Low Dose Medication Strategies in the Maintenance Treatment of Schizophrenia

by John M. Kane

Abstract

Research on strategies using low doses of neuroleptics in the long-term maintenance and/or prophylactic treatment of schizophrenia is reviewed. The evidence available from prospective controlled trials suggests that substantial dosage reduction is feasible for a subgroup of outpatient schizophrenics and that the incidence of abnormal involuntary movements might be reduced by such a strategy. In addition, lowering dosages may bring about some improvement in psychosocial adjustment. Further work is clearly needed to explore fully the benefit to risk ratio of this strategy and to identify those patients for whom it is most appropriate.

The efficacy of long-term neuroleptic treatment in reducing psychotic relapse among schizophrenics has been well-established and recently reviewed (Davis 1975). Despite considerable variation in methodology, the overwhelming majority of controlled, long-term trials show a clinically and statistically significant advantage for drug over placebo in preventing psychotic relapse and rehospitalization. This appears to be the case even following recovery from an acute onset in the first episode of illness (Kane et al. 1982). Many early studies in this area, however, focused largely on the recurrence of positive symptoms as the outcome measure, with relatively less attention being paid to psychosocial adjustment, neurological side effects, and subjective dysphoria. In recent years, these issues have received increasing attention, and new strategies are being investigated in an attempt to improve the benefit to risk ratio of long-term drug treatment.

In this context, it is striking how little is known regarding the minimum effective dosage requirements for long-term maintenance treatment. The potential for reducing a variety of untoward effects—such as tardive dyskinesia and behaviorally manifested extrapyramidal side effects (e.g., akathisia and akinesia)—by using lower maintenance doses should be considered. Though at present there are few data that define the relationship of dose to subsequent development of tardive dyskinesia (Kane and Smith 1982), the hypothesis that substantial reductions in dosage could reduce the incidence is too compelling to resist.

Adverse side effects are an undesirable component of maintenance/prophylactic drug treatment. Van Putten (1974) has suggested that adverse reactions are a frequent reason for drug noncompliance. Rifkin et al. (1978) demonstrated the occurrence of clinically significant extrapyramidal side effects in over 50 percent of patients participating in a double-blind, placebo-controlled study in which the antiparkinsonian drug, procyclidine, was withdrawn. The fact that these patients had been on maintenance neuroleptic treatment for at least 3 months before procyclidine withdrawal suggests that significant extrapyramidal side effects can continue to be a problem even during long-term maintenance treatment. The difficulty in differentiating akinesia from postpsychotic depression, demoralization, or residual schizophrenia has been recognized by several authors (McClashan and Carpenter 1976a, 1976b; Rifkin et al. 1978; Siris, van Kammen, and Docherty 1978; Van Putten and May 1978). Therefore, an...
additional rationale for a substantial reduction in dose of antipsychotic medication is the hope for a reduction in various side effects of drugs.

Drug dosage may also interact with other treatment variables and environmental factors in ways that would allow substantial dosage reduction in some situations, but not in others. It has also been suggested that low dose strategies might be useful as an intermediate step in ultimately identifying those patients who may maintain remission without continued drug therapy.

Assuming some advantages will be associated with dosage reduction, are there data defining minimal dose levels for effective treatment? Two approaches to this issue are: (1) examining the dose-relapse association in controlled studies; (2) conducting prospective studies comparing different fixed dose levels.

Baldessarini and Davis (1980) reviewed those controlled studies which permitted estimates of the equivalent dose of chlorpromazine to be plotted against reduction of relapse. They found no significant dose effect between 100 and over 2000 (median = 310) mg/day and no mean difference in outcome at doses above versus below 310 mg. These authors also considered the possibility that differences in patient populations and treatment settings could have obscured dosage effects on relapse rates. They, therefore, examined the correlation between relapse rate on placebo, which they suggested could be used as an indicator of illness severity, and mean dose of medication to which the drug-treated group had been assigned. The absence of a significant correlation between placebo relapse rate and drug dose suggested that those patients who were at greater risk of relapsing following drug discontinuation were not necessarily treated with higher doses of medication.

Some reports have suggested that the probability of relapse following drug discontinuation is significantly related to the dose of neuroleptic before withdrawal. Six series of studies with chronic inpatients indicated that the higher the dose before withdrawal, the greater the probability of relapse (Prien, Cole, and Belkin 1968; Andrews, Hall, and Snaith 1976). However, a study of outpatients (Hogarty et al. 1976) failed to confirm these findings, as did our own experience.

If such a relationship were to be confirmed, two possible explanations are: (1) low dose treatment is no better than placebo, and those patients who can maintain remission despite substantial dosage reduction would do just as well off medication; (2) the neuroleptic treatment itself increases the risk of relapse following drug discontinuation (for example, via a drug-induced supersensitization of dopamine receptors) and withdrawal from a higher dose may, therefore, be more risky.

Few studies have attempted to assess prospectively the efficacy of different fixed doses or dosage ranges in preventing relapse. Goldstein et al. (1978) studied the efficacy of two dose levels of fluphenazine enanthate, with and without crisis-oriented family therapy, for a 6-week period in recently discharged, schizophrenic patients.

One hundred and four (mean age 23 years; SD 4.2 years) schizophrenic patients, who were predominantly (69 percent) in their first episodes, were randomly assigned following hospital admission to fluphenazine enanthate, 1 ml (25 mg), or .25 ml (6.25 mg). During the average 14-day hospitalization, additional oral phenothiazines could be given; following discharge, however, patients received only fluphenazine enanthate injections every other week for the 6-week outpatient phase. Relapse was defined as the need to alter medication substantially or to rehospitalize the patient. Although the overall relapse rate was only 10 percent within the 6 weeks following discharge, 24 percent of those in the low dose, no family therapy condition relapsed as compared to none of those in the high dose plus family therapy group. The low dose plus family therapy and the high dose, no family therapy groups had relapse rates of 9 percent and 10 percent, respectively. Though this study involved a relatively brief period of controlled treatment, the results suggest that crisis-oriented family therapy may increase the feasibility of a low dose treatment strategy.

Kane et al. (1979, 1982) have conducted a series of studies using low dose fluphenazine decanoate—1.25 mg to 5.0 mg biweekly, which is one-tenth of the standard 12.5 to 50 mg biweekly dose used in previous maintenance medication studies at the same institution (Rifkin et al. 1977; Quitkin et al. 1978; Kane et al. 1982). To test the efficacy of this lower dosage range, three separate experiments were carried out: (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; (3) a double-blind year-long study comparing low dose and standard dose fluphenazine decanoate in 126 patients.

Study I

The 57 patients participating in the open trial met the following criteria: (1) probable or definite
schizophrenia, any subtype (except acute first episode), according to the Research Diagnostic Criteria (RDC) (Spitzer, Endicott, and Robins 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 occasional benzodiazepines; (4) free of clinically significant side effects; and (5) receiving standard doses of fluphenazine decanoate. The sample had the following demographic characteristics: mean age 27.2 (SD 6.4) years; mean number of previous episodes 2.4 (SD 1.3); mean number of months in remission 12.5 (SD 12.3); mean age at illness onset 21.2 (SD 6.4) years; 39 males and 18 females.

Patients were openly switched to a dilute preparation of fluphenazine decanoate (2.5 mg/ml). The starting dose of the dilute preparation was determined by baseline dosage of standard fluphenazine. Relapse was defined as any increase in or reemergence of significant symptoms suggesting imminent psychotic relapse. Patients were seen biweekly by the research psychiatrist.

Eight patients dropped out of the study after a mean of 9.6 weeks (SD 7; range 2-26) without evidence of clinical deterioration. One patient manifested abnormal involuntary movements following dosage reduction and was removed from the study. Fifteen patients relapsed after a mean of 16.7 weeks (SD 6.2; range 6-26). The cumulative proportion of patients relapsing by the end of 6 months was 30 percent (95 percent confidence interval 17-43 percent).

However, only one of the patients who relapsed required rehospitalization and 12 of the 15 were rehospitalized within 1 month of dosage increase. These results suggested that the low dose treatment is a viable strategy for maintaining patients in the community, while keeping total cumulative dose to a minimum.

Study II

In an open, uncontrolled pilot study it was not possible to determine whether the patients successfully treated with minimal doses were patients in whom the medication was exerting a prophylactic effect or patients who would have maintained remission without drug treatment. Therefore, a double-blind drug discontinuation study was carried out in the 16 patients who completed 6 months of open, low dose treatment without signs of clinical deterioration. Patients were matched for age, sex, age of onset of illness, and length of remission, and one member of each pair was randomly assigned to placebo and the other to continuation of low dose treatment. This design allowed for sequential analysis. A statistically significant difference between the two groups was detected when five patients relapsed on placebo and one on active medication (p < .04 Spicer’s closed plan; one-sided alternative) (Spicer 1962). No new patients entered the study at that point and the outcome for those patients already entered was that seven of eight placebo-treated patients relapsed at a mean of 18 weeks (SD 8.5; range 7-26) and one patient on active drug relapsed at the 25th week. These results supported our conclusion that the low dose range used is clinically effective.

Study III

Subsequently, a double-blind comparison of the study I low dose fluphenazine decanoate (1.25 to 5.0 mg) and standard dose (12.5 to 50.0 mg biweekly) was initiated. Only preliminary results have been reported to date (Kane et al. 1982) involving 126 patients at three different sites.

Subjects included in the trial were remitted or partially remitted RDC schizophrenics. Criteria for remission and relapse were defined by Brief Psychiatric Rating Scale (BPRS) and Global Adjustment Scale (GAS) ratings. Relapsed patients were treated openly with standard doses of fluphenazine decanoate as needed (in addition to experimental medication). Following recovery from relapse, patients were continued in the study on experimental medication only. The length of the study for each patient was 1 year. Extrapyramidal side effects and abnormal involuntary movements were assessed every 12 weeks.

The demographic characteristics of the 126 patients on whom data have been reported are: mean age 29 (SD 7.1) years, mean age at first hospitalization 23 (SD 5.2) years; average number of previous hospitalizations 3.2 (SD 1.9); mean number of weeks since hospital discharge 64 (SD 78.5).

Twenty-six of the 62 patients assigned to low dose treatment relapsed a total of 31 times (five relapsed twice). Seven of these required hospitalization. Among the 64 patients receiving standard dose, three patients relapsed a total of four times, none required rehospitalization.

In a comparison of treatment strategies, it is desirable to assess effects on illness attributes other than relapse rates (Carpenter 1980). The hypothesized advantages for the low dose strategy were discussed above. Preliminary findings in the present study demonstrate that medication reduction is achieved despite increased dosage used during relapses. Nine low dose patients who relapsed but completed the 1-year
study were compared to 20 patients on standard dose who completed 1 year without relapse. The low dose patients received significantly less medication despite the relapses (16 cc as compared to 27.5 cc in standard dose equivalents; $t = 2.39, p < .05$).

To examine possible benefits concerning tardive dyskinesia, we studied a subgroup of 51 patients at the Long Island Jewish-Hillside Hospital, who completed at least 24 weeks in the study. An analysis of covariance (ANCOVA) involving the end point Simpson Dyskinesia Scale scores revealed a significant advantage for low dose treatment. Though these rating scale scores are very low, and could not be considered evidence of tardive dyskinesia, the fact that any statistically significant differences were evident after a relatively brief period of time suggests the potential importance of this strategy in reducing the incidence of tardive dyskinesia.

To assess social adjustment and family burden, interviews with the patient and separately with the family were conducted by a trained research assistant who was unaware of treatment assignment. There were 13 patients receiving low dose and 21 patients receiving standard dose treatment at the Hillside site who had completed at least 44 weeks in the study and were not in a state of relapse at time of interview. Six global ratings and two composite scores were examined in a preliminary analysis. Using ANCOVAs with baseline as the covariate, there were three items (social leisure, general adjustment, and the mean of all “satisfaction” items) on which the low dose patients were rated significantly better than the standard dose patients. There were no items which favored the standard dose group. The fact that these differences (though preliminary) favored low dose treatment despite the significantly higher relapse rate is intriguing.

Further conclusions must await full analyses of the controlled trial. However, the low dose strategy appears viable for at least a subgroup of remitted or partially remitted outpatient schizophrenics. Further work is required to identify this subgroup to help the clinician in selecting patients most suited for this treatment strategy.

References


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