline state, and one patient proved refractory to increased dosages. The types of relapses are summarized in Table 4.

Table 4. Type of patients relapsing

Schizophrenic	8
Nonschizophrenic	4[1]
Manic or hypomanic	3
Total	15

1. The symptoms of each nonschizophrenic patient who relapsed are summarized below:
   - Anxiety; insomnia; severe obsessive thoughts.
   - Irritability; withdrawal; marked increase in referential ideation.
   - Inability to concentrate; withdrawal; bizarre behavior characteristic of previous episodes.
   - Depression; agitation; inappropriate affect.

Study II—Double-Blind Discontinuation. Sequential analysis reached significance when five patients relapsed on placebo and one on active medication ($p < 0.04$; Spicer's closed plan; one-sided alternative, Spicer, 1962). No new patients entered the study from that point. The 16 patients already entered continued on whatever medication they were receiving for a total of 6 months. The results are summarized in Table 5. Seven of the eight placebo-treated patients relapsed at a mean of 18 weeks (SD = 8.5; range 7-26). One patient on active low dose relapsed in the 25th week, and one patient dropped out at 19 weeks (with no signs of clinical deterioration). When relapses and dropouts are combined, the superiority of active low dose is apparent (Fisher's exact probability = 0.02).

These results support our conclusion that the low dose ranges used are clinically active.

Table 5. Double-blind discontinuation study

Subjects ($n = 16$)	Relapsers and dropouts	Well patients
Placebo ($n = 8$)	7	1
Active drug ($n = 8$)	2	6

Fisher's exact probability = 0.02.

Discussion

These findings suggest that lower doses of fluphenazine decanoate than those usually used may be effective for some schizophrenic outpatients in preventing psychotic relapse. The 6-month relapse rate of 26% compares favorably with 6-month relapse rates on placebo of 44% in a previous study (Rifkin et al., 1977).

Relapse rates in the current study are higher than the 5% relapsing in 6 months on standard doses of FD in the same study; however, 35% of the patients receiving standard dose FD were terminated due to toxicity (i.e., akinesia).

It is also important to emphasize that only 1 of the 15 patients relapsing on low dose FD required rehospitalization, and 12 of the 15 patients recovered within 1 month of dosage increase. This suggests that low dose treatment may be a viable strategy for maintaining patients in the community while keeping total cumulative dose to a minimum.

In an open, uncontrolled pilot study it is not possible to determine whether the patients successfully treated with minimal doses were patients benefiting from that low dose or patients who would have maintained remission without medication. The double-blind discontinuation study was designed to tease apart "placebo response" from the true effect of minimal dose. The results (seven relapses on placebo and one on low dose) strongly suggest that for patients who do not relapse on low dose the drug does have a prophylactic effect.

Whether reduced medication exposure will actually decrease the incidence of tardive dyskinesia remains to be determined, but these findings suggest that low dose maintenance therapy might improve the risk-benefit ratio of long-term neuroleptic treatment for some patients. We wish to emphasize, however, that further controlled investigations are required to establish the efficacy of low dose treatment. We are presently conducting such trials.

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