Low-Dose Depot Medication in Schizophrenia

by Peter L. Burnett, Cherrie A. Galletly, Robert J. Moyle, and C. Richard Clark

Abstract

Depot antipsychotic medication is a major component of the maintenance treatment of schizophrenia, but it is still not clear what constitutes an appropriate dose. A number of studies comparing low with standard doses of depot antipsychotic medication on a variety of outcome measures have been published in the last decade. A review of these studies indicates that, compared to standard-dose treatment, low-dose medication tends to improve psychosocial function and reduce the frequency of side effects but may result in an increase in positive symptoms. In such cases, a temporary increase in dose appears to control symptoms and terminate relapse episodes. An explanation of the relative efficacy of low-dose treatment may be derived from recent work in radioreceptor ligand binding.

Although most patients with schizophrenia are prescribed maintenance antipsychotic medication to prevent relapse, the amount of medication necessary to maintain remission or clinical stability remains unclear. Antipsychotic medications have serious dose-related side effects that cause considerable patient discomfort and impairment. Poor compliance often results. To minimize these effects, it is essential that the lowest therapeutic doses be prescribed, but there is little consensus on what these doses are for most antipsychotic medications. In most cases, definitive dose-response relationships have not been determined (Baldessarini and Davis 1980), and the standard doses employed tend to follow clinical rules of thumb. A recent review of dose-response studies (Baldessarini et al. 1988) indicates that routinely prescribed doses may be unnecessarily high and that these high doses may be less effective than moderate doses because they produce neurotoxic side effects.

The issue of the relative efficacy of standard- versus low-dose antipsychotic medication has been the subject of a number of research reports over the last decade. However, in order to interpret these reports, we must have a clear definition of appropriate outcome measures. Emphases are placed variably on prevention of relapse (Johnson et al. 1987), on the minimization of side effects, or on quality of life (Kane et al. 1986). There is little agreement on the relative weighting of these measures, and there has been a proliferation of measurement standards. Further, improvement obtained on one outcome measure may be associated with deterioration on another measure. A high dose of medication might be more likely to suppress psychotic symptoms than a low dose, but it might also produce significant side effects. On the other hand, low-dose regimens may allow more frequent emergence of psychotic symptoms but produce a superior level of social and occupational functioning and patient well-being because of a lower incidence of side effects. Clearly, many factors influence dose-response relationships in the individual patient. These effects interact and may also

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change over time, so there is no ideal dose and a flexible approach to dosage is very important. However, it has been shown that prescribing practices can result in a routine prescription of doses that are probably excessive for many patients (Baldessarini et al. 1984). Studies that compare different medication regimens and offer guidance about the usual optimal dosage range can therefore provide important input into clinical practice.

Targeted, or intermittent, medication regimens offer another approach to maintenance medication. Early studies of this approach reported encouraging results (Herz et al. 1982; Pietzcker et al. 1986; Carpenter et al. 1987). Unfortunately targeted regimens are not suitable for many patients (Chiles et al. 1989) who will continue to require long-term depot medication. Reports of 2-year followup (Carpenter et al. 1990; Herz et al. 1991) have been more pessimistic. Targeted treatment regimens and low-dose treatment have recently been reviewed by Schooler (1991) who concludes that while intermittent treatment strategies are effective in reducing medication dosage and side effects, they result in increased relapse rates and hospitalization, especially in the second year of treatment. Further, this method resulted in no consistent improvement in social functioning.

Another issue in the treatment of schizophrenia is the identification of the long-term consequences of psychotic relapse. Wyatt (1991) concluded that stable schizophrenic outpatients who relapse following discontinuation of antipsychotic medication may have difficulty returning to their previous level of functioning. He suggested that the experience of initial psychosis and subsequent relapse may have a long-term effect on morbidity. If so, the consequences of relapse may extend beyond the immediate occurrence and treatment of psychotic symptoms. This concern must therefore be weighed against the risks and side effects of antipsychotic medication.

This review focuses specifically on the relative effects of standard-versus low-dose depot antipsychotic medication. Particular emphasis is placed on fluphenazine decanoate because it has been the agent most commonly studied and is the most widely used depot-preparation antipsychotic drug.

Pharmacological Determinants of Dose

Fluphenazine decanoate was introduced into clinical practice in the 1960s and proved more popular than its predecessor, fluphenazine enanthate, because of its longer duration of action and its tendency to produce fewer side effects (Ayd 1975). Compared to oral medication, depot fluphenazine decanoate has the advantages of ensuring patient compliance, avoiding first-pass metabolic effects in the liver, and producing more even plasma levels (Dencker 1984). Fluphenazine decanoate is an ester of fluphenazine in a sesame oil base. Hydrolysis and slow diffusion from the depot site in muscle result in reasonably steady serum concentrations following an initial peak between 8 and 18 hours after the injection (Altamura et al. 1985). By 2 weeks after a single initial injection, serum levels are barely measurable in 50 percent of patients (Chang et al. 1985). Three to 6 months of regular treatment are required to reach a steady plasma level (Marder et al. 1986). It has been shown that serum levels of fluphenazine do not reliably reflect tissue concentration levels (Cohen et al. 1985), and that the drug may preferentially accumulate in the brain. Hence there may be appreciable antipsychotic activity even when there is no measurable serum level (Campbell and Baldessarini 1985).

Determination of plasma levels of fluphenazine after either oral or intramuscular depot administration is very complex and widely varying results have been reported by different laboratories (Sakalis and Traficante 1981). Fluphenazine decanoate yields much lower plasma neuroleptic levels than oral fluphenazine (Snyder 1981). Indeed, the questions of appropriate methods of measuring plasma levels, which metabolites should be measured, and in which tissues, are largely unresolved for all antipsychotic drugs (Midha et al. 1987). Fluphenazine is one of the more difficult drugs to analyze because of its relatively low concentration in plasma and the presence of active metabolites (Sakalis and Traficante 1981). A technique that may overcome these problems is radioreceptor assay (KRA), which measures the ability of a drug and its active metabolites to bind to specific receptors (e.g., dopamine) and gives a measure of the neuroleptic activity of the drug in plasma, usually expressed in chlorpromazine equivalents. Early reports using this technique to investigate fluphenazine decanoate levels in schizophrenia have yielded varying results (Brown and Silver 1985; Turbott et al. 1985).

A promising preliminary report of a study of oral fluphenazine
using RRA techniques is referred to in a recent comprehensive review of antipsychotic drug plasma levels by Van Putten and colleagues (1991). Their study suggests an association between plasma levels and both clinical response and side effects. Marder and colleagues (1991) studied the plasma levels of fluphenazine and fluphenazine sulfoxide in 53 patients who participated in a double-blind comparison of 5- and 25-mg doses of fluphenazine decanoate administered biweekly. Although there was a wide range of plasma concentrations within each group, an association was found between lower plasma levels of fluphenazine and the risk of psychotic exacerbation at the 6- and 9-month followup. A weak association was found for akinesia, but no significant association was found for other side effects. We will describe this study in greater detail later in this article.

A possible explanation for the lack of clear correlation between clinical response and either dose or plasma levels of antipsychotic drugs comes from recent work using positron emission tomography (PET) to measure the in vivo occupancy of brain dopamine receptors (Farde et al. 1988; Waddington 1989). Occupancy of between 70 percent and 84 percent was achieved with low to moderate doses (200–400 mg/day chlorpromazine equivalents) of a number of antipsychotic drugs. Increasing the dosage did not increase occupancy levels. Occupancy was sustained for many hours after drug cessation despite a substantial decrease in the plasma levels of the drug.

The strength of fluphenazine decanoate compared to other antipsychotic drugs is also a matter of controversy. The dose of 25 mg every 2 weeks has generally been regarded as standard (Ayd 1975). Formulas for converting doses of fluphenazine decanoate (and other antipsychotic drugs) to the common denominator of chlorpromazine equivalents vary widely and are often stated arbitrarily. For example, a 25-mg dose of fluphenazine decanoate every 2 weeks has been claimed to equal as little as 360 mg chlorpromazine equivalents per day (Baldessarini et al. 1988) or as much as 1,500 mg per day (Inderbitzen et al. 1989). These large differences make it difficult to judge whether a particular dosage of fluphenazine decanoate should generally be regarded as high or moderate.

Fluphenazine decanoate’s duration of action is another pharmacological issue that is not yet clearly understood. Although biweekly intervals between injections are most common, recent research indicates a longer interval may be more appropriate. A pilot study investigating the persistence of fluphenazine in plasma following cessation of chronic administration of fluphenazine decanoate (Gitlin et al. 1988) found that the drug persisted without significant decrease in concentration for 6 weeks, and 33 percent of subjects still had substantial plasma levels 12 weeks after the drug was stopped. Also, plasma fluphenazine levels varied widely across individuals.

In summary, three main points can be drawn so far. First, despite some recent advances, research has not shown a sufficient correlation between serum levels, clinical response, and side effects to establish whether or not the standard dose is optimal. Second, recent evidence regarding the duration of action of fluphenazine decanoate indicates that the standard biweekly administration may be too frequent. Third, recent PET studies indicate that low to moderate doses of antipsychotic drugs are sufficient to obtain maximal receptor site occupancy and thus may provide adequate treatment for most individuals.

**Studies of Low-Versus Standard-Dose Depot Antipsychotics**

This section reviews five controlled studies (see table 1) of the comparative effect of low- and standard-dose depot antipsychotics in the maintenance treatment of schizophrenia.

We have not included studies that used oral medication or those in which assignment to experimental groups was not carried out in a blind fashion (e.g., Lehmann et al. 1983; Faraone et al. 1988). Two of the studies (Goldstein et al. 1978; Hogarty et al. 1988) examined the effects on outcome of both drug dosage and family factors; data relating to the latter will not be included in this review in order to facilitate cross-study comparison.

Goldstein and colleagues (1978) compared the efficacy of two fixed doses (6.25 mg and 25 mg biweekly) of fluphenazine enanthate in patients who had been discharged from the hospital following their first or second admission for schizophrenia, as diagnosed by a score of 4 or higher on the New Haven Schizophrenia Index (Astrahan et al. 1972). Relapse was defined as deterioration in clinical state to the point where either readmission or substantial alteration in medication was judged to be necessary. These judgments
Table 1. Controlled, double-blind studies (1978–88) of the comparative effect of low- versus standard-dose depot antipsychotic medication in the maintenance treatment of schizophrenia

<table>
<thead>
<tr>
<th>Study</th>
<th>Diagnostic criteria</th>
<th>Dose employed(^1) mg/2 wks</th>
<th>Study duration Months</th>
<th>Relapse index</th>
<th>Social function</th>
<th>Side effects</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldstein et al. 1978 (n = 104)</td>
<td>New Haven Schizophrenia Index</td>
<td>6.25</td>
<td>1.5</td>
<td>Readmission or dose increase</td>
<td>NR</td>
<td>NR</td>
<td>16/5 (^6)</td>
</tr>
<tr>
<td>Kane et al. 1983, 1985 (n = 132)</td>
<td>RDC</td>
<td>1.25–5.0</td>
<td>12</td>
<td>BPRS(^2)</td>
<td>SAS</td>
<td>SA, SD</td>
<td>56/147(^7)</td>
</tr>
<tr>
<td>Marder et al. 1984 (n = 50)</td>
<td>DSM–III</td>
<td>5</td>
<td>12</td>
<td>BPRS(^3)</td>
<td>SAS</td>
<td>SERS, IMEPS</td>
<td>22/207(^7)</td>
</tr>
<tr>
<td>Marder et al. 1987 (n = 50)</td>
<td>DSM–III</td>
<td>5</td>
<td>24</td>
<td>BPRS(^3)</td>
<td>SAS</td>
<td>SERS, IMEPS</td>
<td>44/31(^8)</td>
</tr>
<tr>
<td>Johnson et al. 1987 (n = 57)</td>
<td>Feighner Criteria</td>
<td>Variable</td>
<td>12</td>
<td>BPRS or CGI(^4)</td>
<td>SSS</td>
<td>AIM, EPRS</td>
<td>NS (^\downarrow)</td>
</tr>
<tr>
<td>Hogarty et al. 1988 (n = 70)</td>
<td>RDC</td>
<td>3.8 ± 2.1</td>
<td>24</td>
<td>BPRS(^5)</td>
<td>SAS</td>
<td>Not specified</td>
<td>24/30(^9)</td>
</tr>
</tbody>
</table>

Note—New Haven Schizophrenia Index (Astrachan et al. 1972); NR = not reported or not done; RDC = Research Diagnostic Criteria (Spitzer et al. 1978); BPRS = Brief Psychiatric Rating Scale (Overall and Gorham 1962); SAS = Social Adjustment Scale (Weissman and Bothwell 1976); SA = Simpson-Angus Scale (Simpson and Angus 1970); SD = Simpson Dyskinesia Scale (Simpson et al. 1979); \(^\downarrow\) = decrease in low-dose group compared to standard-dose group; DSM–III = Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association 1980); SERS = Subjective Extrapyramidal Rating Scale (Marder et al. 1984); IMEPS = Involuntary Movement and Extrapyramidal Side-Effects Scale (Marder et al. 1984); NS = no significant difference; Feighner Criteria (Feighner et al. 1972); CGI = Clinical Global Impressions (National Institute of Mental Health 1985); SSS = Stevens Social Scale (Stevens 1973); AIM = Abnormal Involuntary Movements Scale (Stevens and Weisler 1974); EPRS = Extrapyramidal Rating Scale (Simpson et al. 1964); \(^\uparrow\) = increase in low-dose group compared to standard-dose group.

\(^1\) Goldstein et al. used fluphenazine enanthate; Johnson et al. used flupenthixol decanoate; all other studies used fluphenazine decanoate.

\(^2\) Increase of 1 or more points on psychotic items of BPRS.

\(^3\) Increase of 3 or more points on psychotic items of BPRS and no response to medication increase.

\(^4\) Increase in BPRS of more than 3 points or a CGI score of 3 or more.

\(^5\) Changes from mild or not present to moderately or markedly severe on psychotic items of BPRS and unanimous clinical decision.

\(^6\) 6-wk followup.

\(^7\) 1-yr followup.

\(^8\) 2-yr followup.

\(^9\) Not specified.
were not carried out blind to dose condition, but the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) was administered on a double-blind basis. A group of 104 patients completed the 6-week treatment period; 5 percent of the high-dose group relapsed compared to 16.5 percent of the low-dose group.

This study used acutely ill patients who were unlikely to have reached stable clinical remission, and the 6-week controlled treatment period was insufficient to provide conclusive results.

Kane and colleagues (1979, 1983, 1985, 1986) reported a series of studies testing the efficacy of low-dose fluphenazine decanoate in clinically stabilized outpatients. In the first study (Kane et al. 1979), 57 patients were openly switched to a diluted preparation containing one-tenth of their baseline dosage so that they received between 1.25 and 5.0 mg every 2 weeks for 6 months. Relapse was defined as any increase in significant symptoms suggesting imminent psychosis. Fifteen patients (26%) were considered to have relapsed. These patients were then treated with standard doses of fluphenazine decanoate. Twelve recovered within 1 month of returning to standard-dose treatment, one required 2 months of increased dosage, and one proved refractory to increased dosages. Only one patient required rehospitalization.

In the second study (Kane et al. 1979), 16 patients who had maintained good remission for the 6 months of the first low-dose study entered a double-blind, drug discontinuation study. Eight patients remained on low-dose treatment while the remainder were given a placebo. After 6 months, seven of the eight patients on placebo relapsed, compared to only one of the eight patients on low dose. This study indicated that low-dose treatment is significantly superior to placebo in reducing relapse.

Kane and colleagues (1983, 1985) then studied 132 outpatients over a 12-month period, using a design in which outpatients were randomly assigned to one of two treatment groups. A low-dose group received 1.25 to 5.0 mg of fluphenazine decanoate every 2 weeks, and a standard-dose group was given 12.5 to 50.0 mg every 2 weeks. Relapse was defined as an increase of 2 or more points (depending on baseline) on any of the psychotic items of the BPRS. Other measures included the Clinical Global Impression (CGI; National Institute of Mental Health 1985) and the Hopkins Symptom Checklist (SCL-90; Derogatis et al. 1973). Extrapyramidal side effects were assessed by the Simpson Angus Scale (Simpson and Angus 1970) and the Simpson Dyskinesia Scale (Simpson et al. 1979). A modified Social Adjustment Scale (Weissman and Bothwell 1976) was administered to patients and to a family member. BPRS scores showed significant differences or trends in favor of low-dose treatment on items of blunted affect, emotional withdrawal, tension, and motor retardation. Low-dose patients also rated themselves as less distressed on SCL-90 items.

Few persistent differences were observed on the side-effects rating scales, although there were significant differences in favor of low-dose treatment at various points in the followup. Ratings for patients who were in relapse or in the prodromal stages of relapse were excluded from the analysis. Three patients from the standard-dose group relapsed, compared to 26 from the low-dose group. It was concluded that "substantial dosage reduction may lead to significant improvement on some objective and subjective measures of symptomatology" (Kane et al. 1985, p. 536). However, the cumulative relapse rate for the low-dose group was 56 percent within 1 year, although it should be noted that the relapse index used in this study is by far the most sensitive of those reported in this review.

Kane and colleagues (1986) also refer briefly to a fourth study that used an intermediate dose of 2.5 to 10 mg every 2 weeks and resulted in a cumulative relapse rate of 20 percent in 1 year.

Marder and colleagues (1984) studied 50 male patients with schizophrenia who had been stabilized on fluphenazine decanoate for at least 2 months. The patients had been ill for an average of more than 10 years. Patients were randomly assigned in a double-blind design to one of two treatment conditions: 5 or 25 mg of fluphenazine decanoate every 2 weeks. A two-level rating of relapse was employed. A minor exacerbation (mild relapse) was defined as an increase of 3 or more points on BPRS cluster scores for thought disorder or paranoia. Following a minor exacerbation, a 100 percent increase in the patient's medication was permitted. If the patient still did not improve, his condition was classified as psychotic relapse, a more serious form of relapse. Ratings of extrapyramidal side effects were made using the Involuntary Movement and Extrapyramidal Side-Effects Scale (IMEPS) and the Subjective Extrapyramidal Rating Scale (SERS) as described by Marder and colleagues (1984, p. 1026). The SCL-90 was used to measure gen-
eral clinical state. A survival analysis of data from the first 12 months of the study demonstrated no significant difference between the groups on either measure of relapse. Three patients from each group required hospitalization. Further, of the seven patients who dropped out of the study, five were from the 25-mg group.

SCL-90 measures taken 1 month into the study indicated significantly higher levels of distress (obsessive-compulsive symptoms, interpersonal sensitivity, depression, phobic anxiety) for the 25-mg group. Similar results were obtained at 3 months, when higher levels of motor retardation and akathisia were also found for this group.

Marder and colleagues (1987) reported the 2-year outcome of this study. Again, there was no group difference in the number of serious relapses (44% for the low-dose and 31% for the standard-dose group), but there were significantly more mild relapses in the low-dose group (69% over 2 years) as compared to the standard-dose group (36%).

Johnson and colleagues (1987) reported a dose-reduction study using flupenthixol decanoate, another long-acting intramuscular neuroleptic. They studied 59 patients who had been stable for at least 6 months on a dose of no more than 40 mg every 2 weeks (fluphenazine dose equivalent: 25 mg/2 weeks). Patients were randomly assigned to one of two groups. Group A continued on their pretrial dose (standard-dose) for 12 months followed by 24 months on half this dose (low-dose). Group B received half their pretrial dose (low-dose) for the full 36 months of the study. The mean dose for group A for the first 12 months (standard-dose) was 9 mg (range = 4–20 mg), and the mean dose for group B (low-dose) was 6 mg (range = 1.7–10.0 mg).

Side effects were measured by the Extrapyramidal Rating Scale (EPRS; Simpson et al. 1964), social functioning by Stevens Social Scale (SSS; Stevens 1973). Relapse was defined as an increase of more than 3 points on the BPRS or a score of 3 or more on the CGI. In the first 12 months, there were significantly more relapses in the low-dose group (32%) compared to the standard-dose group (10%). On the other hand, there was some tendency in the low-dose group for less tardive dyskinesia, fewer extrapyramidal side effects, and greater improvement in social functioning. By the end of the 3-year followup period, 56 percent of group A and 70 percent of group B had relapsed, and 75 percent of the patients had had their medication increased to at or above the prestudy dose level. Johnson and colleagues concluded that the risk of relapse was considerably increased in the low-dose group.

This study presents several difficulties in interpretation. Many subjects were already on a low dose of medication before entering the study. Some subjects in group A when on standard dose appear to have received lower doses than some of those in group B. Also, the group B patients had a mean of 12.3 months of inpatient care before the study compared with 7.4 months for those in group A. While the authors state that this difference was not significant, it does seem to suggest that group B subjects may have had more severe illnesses. Similarly, the number of relapses in the first 6 months on low dose was higher for group B than for group A. This difference was not discussed but suggests that group B may have been less well stabilized at entry to the trial.

Hogarty and coworkers (1988) reported a 2-year followup of 70 patients who met study criteria for stabilization of illness symptoms. Patients were randomly assigned to either a variable low dose of fluphenazine decanoate (3.82 ± 2.1 mg/2 weeks) or to a variable standard-dose (25 ± 25.7 mg/2 weeks) treatment. Post hoc analysis revealed that the mean standard dose decreased gradually over the period of the study. Criteria for relapse were a change from "mild" or "not present" to "moderately" or "markedly severe" on BPRS psychotic items and an unanimous clinical decision. Other ratings included social adjustment, subjective symptomatology, and extrapyramidal side effects. There was no significant difference in relapse rate at 1 year between standard- (13.8%) and low-dose (21.9%) groups or at 2 years (24% and 30%, respectively). In addition, 45 percent of standard-dose patients and 49 percent of low-dose patients experienced what was termed a "minor episode," defined as a less severe emergence of schizophrenic symptoms that responded quickly to adjustment of the dose and/or increased surveillance. There were significantly fewer extrapyramidal side effects in the low-dose group at 1 year, although scores for both groups were in the very mild range. At 2 years, these differences had disappeared. Among the nonrelapsed survivors at 1 year, the low-dose patients reported less distress, were less emotionally withdrawn, and were assessed as having bet-
ter overall functioning. By 2 years the low-dose group reported more increased frequency of mild symptoms than the standard-dose group and were better adjusted socially.

Summary and Conclusions

This review highlights the differences in approach to studying the efficacy of low-dose maintenance medication in schizophrenia. The mean age of subjects ranged from 23 years in Goldstein and colleagues (1978) to 42 years in Johnson and colleagues (1987), and the sex distribution of the samples also varied considerably. A lack of standardization in the definition of relapse renders comparison between studies difficult (see table 1). In some studies, no distinction was made between minor exacerbations and full relapse (Kane et al. 1985; Johnson et al. 1987). In one case (Goldstein et al. 1978), relapse was determined on the basis of rehospitalization alone.

The duration of studies varied between 6 weeks (Goldstein et al. 1978) and 2 years (Marder et al. 1987; Hogarty et al. 1988), and the subjects in Johnson and colleagues’ (1987) study were followed up for 3 years. While clinical outcome was always measured, some studies did not measure indices of social function or side effects (Goldstein et al. 1978; Marder et al. 1984). Finally, the amounts of the low doses employed raise some difficulties. Some studies (Kane et al. 1979, 1985; Hogarty et al. 1988) used doses below 5 mg every 2 weeks, which is reported to be the minimum effective dose (Teicher and Baldessarini 1985). In one study (Johnson et al. 1987) some patients in the low-dose group appear to have received a higher dose than some of those in the standard-dose group. In another study (Goldstein et al. 1978) determination of relapse was not made blind to dosage condition.

Despite these difficulties, a number of important findings emerge. First, there is no evidence indicating a higher risk of relapse in the low-dose range of 5 to 10 mg every 2 weeks. Relapse rate increases when dose levels are reduced below 5 mg every 2 weeks. However, even then, it appears that a temporary dose increase will alleviate symptoms and terminate the relapse episode. It is recommended that these short-term relapses that respond to a temporary increase in dose be termed “minor episodes” and be considered separately from relapses (see Hogarty et al. 1988). They equate to the “psychotic exacerbations” defined by Marder and colleagues (1987).

Second, the use of a low-dose regimen generally results in lower subjective ratings of psychological distress. Third, side effects are marginally reduced. While the small size of this reduction is somewhat surprising, it should be noted that the rating scales used to measure extrapyramidal side effects were largely derived from neurological scales designed to measure a much greater range of pathology. The three studies (Kane et al. 1983; Johnson et al. 1987; Marder et al. 1987) that specifically measured tardive dyskinesia all reported that this was reduced in the low-dose groups. The emotional and cognitive side effects of antipsychotic drugs are difficult to measure, but patients’ self-reports suggest that there may be considerable dysphoria associated with these medications (Emerich and Sanberg 1991). Those studies that included assessment of subjective distress (Marder et al. 1984; Hogarty et al. 1988) reported that this was less for patients receiving low-dose treatment. Finally, there appears to have been a slight improvement in social and occupational functioning in the studies that included these measures.

It is of course important to recognize that these results were obtained from studies of research patients who tend to be more cooperative and compliant than patients seen in routine clinical practice. In this latter group, early detection of relapse may be more difficult due to factors relating both to patient characteristics and the exigencies of service delivery. The patients in all of the studies except Goldstein and colleagues’ (1978) were clinically stable outpatients. These patients are likely to have a lower risk of relapse than patients who have recently been treated for an acute psychotic episode or those who would not meet research criteria for remission or clinical stability.

While the studies described above do provide some evidence for the efficacy of lower doses of maintenance medication, a definitive study is still lacking. Such a study may require a significant change in the methodology employed thus far and perhaps even reconsideration of a within-subjects design. However, any such design would need to consider the issues of absorption, distribution, and release of fluphenazine decanoate over time, because with chronic administration these factors could themselves become confounding variables. An adequate lag period (about 10 weeks) would need to be introduced to minimize carry-over effects. A within-subjects design that included these conditions might circumvent the difficulties associated with the compilation of experimental groups.
The findings of the studies reported here and the recent developments in psychopharmacology have important implications for clinicians. There is now good theoretical and empirical evidence for the efficacy of lower dose regimens in stabilized outpatients. Such regimens are generally tolerated better than standard doses as measured on a variety of parameters, including emotional well-being, extrapyramidal side effects, and social functioning. The lower incidence of tardive dyskinesia with low-dose treatment is particularly important. These advantages come at the cost of a higher risk of psychotic exacerbations, although these may be treated quickly and effectively with a temporary increase in medication. Low-dose treatment therefore requires an increased frequency of contact and closer surveillance. The possibility that additional psychotic relapses may have an adverse effect on prognosis (Wyatt 1991) must also be considered.

The pharmacological data show wide variation in serum levels between individuals, which reinforces the need for dosages to be flexible and tailored to meet each patient’s needs. There is now a need to identify those individual patient characteristics that might help to predict optimal dosage. Some preliminary suggestions based on measures of information-processing ability have been made (Asarnow et al. 1988). Clinical variables are clearly also important, and much more specific research in this area is needed.

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