Relapse and Rehospitalization: Comparing Oral and Depot Antipsychotics

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A review of studies that compared conventional oral and depot antipsychotic medications highlighted the following points. Mirror-image studies in which patients served as their own controls provided evidence of substantial benefit for depot injectable medications. The randomized clinical trials did not, in general, support the findings of significant decrease in relapse rates between these 2 routes of administration. Across the studies reviewed, the 1-year relapse rate for long-acting depot medication was 27% compared with 42% for patients who received oral medication. The 27% risk of relapse in patients who received guaranteed depot medication suggests that relapse is not always driven by noncompliance. In the only study that lasted for 2 years, the risk of relapse decreased substantially in the depot-treated patients, suggesting that risk of noncompliance may be a more important factor in relapse over extended periods of time. A recent formal meta-analytic review of depot medications concluded that this route of administration resulted in clinical advantages in terms of global outcome.

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Antipsychotic medication provides the bedrock on which all long-term treatment for schizophrenia rests. Discontinuation of antipsychotic medication leads to symptom exacerbation, relapse, and often rehospitalization. The evidence for this assertion comes from long-term controlled trials, naturalistic prospective follow-up studies, and clinical experience. Medication discontinuation may occur in a clinical trial in which there is a "no medication" or placebo condition. It may represent a clinical decision made by the treating physician in collaboration with the patient receiving the medication. Or, it may happen because a patient stops medication without agreement or even awareness by the prescribing physician.

The strongest evidence for the effectiveness of antipsychotic medication comes from long-term, randomized clinical trials with placebo controls in patients with schizophrenia whose illness is well established.[1–3] Further, the risk of relapse without medication is high even in patients who are experiencing their first episode of illness, as shown in both controlled trials and prospective, naturalistic follow-up studies.[4,5] Finally, even the use of an early intervention strategy designed to introduce medication at the earliest signs of symptom exacerbation is unsuccessful if patients are not receiving antipsychotic medication on a continuous basis.[6] Davis and colleagues[7] estimate that relapse among patients receiving placebo occurs at a constant hazard rate that varies between 10% and 15% per month, depending on whether studies are conducted in inpatient or outpatient settings. Relapse rates among patients receiving antipsychotic medication in these studies vary between 1.5% per month for inpatients and 3% to 4% per month for outpatients. These differences in relapse on medication that are a function of setting in clinical trials are hypothesized to be due to increased unreliability in medication taking—nonadherence or noncompliance—among outpatients.

Although noncompliance may have many causes, delivery of medication via a long-acting injectable antipsychotic has been one clinical strategy employed to enhance medication adherence, particularly among patients who have a clinical history of relapse associated with noncompliance. This article will review the available data regarding this strategy, drawing upon reports of mirror-image studies and randomized clinical trials of conventional oral and depot antipsychotic medications. Each of these methods has advantages and disadvantages in terms of estimating the actual benefits that are provided by delivery of medication using a strategy that guarantees that the patient will receive the amount of medication that is prescribed. Studies were included in this review if the reports were in English and provided information regarding relapse or rehospitalization. Reference lists from earlier reviews and the Citation Index were used to identify articles for inclusion.

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MIRROR-IMAGE STUDIES

In mirror-image studies, a period prior to an index event, in this case starting treatment with a depot antipsychotic medication, is compared with a period of equal length following that event. Thus, a patient who had been followed for 3 years after the switch of medication to depot injections and had experienced 1 hospitalization compared with the previous 3-year period when he had experienced 2 hospitalizations would have a reduction of 0.33 hospitalizations per year. In addition to numbers of hospitalizations, studies also often examined the number of days of hospitalization during the 2 exposure periods. The strengths of the method are that each patient serves as his own control, the length of observation does not need to be the same for all patients, and, at the time these studies were conducted, informed consent from participants was not required to allow investigators to collect and report these data. However, these studies could not control for factors like patients' decreasing risk of rehospitalization over time and secular trends such as the change in access to hospitalization over time. Further, there are questions about exactly which patients should be included in the analyses. In most of the studies, only patients who had been receiving depot injections for some time (for example, 12 months) are included. Thus, patients who are noncompliant with injections are left out of the mirror-image comparisons.

A series of mirror-image studies following this model was conducted during the 1970s.[8–12] Despite the limitations noted, the results of these studies were impressive. Hospitalizations were dramatically reduced. Number of hospitalization days was also cut substantially. Also, the suggestion was made that, in addition to reducing the burden of rehospitalization, there were additional benefits in symptomatic improvement and community functioning.

For example, Denham and Adamson[8] examined records of 212 chronic schizophrenic patients who were currently receiving either fluphenazine enanthate or decanoate. They restricted the analysis to patients who had been receiving depot injections for at least 12 months and who had previous hospital admissions. One hundred three patients met criteria for inclusion in the analysis. During the period prior to initiating depot medication, 191 admissions were recorded with a total of 8713 in-hospital days; during the period following initiation of the depot medication, 50 hospitalizations were recorded with a total of 1335 in-hospital days. The authors note that antiparkinsonian drugs were used "routinely." The number of hospitalizations was reduced by 73% and the number of days of hospitalization by 82%.

DOUBLE-BLIND CLINICAL TRIALS

The encouraging results of the mirror-image studies coupled with questions about the rigor of the methods led to a series of double-blind randomized clinical trials. In these trials, all participants—almost all with schizophrenia or schizoaffective disorder—provided informed consent. In order to maintain the blind, most of these studies incorporated "double-dummy" designs, in which participants received either oral medication and placebo injections or oral placebos and active depot injections. Most compared oral and depot versions of the same medication for fixed trial durations ranging from 9 months to 2 years.[13–18] The strengths of these studies are the well-known strengths of randomized clinical trials. Randomization controls for differences between the 2 treatment groups. The studies are prospective so that exposure to the 2 treatments is not confounded by differences that may be introduced by comparing 2 time periods. Blinding of medication delivery controls for differences that may result from expectations on the part of participants or the clinicians treating them. There are also limitations. Virtually all of these studies required that participants provide informed consent before participating, and patients who agree to participate in trials, particularly a trial that requires taking both oral tablets and injections, may be less likely to stop taking oral medication than patients who do not participate in such studies. Only the study by Hogarty and colleagues[16] was 2 years long. Most of the other studies were only 1 year long, which may be too short a period for noncompliance to affect outcome, particularly in participants who are cooperative enough to enter such trials.[19]

Table 1 presents the demographic characteristics of patients included in these trials, and Table 2 summarizes the results in terms of relapse rates. Although the studies are essentially similar in design, they do have a number of characteristics that distinguish them. The study by del Giudice and colleagues[14] is the only one that includes 2 groups of participants who received oral medication: one that received placebo injections and one that did not. The data suggest that this distinction did not make a difference in terms of reported relapse rates. The study by Rifkin

Table 1. Demographic Characteristics of Participants in Randomized Clinical Trials of Oral and Depot Antipsychotic Medications

Study	Year Published	Gender (% female)	Age, y (mean)	Chronicity
Crawford and Forrest[13]	1974	71	46	12.3[a]
del Giudice et al[14]	1975[b]	…	35	6.4[c]
Rifkin et al[17]	1977	33	24	22%[d]
Falloon et al[15]	1978	57	39	17%[d]
Hogarty et al[16]	1979	54	34	4.6[c]
Schooler et al[18]	1980	41	29	3.3[c]

[a]Mean duration of illness (years).
[b]Study completed in 1970.
[c]Mean number of prior hospitalizations.
[d]Percentage of patients experiencing first episode.

Table 2. Relapse Rates in Randomized Clinical Trials Comparing Oral and Depot Antipsychotic Medications

Study	Total N	Study Duration (mo)	Relapse % Oral	Relapse % Depot	Relapse % Difference
Crawford and Forrest[13]	29	10	40[a]	14[b]	26
del Giudice et al[14]	82	16			
12 mo			89[c]	44[d]	45
16 mo			98[c]	76[d]	22
Rifkin et al[17]	51[e]	12	11[c]	9[b]	2
Falloon et al[15]	44	12	24[f]	40[b]	–16
Hogarty et al[16]	105	24			
12 mo			40[c]	35[b]	5
24 mo			65[c]	40[b]	25
Schooler et al[18]	214	12	33[c]	24[b]	9

[a]Trifluoperazine.
[b]Fluphenazine decanoate.
[c]Fluphenazine hydrochloride.
[d]Fluphenazine enanthate.
[e]Study was placebo-controlled. N in table reflects only oral/depot comparison.
[f]Pimozide.

and colleagues[17] was the only study to include a group of participants that received a placebo, a condition that assesses the sensitivity of the trial to differences. In that study, the only significant difference was between the placebo group and the combined groups that received active medication, either via the oral or injectable route of administration.

As shown in Table 1, the studies differed in terms of the percentage of women included in the trials, ranging from 71% in the Crawford and Forrest study[13] to 33% in the study by the Rifkin group.[17] Since there are data that suggest that women respond more positively to medication than men,[20] a larger proportion of women in the trial could account for the substantial advantage for depot medication found by Crawford and Forrest. The age of participants also differed among the trials, ranging from a mean age of 24 years in the Rifkin et al. study[17] to one of 46 in the Crawford and Forrest study.[13] Chronicity also varied among the studies. Chronicity of participants was not measured in a uniform way among the trials. The measures that have been extracted include duration of illness in years (in the Crawford and Forrest trial[13]), number of prior hospitalizations,[14,16,18] and percentage of first-episode patients (Rifkin et al.[17] and Falloon et al.[15] studies). In terms of chronicity, the Crawford and Forrest study[13] appears to have the most chronic patient population and the Rifkin et al. study[17] the least.

Outcome as indexed by relapse rate is shown in Table 2. None of the studies found significant differences between oral and depot medication administration. However, the absolute rates of relapse differ widely among the trials. If we take the relapse rate on depot medication as representing a relatively reliable estimate of relapse associated with receipt of medication, it differs between 9% at 1 year in the Rifkin et al. study[17] and 76% at 1 year and 4 months in the del Giudice et al. trial.[14] The del Giudice et al.[14] and Hogarty et al.[16] trials offer an interesting difference in outcome. These studies are the only 2 that treated patients for longer than 1 year. At 1 year, the depot relapse rate in the Hogarty et al. study was 35% compared with the del Giudice and colleagues' rate of 44%. However, the depot relapse rate climbed to 76% in the following 4 months in the del Giudice et al. study, while the rate rose to only 40% after an additional 12 months in the Hogarty et al. study. The study by Schooler and colleagues[18] may be considered to offer the most stable estimate of relapse on guaranteed medication because it is by far the largest of the trials, with over 100 participants in each group. The relapse rate in the depot group was 24% after 1 year.

Relapse rates in the oral group provide an estimate of rates that incorporate both relapse on medication and the additional burden of noncompliance. In both studies that continue for more than a year, the rates rise in the oral medication group. In the del Giudice et al. study,[14] virtually all patients (98%) relapsed by the end of the 16-month study. In the Hogarty et al. study,[16] the rate rose to 65% by the end of the second year. With the exception of the Falloon et al. study,[15] relapse is higher in the oral than in the depot group in all the studies. The difference ranges from 2% to 45%. The mean oral relapse rate at 1 year across all the studies, adjusted for the number of study participants, is 42%; the rate for depot-treated patients is 27%. The recent report drawn from the Cochrane Database[21] concluded that there were no significant differences in "leaving the study early" between oral and depot antipsychotic medications. That measure differs from the "relapse" measure calculated in the present review by including patients who left the trial for reasons other than clinically judged relapse or rehospitalization. However, the Adams et al. meta-analytic review[21] of depot antipsychotic medications compared with oral antipsychotics did conclude that there were advantages in terms of global change that favored depot administration.

CONCLUSIONS

Studies of conventional antipsychotic medications that compared depot medications to orally administered agents suffered from a number of methodological limitations. The early mirror-image studies fail to meet the generally accepted standards for evidence-based medicine because they were retrospective and the comparisons were not based on randomization to treatment. The double-blind studies addressed these concerns in elegant ways, including randomization and elaborate blinding of treatment. In most of the studies, participants received both forms of medication—one of which was placebo. Unfortunately, the elegance of the designs may have compromised the primary goals of the studies. The requirements of in-

formed consent and that participants take both forms of medication may have biased the studies toward the inclusion of patients who were at lower risk for noncompliance, at least in the short run. Of course, informed consent was, and will continue to be, an essential element of all studies. But studies in the 21st century that seek to investigate the benefits of injectable medications will profit from using simpler research designs that incorporate randomization but do not require participants to take medication via 2 routes of administration.

Even with these limitations, there is a suggestion that the oral route of administration results in a higher risk of relapse than depot injections. Earlier reanalyses by Kane and Borenstein[19] as well as that by Davis and colleagues[7] point to evidence of an advantage for depot medication. In the present review, when relapse rates for the studies presented in Tables 1 and 2 are weighted by the numbers of cases in the studies, the rate at 1 year is 42% for oral administration compared with 27% for the depot route, suggesting an advantage for injectable medication.

As noted, only 1 of the studies was 2 years long, a period potentially long enough to allow the positive effects of study participation on medication-taking to erode. In that study by Hogarty and colleagues,[16] a post hoc examination of relapse in the second year found that the monthly relapse rate among the subjects who received fluphenazine decanoate alone was 1.7% per month compared with 5.0% per month for oral fluphenazine.

On balance, studies of oral versus depot conventional medications provide valuable information. First, relapse occurs even when medication is guaranteed via injection. This is a valuable reminder that lack of compliance or adherence with medication is not the only source of relapse. Medication administration via long-acting injection serves to simplify the medication regimen and to insure that a patient's lack of compliance is not inappropriately considered the culprit when a relapse occurs. Second, the role of noncompliance with oral medication in relapse may increase over time. This increase represents a cautionary tale to clinicians who care for these patients over extended periods of time. Clinicians should be alert to the fact that given enough time, many patients who receive oral medication are at risk for relapse that could potentially be prevented by the use of a long-acting injectable medication.

Drug names: fluphenazine (Prolixin, Permitil, and others), pimozide (Orap), trifluoperazine (Stelazine and others).

Disclosure of off-label usage: The author of this article has determined that, to the best of her knowledge, pimozide is not approved by the U.S. Food and Drug Administration for the treatment of schizophrenia.

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