Maintenance Medication for Schizophrenia: Strategies for Dose Reduction

by Nina R. Schooler

Abstract

Balancing the demonstrated effectiveness of antipsychotic medication for long-term maintenance treatment of schizophrenia with the risk of developing tardive dyskinesia (TD) has led to attempts to reduce dosage. Research using two methods is reviewed in this article: continuous low dose and intermittent or targeted medication. Both methods require monitoring of patients and treating decompensations with medication. Studies reviewed in this article indicate that these strategies are feasible for many patients, but are associated with higher risk of relapse than maintaining an established moderate dose. For low dose, relapse rates are higher if treatment continues for a second year, if dosage is very low, or if patients are not stable. However, low dose administration also leads to reduced adverse effects (including TD in at least one study) and improved subjective well being. Targeted medication leads to reduction of administered dose and side effects but to no clear benefit in terms of TD or social functioning. No studies reported to date have compared these strategies directly. Ongoing and future research will do this and identify those patients for whom these strategies can be implemented without increased relapse risk.

Medication Efficacy During the Maintenance Phase

The efficacy of antipsychotic medication for long-term maintenance treatment of schizophrenia has been established both through formal clinical trials and clinical experience accumulated during the 30 years that these drugs have been available. Davis (1975), in his review of the experimental literature, concluded that the risk of relapse increased to 52 percent without maintenance medication compared to 20 percent with continuation of treatment.

Clinical experience appears to validate this conclusion. A familiar clinical scenario involves a patient whose acute symptoms improve with antipsychotic medication in hospital. The patient is discharged to outpatient treatment that includes continuation of medication. The patient attends the outpatient clinic for a time, then becomes more erratic in attendance. He or she experiences an exacerbation of symptoms and is readmitted to the hospital. On questioning, the patient or family reports that during the month or so prior to admission, the patient had not been sleeping well, had become increasingly withdrawn or irritable, and had stopped taking medication. The clinical team concludes that medication noncompliance triggered the relapse and, on the subsequent discharge, strongly warns the patient and the family that medication must be taken in order to avoid another relapse. The assumptions of this clinical recommendation are that antipsychotic medication is effective in preventing relapse and that the sequence of events that led to rehospitalization was noncompliance followed by symptom exacerbation.

A series of experimental studies conducted during the 1970's tested the hypothesis that ensuring regular administration of antipsychotic medication would significantly reduce the risk of relapse. Fluphenazine deca-
nate (FD), a long-acting phenothiazine administered via depot injection at intervals of 2 to 4 weeks, served as the treatment arm defining regular medication administration. Mirror-image studies comparing patients’ hospitalization experiences subsequent to starting long-acting injections to a similar period prior to initiating depot injections reported dramatic reductions both in number of hospitalizations and amount of time in hospital (Johnson and Freeman 1972; Marriott and Hiep 1976). These naturalistic studies, the kind of clinical observation described above, and the potential public health importance of reducing rehospitalization by as much as 50 percent provided the stimulus for comparisons of depot fluphenazine (FLU) to oral antipsychotic medication. Most frequently the oral medication used was FLU hydrochloride. Treatment duration ranged from 12 months to 2 years. As reviewed by Schooler (1985), none of the studies found a significant difference in relapse rate in patients treated with oral or with injectable medication. The studies did vary in the overall relapse rates, ranging from 14 percent in a sample drawn from a clinic with stable outpatients to 40 percent in a sample drawn from a recently discharged population.

The clinical implications of these findings are substantial even though they are not as hypothesized. First, it is clear that some patients do experience a relapse or symptom exacerbation while receiving neuroleptic medication. Medication discontinuation does not always precede symptom exacerbation. For some patients, the process of relapse may begin while they are taking medication and their failure to continue to take medication is a consequence of the relapse process rather than its cause. The advantages of depot medication for maintenance treatment are that it eliminates covert noncompliance and, in the case of a relapse, eliminates noncompliance as a possible cause.

**Rationale for Dosage Reduction Strategies**

Given the recognition of the need for antipsychotic medication in maintenance treatment for schizophrenia and the fact that medication does not eliminate the risk of relapse, research attention turned toward strategies that would maximize the benefits and minimize the problems with long-term medication administration. Is there an amount of antipsychotic medication that would prevent relapse as effectively as conventional doses but that might minimize some of the negative effects of neuroleptic drugs?

The most serious adverse effect of long-term neuroleptic exposure is tardive dyskinesia (TD); however, parkinsonian side effects and the possibility of neuroleptic-induced depression, akinesia, and akathisia, as well as the frequent complaints from patients that the medication makes them “feel bad,” have provided a major impetus for research designed to identify treatment strategies that would reduce medication exposure and identify patients who might be particularly good candidates for such treatments.

Attempts to establish minimum dosage requirements for maintenance treatment have used three approaches: (1) exploration of the relationship between dosage and relapse in those reported clinical trials that allow such analyses; (2) conduct of prospective studies comparing patients undergoing dosage reduction to controls maintained on stable doses of medication; and (3) random assignment of patients to different dose levels, for comparison of dosage ranges or of an “intermittent or targeted treatment” strategy to standard dosage.

None of these methods is perfect. Reanalysis of data from existing trials is limited because the dosage used by clinicians employing flexible dosing strategies may have been influenced by a variety of factors other than the precise dosage administered. Dosage changes may not have been carried out in a systematic, objective, or reproducible fashion.

In prospective studies of dosage reduction, elapsed time may be a confounding factor. Even if patients discontinue medication completely, a psychotic relapse may not occur for several weeks or months so that the relapse may not be attributable to the dose at which it occurred. In such studies, it is difficult to determine minimal dosage requirements because of the unpredictable timeframe in which a subsequent relapse may occur.

The third strategy, using concurrent comparison groups, can minimize some of these concerns. However, the fixed doses or dosage ranges studied have generally been selected arbitrarily because of the lack of data regarding bioavailability or prior evidence regarding minimal effective doses. Such designs will not necessarily identify the smallest effective dose for a given individual but will generate group response data.

The goals of this article are to review the experimental evidence from clinical trials for two long-term strategies that address the question of the minimal dose of antipsychotic medication that will be effective to prevent relapse and enhance functioning in schizophrenic patients. These strategies are continuous low-dose...
and intermittent or targeted medication. A third potential strategy, the fixed-length drug holiday, is only a long-term strategy if applied repeatedly. To date, this approach has not been employed in clinical trials, and, therefore, will not be included.

Continuous Low-Dose Medication

The use of continuous low-dose pharmacotherapy is predicated on the assumption that antipsychotic medication can be maintained at a substantially lower dose during periods of symptom remission or stable symptomatology than is required to treat acute symptomatology. Further, a second assumption in many of the longer term outpatient studies is that the increased dose necessary to treat emergent symptoms can be reduced to a lower dose again once symptoms have remitted.

Caffey et al. (1964) conducted the first controlled dosage-reduction study among hospitalized inpatients and found that patients whose dose was reduced to three-sevenths (43%) of their original dose experienced a 15 percent relapse rate within 4 months as compared to a 45 percent relapse rate for those patients receiving placebo (PBO) and a 5 percent relapse rate for those continuing on their original dose. The mean dose of either chlorpromazine (CPZ) or thioridazine that patients had been receiving for at least 3 months before the study began was 350-400 mg/day.

This study differs from the later studies to be reviewed: it was carried out with inpatients rather than outpatients; it used oral medication; and it included a PBO comparison group. The inclusion of a PBO group is valuable because the results in that group make clear that although the relapse rate in the reduced-dosage group is higher than that experienced by patients who continue medication at "standard" dosage, it is lower than that of patients who receive only PBO.

Outpatient studies of low-dose treatment are presented in Table 1. Goldstein et al. (1978) studied the efficacy of two dose levels of FLU enanthate, with and without crisis-oriented family therapy, in 104 recently discharged schizophrenic patients. These predominantly first-episode (69%) patients were randomly assigned to FLU enanthate, 25 mg or 6.25 mg i.m. every 2 weeks, and studied for 6 weeks following a brief 14-day hospitalization. Relapse was defined as the need to alter medication substantially or to rehospitalize the patient. Ten percent experienced a relapse within the 6 weeks following discharge; 24 percent of those in the 6.25 mg/no therapy increased exacerbations in low dose (69%) compared to standard dose (36%).

Table 1. Maintenance low-dosage treatment studies

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<td>5/10</td>
<td>5.5-20</td>
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<tr>
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<td>Standard 25</td>
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</table>

¹All studies except Johnson used injectable long-acting fluphenazine (FLU) administered biweekly. The Johnson group used flupenthixol decanoate, a long-acting injectable medication not marketed in the United States, but widely available in Europe and Canada with 40 mg b.i.w. equipotent to 25 mg FLU decanoate.
²Increased exacerbations in low dose (69%) compared to standard dose (36%).
³Increased minor episodes in low-dose, high-EE patients.
apy condition relapsed as compared to none of the 25 mg/therapy patients. The low dose/therapy and the standard dose/no therapy groups had relapse rates of 9 percent and 10 percent, respectively. Although this study involved a relatively brief period of controlled treatment, it is a classic study in suggesting the potential additive effects of medication and a psychotherapeutic strategy such as crisis-oriented family therapy in a community setting.

Kane et al. (1983, 1985) have reported results from a 1-year, random assignment study of different dosage ranges of FD (standard dose 12.5–50 mg compared to low dose 1.25–5 mg every 2 weeks) in stable schizophrenic outpatients. At the end of 1 year, the cumulative relapse rate (defined by the psychotic items of the Brief Psychiatric Rating Scale [BPRS; Overall and Gorham 1962; Woerner et al. 1988]) on the low dose was 56 percent compared to 7 percent for the standard dose. An intermediate dose (2.5–10.0 mg every 2 weeks) was also studied and produced an intermediate cumulative relapse rate of 24 percent (Kane et al. 1986). Despite the significantly higher relapse rate among patients receiving the low-dose treatment, most of the patients who did relapse were re-stabilized with temporary dosage increases and without rehospitalization. On average, patients had returned to their baseline state within 9 weeks of resuming standard-dose treatment.

Further, patients receiving the low dose showed better functioning on some measures of psychosocial adjustment than the patients treated with the standard dose. Interestingly, patients receiving the low dose also showed less emotional withdrawal, blunted affect, tension, and psychomotor retardation. These statistically significant differences were not of such magnitude as to be obvious in individual patients. However, these findings emphasize the potential importance of the continuing presence of parkinsonian side effects even during the maintenance phase of treatment and highlight the complexity of assessing so-called negative symptoms.

Marder et al. (1984, 1987) studied 66 male outpatients in a Veterans Administration Hospital, who were randomly assigned to 5 mg or 25 mg of FD administered every 2 weeks. Patients were followed for 2 years and were maintained on the assigned fixed dose of 5 or 25 mg as long as they “did well.” The investigators defined three levels of unfavorable outcome that could lead to a dosage change. When patients had an increase of three or more points on the BPRS cluster scores for thought disturbance or paranoia they were considered to have had a “psychotic exacerbation.” These exacerbations were relatively mild and seldom led to rehospitalization, but the clinician was allowed to increase the dose up to 10 or 50 mg for the respective groups. When patients’ symptoms could not be controlled adequately within this range, they were considered to have had a “relapse.” The third level of outcome was rehospitalization. In a preliminary report based on the first 50 cases in the study, at the end of 1 year, the “exacerbation” rate was almost identical in the two treatment groups (35% on 5 mg and 43% on 25 mg). The relapse rates (shown in table 1) were lower (22% vs. 20%) but not significantly different between the two groups. During the second year, however, the two doses produced different rates of exacerbation: 69 percent experienced an exacerbation on 5 mg compared to only 36 percent on 25 mg. When the outcome of “relapse” is considered (indicating those patients who could not be controlled by the dosage increase), then the two treatments still produced similar results after 2 years: 44 percent relapsed on the lower dose and 31 percent on the higher dose. The results of this study highlight the importance of a long-term perspective—at least longer than 1 year.

Johnson and his colleagues (1987) compared a 50 percent dose reduction to continuation of current dose in 59 well-stabilized patients receiving flupenthixol decanoate at a dose of no more than 40 mg every 2 weeks for over 1 year. That dosage is considered equipotent to 25 mg of FD (Trueman and Valentine 1974). In terms of initial dosage requirements, the patients are quite similar to those included in the Marder (1984, 1987) study. Patients were randomly assigned to either continuation of initial dosage or double-blind substitution of a 50 percent dosage for 12 months. During this period, there was a significantly higher relapse rate in the half-dose group: 32 percent versus 10 percent. At the end of 12 months, patients initially assigned to full dose had their doses reduced to 50 percent and all patients were followed for an additional 2 years. Seventy percent of patients followed on reduced dose for 3 years experienced a relapse; 56 percent of those followed on reduced dose for 2 years relapsed. Perhaps the most striking clinical finding is that between 76 percent and 78 percent of all patients had resumed their former full-dose level by the end of the followup period.

In contrast to the studies that employed more drastic dosage reduction, there were no significant differences in acute extrapyramidal side effects (EPS)—tremor, akathisia, ri-
rigidity, and hypokinesia. The levels of all these side effects rose in the full-dose group and fell in the reduced-dose group, but the differences were not statistically significant. Comparisons of social functioning and psychopathology between the groups are less clear but suggest some advantages for the reduced-dose group in social functioning at the end of 1 year, especially in "relatives' anxiety."

Hogarty et al. (1988) have reported on 70 stable schizophrenic outpatients living in high- or low-expressed emotion (EE) households who were randomly assigned, double-blind, to receive a standard dose of FD (mean 25 mg every 2 weeks) or a minimal dose representing approximately 20 percent of the dose prescribed (mean 3.8 mg every 2 weeks).

After 1 year, the relapse rate for the patients receiving standard dose was 14 percent as compared to 22 percent for the minimal-dose group; after 2 years the relapse rates were 24 percent and 30 percent, respectively. No significant differences between dose groups at either time point or between EE levels were observed. However, within the standard-dose group, patients in high-EE households had a lower relapse rate (43%) than patients in low-EE households (83%).

Four behavioral side effects and a total score, as well as 11 central nervous system side effects and a total score, were evaluated. After 1 year, minimal-dose recipients clearly experienced significantly fewer EPS than did standard-dose recipients, although ratings for both groups were in the very mild range. However, at 2 years (except for nonsignificant trends on muscle rigidity and the total behavioral side effects scores favoring standard dose) all differences had disappeared. The investigators attributed this to the fact that standard-dose recipients received decreasing doses during the second year. Further, among 11 patients participating in the study who had evidence of TD, relapse rate was not higher with the minimal dose than with the standard dose. The investigators also reported that at the end of 1 year minimal-dose recipients were less emotionally withdrawn and psychomotorically retarded than were standard-dose recipients, in agreement with the report by the Kane et al. (1986) group. In the second year, minimal-dose, high-EE-household patients experienced more minor episodes. The minimal-dose patients had somewhat higher symptom levels—not surprising in view of the increased number of minor episodes—but they were ranked as better socially adjusted, not only in their relationships with family members, but also in employment and overall adjustment.

Results from these studies suggest that dosage reduction is feasible for some stable schizophrenic outpatients. If the reduction is large enough, it can lead to a diminution in adverse effects and improvement in some subjective and nonsubjective measures of well-being. However, the risk of psychotic exacerbation does increase, earlier with very low dosage (Kane et al. 1986) or less stable patients (Goldstein et al. 1978) and in the second year even with moderately low dosage (Marder et al. 1987; Hogarty et al. 1988). The Johnson et al. (1987) study stands in contrast to this orderly progression. The length of stabilization is apparently the longest of any study in this group and the dosage reduction was the smallest. Yet a significant increase in relapse was seen within 1 year in these stable patients. Although these investigators did not use injectable FLU, they did use an injectable medication and the dosages reported were in a range considered equipotent.

Only the Caffey et al. (1964) and Kane et al. (1986) studies compared more than two dose levels. In both of these studies, a linear relationship between dose and relapse rate was observed. In all of the studies, relapse or symptom exacerbation was higher in the low-dose than in the higher dose group—in most cases significantly so. None of the studies reported to date have examined multiple fixed doses or multiple dosage ranges. An ongoing study is comparing four fixed doses of haloperidol (HPL) decanoate (25, 50, 100, and 200 mg monthly) in schizophrenic patients who have been clinically stable for at least 3 months (P. Bookman, personal communication, 1990). The results of this study will be important because it includes a dose (200 mg per month) that is higher than the doses administered in any of the trials reported to date as well as a dosage level that is comparable to some of the lowest doses studied.

Given the increased risk, but not the certainty of relapse seen with dosage reduction, the important question that remains to be addressed is which patients are good candidates for lowered dose and, further, how low? In several of the studies, an explicit criterion for inclusion was clinical stability on an already relatively low dose of medication. None of the studies reviewed have included patients who are stable at higher dose ranges. The logic of including patients who have been stable at low doses is clear, but it may be that clinically valuable opportunities for dosage reduction, albeit not to 10 or 20 percent of origi-
The term intermittent treatment has administration schedules that incorporate medication-free days (e.g., 3 days of each week; McCreadie et al. 1980). Generally, the goals of such fixed intermittent treatment schedules are to simplify medication administration for nursing staff and patients and to reduce costs without reducing medication efficacy. A stated secondary goal may be to reduce side effects such as TD.

Intermittent or targeted treatment is also used to refer to the use of medication only during periods of incipient relapse or symptom exacerbation rather than continuously. The goals of this strategy include reduction of the risk of TD by reducing long-term medication exposure for patients who are receiving maintenance treatment while limiting the risk of relapse. A further goal may be to improve social functioning through reduction of neuroleptic-induced side effects such as akinesia and akathisia. Neuroleptic treatment only when "needed" is a long-term strategy that depends on both the existence of a prodromal period that allows for intervention with medication to prevent relapse and a strategy for careful clinical monitoring to detect prodromal symptoms so that medication can be introduced.

Targeted treatment is based on the assumption that patients require neuroleptic medication only during times of symptom exacerbation and that introduction of medication during the prodromal period can avert the development of more florid symptoms. According to this model, the advantage of continuous medication administration is that it ensures the availability of medication when the need arises. In the targeted or intermittent treatment model, the reduction of total medication exposure over time reduces the risk of TD.

The successful use of intermittent or targeted treatment depends on the accurate identification of times when medication needs to be administered. In a retrospective study of newly hospitalized patients and their family members, Herz and Melville (1980) found that early signs of schizophrenic decompensation could be recalled. The questionnaire included items dealing with sleep disturbance, depression, reduced attention, and changes in energy level, as well as some psychotic signs and symptoms. Both patients and family members were able to describe signs and symptoms. Further, there was substantial agreement between them regarding the nature of these early signs. Herz and Melville suggest that these signs could be used prospectively as indicators of when medication needs to be administered.

The Early Signs Questionnaire (Herz and Melville 1980), developed by these investigators, provides a systematic method for detecting periods when nonpsychotic signs and symptoms occur and, by implication, when medication should be introduced. However, whether early signs inevitably lead to full episodes of symptom exacerbation, or whether the waxing and waning of such early signs is a characteristic of schizophrenic illnesses that is not inevitably associated with relapse, has not been tested systematically.

A second requirement for the use of a targeted medication strategy is the creation of a treatment structure that incorporates an ongoing therapeutic relationship for patient monitoring and support. Patients need to be educated regarding the nature of early signs and their implications. They must also be seen frequently in order to ensure that early signs of relapse are detected and medication started before a major symptom exacerbation has occurred. Family members and significant others also...
need to be aware of the variable course of schizophrenic illnesses, the nature of prodromal signs, and the importance of their identification in the targeted or intermittent treatment model. A point stressed by one of the groups working with this approach (Carpenter and Heinrichs 1983) is that it is not a "no-medication" strategy but instead a way of using medication.

Four groups have reported on intermittent or targeted treatment strategies. Table 2 summarizes the comparative design features of the studies and their results in terms of relapse rates.

Herz and his colleagues have reported two studies of intermittent medication. The first (Herz et al. 1982) was an open pilot study of 19 schizophrenic patients who had been stable outpatients in remission for at least 6 months and who had not shown suicidal or assaultive behavior during the preceding 2 years. Patients participated in weekly group therapy sessions led by a psychiatrist. Initial sessions focused on early signs of relapse, the need for medication during the prodromal phase, and monitoring of life events that might precipitate relapse. Families,

<table>
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<tr>
<th>Study characteristics</th>
<th>Herz et al. (in press)</th>
<th>Carpenter et al. (1990a, 1990b)</th>
<th>Hirsch et al. (1987)</th>
<th>Jolley et al. (1989, in press); Pietzcker et al. (1986); Muller et al. (in press)</th>
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<td>Individual case managers</td>
<td>Monthly RN/MD visits</td>
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<td>Random/nonblind</td>
<td>Random/FLU decanoate double-blind</td>
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Study results:

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<th>Dosage</th>
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<td>62</td>
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¹Treatment was 24 months in all studies.

²¹ = low, e.g., < 300 mg chlorpromazine (CPZ); ² = moderate, e.g., 301–600 mg/day.

³Mg/day expressed in CPZ equivalents.

⁴Mean total dose expressed in HPL equivalents.

⁵Cumulative dosage over 2 years in (1,000 grams) CPZ equivalents.
Prodromal episodes were treated by discontinuing double-blind medication and instituting known neuroleptic medication. Once the patient was restabilized, known medication was gradually decreased as double-blind medication was titrated upward. Intermittent medication patients received significantly less medication, measured both as average daily dose (150 compared to 290 mg/day CPZ equivalents) and percent time on medication (27 to 100).

Significantly more patients in the maintenance medication group (72%) completed the 2-year study course than in the intermittent group (38%). Intermittent group patients experienced both more and longer prodromal episodes. However, although the total relapse and readmission rates favored the maintenance group, neither of these differences was statistically significant. Life table analyses using time to first prodromal episode and time to relapse were statistically significant, favoring the maintenance medication group. Assessment of psychopathology, measures of side effects, and ratings by significant others showed few differences, but when differences did occur they favored the continuous medication group.

The second group that has reported on this strategy, Carpenter et al. (1987), randomly assigned recently discharged and stabilized schizophrenic patients to either targeted medication in the context of psychosocial intervention (n = 21) or to standard maintenance medication (n = 20) following a 28-day drug-free period. Treatment was not blind and continued for 2 years. All patients were seen weekly. Patients in the continuous medication group were seen by nursing personnel and, on alternate visits, briefly by a pharmacotherapist. A minimum daily dose of 300 mg CPZ equivalent was administered. Patients in the targeted medication group were assigned to a primary therapist who conducted weekly individual sessions designed to establish a close interpersonal bond and focused on individualized early prodromal signs and the role of environmental stress (Carpenter and Heinrichs 1983). Families/significant others participated with the patient in a six-session program that reviewed the nature of psychosis, precipitants, stressors, strategies for stress reduction, and identification of early signs of relapse. Cooperation of families in prompt intervention was also emphasized. When prodromal signs were identified, patients received antipsychotic medication at therapeutic doses. As soon as the patient was restabilized, medication was discontinued.

Patients randomized to targeted treatment received medication 31 percent of the time and as a result received significantly less medication during the 2 years. Despite this significant dosage reduction, targeted medication recipients did not experience significantly more hospitalizations over the entire 2-year study course. However, they were significantly more likely to be hospitalized during the first 6 months of treatment. Psychopathology and psychosocial functioning at 1 and 2 years did not differ between the groups.

A second report based on 116 newly discharged patients has been completed by this group (Carpenter et al. 1990a, 1990b). After a 4- to 8-week stabilization period and a 4-week medication discontinuation phase, patients were randomized to continuous treatment and targeted medication groups for 2 years. As in the first study, treatment was not blind. In this larger study, both groups received the enriched psychosocial treatment program described
above. Treatment and assessment procedures were similar.

As in the first study, the significant reduction in dosage achieved with the targeted strategy reflected the reduction in proportion of days on medication: targeted patients received medication 52 percent of the time and continuous patients received medication 90 percent of the time. However, significantly more patients in the continuous treatment group completed the full 2-year study. Further, patients on targeted treatment experienced significantly more clinical decompensations, even when controlling for shorter time in treatment, and in general continuous medication group patients were less likely to be hospitalized during the 2-year period. Despite the significant differences in decompensation and hospitalization, cross-sectional comparisons of psychopathology at 1 and 2 years, although favoring the continuous treatment group, were not statistically significant. For the reduced sample still in treatment after 2 years (targeted \( n = 21 \), continuous \( n = 36 \)), the extent of employment and quality of employment were significantly better among continuously treated patients.

The third group (Hirsch et al. 1987; Jolley et al. 1989; Jolley et al., in press) studied 34 schizophrenic outpatients who had been clinically stable for at least 6 months and who had been on stable doses of injectable FD for at least 2 months. Under double-blind conditions, patients were randomly assigned either to continue medication or have PBO substituted for 2 years. Patients were seen every 4 weeks—alternately by a psychiatrist in the clinic and a psychiatric nurse at a home visit. At the outset of the trial, patients and families participated in a 1-hour teaching session focused on schizophrenia and early signs of relapse. Prodromal signs or relapse were treated by the addition of open, oral HPL.

There were no differences in numbers of patients completing the first year of the trial in the two groups (Jolley et al. 1989). Significantly more patients in the intermittent treatment group (76%) experienced prodromal episodes than in the continuous treatment group (27%). Relapse was also significantly more frequent in the intermittent treatment group (using a one-tailed significance test) but number of hospitalizations did not differ. Patients in the intermittent treatment group received significantly less total medication, including both FLU injections and oral HPL. EPS, specifically akathisia, gait abnormality, parkinsonism, and "nonliveliness," were significantly reduced in the intermittent treatment group after 6 and 12 months.

The report of second-year outcome (Jolley et al., in press) provides a somewhat different picture. Dosage administered was still lower in the intermittent treatment group but both relapse and rehospitalization were significantly greater. EPS were significantly lower in the intermittent group, but the trend toward a lower rate of TD observed at 1 year was not seen in the second year.

Pietzcker et al. (1986) and Muller et al. (in press) have conducted a trial comparing prophylactic maintenance medication, neuroleptic crisis intervention, and prophylactic early neuroleptic intervention in 365 patients at four sites. The maintenance medication and early intervention treatments are quite similar in design to the maintenance and targeted or intermittent treatments studied by the Herz, Carpenter, and Jolley groups. This study, however, includes a third treatment condition, "neuroleptic crisis intervention." Patients in this group receive medication only when a relapse occurs, rather than at the identification of prodromal symptoms. Thus, this study directly addresses the question of whether attention to prodromal symptoms can indeed prevent the development of an actual relapse. Patients were recruited at the point of hospitalization and followed prospectively until a 3-month postdischarge stabilization. Preliminary results comparing the three groups 6 months after randomization (\( n = 48 \)) indicate no relapses on maintenance medication, 11 percent with early intervention, and 31 percent with crisis intervention (Pietzcker et al. 1986; Muller et al., in press).

Longer-term results of this study are summarized in table 2. At both 1 and 2 years there was a significantly higher relapse rate in the early intervention as compared to the maintenance treatment group. The rehospitalization rate was not significantly greater in the first year (23% compared to 16%) but did reach significance in the second year (37% compared to 24%). Despite these differences in course reflecting psychopathology, there were no differences in the rates of employment: approximately 50 percent were employed in both groups.

The work of these investigators is remarkably similar in goals, design, and execution. All experimental designs involved identification of stabilized schizophrenic outpatients or a period of prospective stabilization ranging from 8 weeks to 6 months. With the exception of the 1982 pilot study by Herz, all used comparison groups of patients randomly assigned to continuation of medication. In both the Herz et al. (in press) and the Jolley et al. (1989) and Jolley et al. (in press) trials, treatment was administered under double-blind con-
tions. Herz used four neuroleptic drugs, including FD. Medication was restricted to FD in the Jolley study, thereby ensuring that relapse in the continuous medication group could not be due to covert noncompliance. Neither the Carpenter et al. (1987) nor the Pietzcker et al. (1986) studies was carried out under blind conditions and both are subject to the criticism that patients in the targeted medication group received greater surveillance and were therefore more likely to receive medication at the first indication of prodromal signs than patients who were known to be receiving active medication. The design of the Carpenter et al. (1987) study incorporated a difference in level of psychosocial treatment and surveillance between the two groups. Their second, larger study was designed to provide both groups with the same intensive psychosocial support. In this context, the question of whether there was a lower threshold for intervention in the targeted group has to be considered. The Pietzcker et al. (1986) study included a control group for early intervention with a group that received crisis intervention only, but the absence of blind evaluation raises similar questions.

All the studies included some psychosocial supports beyond those usually available in the systems where the treatment was being delivered. In all cases this involved attention to family members or other people in patients’ home milieu who were, or could become, sensitive to emerging symptomatology and the need for intervention with medication. The amount of psychosocial support varied: weekly group support sessions (Herz et al., in press); weekly individual psychotherapy sessions (Carpenter et al. 1990a, 1990b); a single educational session for patients and families as well as routine monthly visits with the physician or nurse (Jolley et al. 1989); a special outpatient clinic (Pietzcker et al. 1986).

All groups studied treatment over a 2-year period. Length of treatment is of substantial importance in understanding the impact of dosage reduction strategies in maintenance treatment of schizophrenia. For example, Marder and his colleagues (1987) found no difference in psychotic exacerbations between 5- and 25-mg doses of FD in the first year, but found a statistically significant and clinically meaningful difference after 2 years that favored the higher dose—36 percent of patients who received the 25-mg dose experienced clinical exacerbations compared to 69 percent on the 5-mg dose.

The reports from Jolley and his colleagues on intermittent treatment are similar. In the first year there were no differences in rehospitalization, but there was a trend toward an increase in relapses ($p > 0.05$ but $< 0.10$). By the end of the second year, using life table analysis, both relapse and rehospitalization were significantly greater in the intermittent treatment group. Inspection of the survival analyses suggests that relapse and rehospitalization began to diverge toward the end of the first year and continued this trend into the second year. Inspection of survival analyses from both the Herz et al. (in press) and Carpenter et al. (1990a, 1990b) groups suggests that the differences between the two treatments emerge earlier. Pietzcker and his colleagues (1986) do not present survival analyses, but differences in relapse appear earlier than differences in rehospitalization.

There are a number of characteristics of the studies that could account for these differences in results. First, the patients in the Jolley et al. (1989) and Jolley et al. (in press) studies received injectable FD as did the patients in the Marder et al. (1984, 1987) study of low dose, so that covert noncompliance with treatment in the continuous medication group could not have influenced the results. Further, the time course of relapse following discontinuation of depot injectable medication may well be different from discontinuation of oral antipsychotic medication. Finally, patients in the Jolley et al. (1989) study may have been more stable clinically or able to tolerate some period of time off medication; clinicians referred patients who “they thought might benefit from the brief intermittent treatment approach” (p. 986).

The results of these well-designed and carefully conducted studies suggest that intermittent treatment strategies can be implemented in outpatient maintenance settings. They result in both reduced medication dosage and side effects. However, particularly over an extended period (2 years in this case), this strategy carries an increased risk of the expected prodromal episodes, as well as of relapses and rehospitalizations. Further, there are no consistent benefits of intermittent treatment in terms of social functioning.

**Effects on TD**

The reports of virtually all the studies that examined dosage reduction state that reducing the risk of TD is at least a part of their rationale. However, clinical trials that last 1 to 2 years are a relatively poor context in which to observe a change in incidence, prevalence, or severity of TD. The best estimate of TD incidence (Kane et al. 1988) places it at 3 percent to 4 percent per year. Thus, in
a cohort of 100 patients, 3 or 4 might be expected to develop TD in the course of a year. Detecting a reduction in that kind of rate would require much larger trials than the ones reported.

**Low-Dose Treatment.** Among the studies of continuous low-dose treatment presented in table 1, only Kane and his colleagues (1983) directly assessed TD. They found significantly lower scores on the Simpson Dyskinesia Scale (Simpson et al. 1979) at the end of treatment exposure in the low-dose group. Hogarty and his colleagues (1988) reported that patients with TD were no more likely to relapse if treated with "minimal" dose than if treated with standard dose, but did not report changes in TD as a result of dosage reduction. Marder (personal communication, 1990) found no difference in either total Abnormal Involuntary Movement Scale (AIMS; Schooler 1988) score or specific body areas between low and standard dose after either 1 or 2 years of treatment.

The finding by the Kane et al. (1983) group does not appear robust, particularly in the absence of supporting data from other studies. However, it is unclear whether the absence of reported findings from other trials of low-dose treatment indicates an absence of effect or reflects the fact that other investigators have not yet examined their data. It should also be noted that the low-dose group in the Kane et al. (1983) study received a substantially lower dose than low-dose groups in the other trials.

**Targeted or Intermittent Treatment.** As shown in table 2, all studies reported that the group randomized to receive intermittent treatment did experience reduced medication exposure during the study period. At the end of 1 year of treatment Jolley et al. (1989) found a reduction in the point prevalence of TD (p > 0.05 < 0.10) in the intermittent as compared to the continuously treated group. However, at the end of 2 years (Jolley et al., in press), there was no difference between the two groups. Herz and his colleagues (in press) found no significant differences between the two groups in TD movements at either 1- or 2-year cross-sectional evaluations. However, inspection of the total AIMS scores reveals that the score remained stable for the maintenance group (3.0 at 1 year; 3.05 at 2 years) but was reduced in the intermittent group (2.33 at 1 year; 1.68 at 2 years).

Perhaps the most sophisticated analysis of the relationship between treatment schedule and development of TD has been carried out by Levine et al. (1990) on data from the Carpenter et al. (1990) study. In order to examine development or incidence of TD, these investigators restricted their population to patients who did not have TD at the beginning of the trial. They set a criterion for TD—two successive ratings of mild or greater on the Global Severity scale of the AIMS at any point during the 2-year trial. According to this criterion there was no significant difference between the two treatment groups. Two other measures of TD, indexing severity and persistence of abnormal movements over the 2-year period, also showed no significant differences between the groups. However, there was a significant relationship between dose received and TD in both groups: patients with TD had received higher doses. Further, within the group that received intermittent or targeted treatment, a relationship was found between the number of on-off cycles of medication and all three measures of TD, such that the more cycles a patient experienced, the more likely he or she was to meet the diagnostic criterion and have more persistent and more severe TD movements. Within the targeted group, both an increased number of cycles and higher dose combined to increase the likelihood that patients would develop TD.

These findings are congruent with the report by Jeste and his colleagues (1979) that patients with persistent TD were more likely to have had breaks in antipsychotic drug treatment than patients whose TD remitted. The implications of these findings are that a targeted treatment strategy may reduce the risk of developing TD in patients for whom the strategy "works," that is, those who do not require repeated cycles of medication administration and, therefore, actually receive a substantially reduced dosage of medication.

**Comparison of Low-Dose and Targeted Treatment**

All the studies reviewed have pitted a strategy for dose reduction—either continuous low-dose or intermittent treatment—against a so-called standard or usual maintenance dosage of medication. No completed studies provide a comparison of these two strategies to each other. Such comparison is particularly important because, as indicated above, they are based on somewhat different principles of medication management. An ongoing study, the National Institute of Mental Health Treatment Strategies in Schizophrenia Study, is comparing these two treatments directly (Schooler et al. 1989).

Schizophrenic patients at five sites in the United States who are clini-
plays in the long-term treatment of schizophrenic illness. Symptom exacerbation and relapse are part of the course of such illnesses for many patients. The variable course makes it difficult to tease apart the interacting role of medication and the illness's natural course in individual cases. Only when controlled treatment studies are carried out over a sufficient length of time and with sufficient numbers of patients can the influences of treatment be detected. It appears that intermittent treatment strategies are not clinically viable for maintenance treatment of most schizophrenic patients.

The relative benefits and risks of maintenance pharmacotherapy in general, or alternative strategies in particular, will undoubtedly vary from patient to patient. In addition, it is likely that the relative desirability or efficacy of specific strategies may vary depending on the stage of illness that a given patient is experiencing. The results of long-term, naturalistic followup studies emphasize the heterogeneity of outcome in this illness. Some patients experience a chronic deteriorating course while others may experience a much more benign outcome after 10 or 20 years.

The observed variability in symptom pattern as well as drug responsiveness also argues for clinical judgments with regard to individual treatment plans. The extent to which maintenance medication treatment actually acts as a prophylactic (i.e., preventing a new episode) rather than suppressing continuously present symptomatology may also vary from individual to individual. If this distinction could be made with a reasonably high degree of reliability, it would clearly be useful in establishing the most appropriate treatment strategy.

Impact on Tardive Dyskinesia. On balance, it appears that TD or TD-related movements show little sensitivity to manipulation of dosage or medication administration schedules. Examination of the effects of a brief (6-week) fixed-length drug holiday in 31 schizophrenic patients by Shenoy et al. (1981) revealed no effect on TD. These patients had been maintained for extensive periods on long-acting antipsychotic medications so that it is unclear whether the study period was long enough to detect changes in TD-related movements. A 3-month discontinuation study by Levine et al. (1980), in which increases in TD-associated movements were detected in patients discontinued from oral medication but not from long-acting injectable medication, supports this interpretation. All the studies of low-dose treatments and the Jolley et al. (1989) study of intermittent medication used long-acting injectable medication and it may be that these drugs have properties that make TD-related movements more difficult to detect.

If one were to hazard a clinical recommendation on the basis of the limited data available, it would be that, although medication reduction and discontinuation may appear to be reasonable treatment approaches, they have significant risks. If medication must be started and stopped frequently in order to prevent clinical symptom exacerbation, the effects on TD may be worse than if the patient is simply maintained on medication continuously. Clearly, more data, and particularly more detailed analyses of existing data regarding dosage reduction strategies, are warranted.

Summary

Clinical Efficacy  On balance, studies of medication reduction strategies serve to underscore the important role that antipsychotic medication plays in the long-term treatment of schizophrenic illness. Symptom exacerbation and relapse are part of the course of such illnesses for many patients. The variable course makes it difficult to tease apart the interacting role of medication and the illness's natural course in individual cases. Only when controlled treatment studies are carried out over a sufficient length of time and with sufficient numbers of patients can the influences of treatment be detected. It appears that intermittent treatment strategies are not clinically viable for maintenance treatment of most schizophrenic patients.

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