

Choice of Maintenance Medication for Schizophrenia

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Unmedicated schizophrenia patients relapse at a rate of approximately 10% per month. Maintenance treatment with antipsychotic medications can reduce this rate dramatically. Ensuring compliance with medication in the maintenance treatment of schizophrenia encompasses 3 areas of concern: (1) choice of antipsychotic medication, accounting for efficacy and side effects; (2) route of administration of medications, considering the benefits and detriments of long-acting injectable and oral medications; and (3) reducing "doctor noncompliance," the failure of some physicians to perceive the need for long-term treatment for patients with chronic schizophrenia. This article focuses on the selection of the antipsychotic medication that will most likely lead to successful maintenance treatment of schizophrenia. Data from acute trials must be relied upon to evaluate the comparative risks and benefits of these agents as long-term treatments since few double-blind, random-assignment studies have compared the newer-generation antipsychotics for maintenance treatment of schizophrenia. Studies of acute treatment, as well as a small number of studies of maintenance treatment, have shown the newer-generation antipsychotics risperidone and olanzapine to be more efficacious and to have a more favorable side effect profile than conventional-generation antipsychotics. Research on the newer-generation antipsychotics, including ziprasidone, aripiprazole, and quetiapine, shows these agents to be efficacious and safe, although the limited amount of data on these agents precludes a definitive evaluation of their efficacy and safety. (*J Clin Psychiatry* 2003;64[suppl 16]:24-33)

This article will focus on which antipsychotic agent to choose as maintenance medication for schizophrenia. Patients (as well as physicians) are concerned about efficacy, and good efficacy would lead to greater compliance. Adams and Howe¹ report that the patient's perception of benefit from medication is the strongest predictor of compliance. Hogan et al.² found that the patient's positive experience with medication was the most important determinant of compliance and that a negative subjective experience had much weaker influence. Therefore, the clinician needs to evaluate which medication to prescribe for the best possible result, and the fact that the patient perceives benefit will only enhance compliance.

There are 3 aspects of ensuring compliance: (1) the choice of medication, taking into account efficacy and side effects; (2) the use of long-acting injectable medication and various means of ensuring that the patient takes

oral medication, such as directly observed treatment; and (3) reducing doctor noncompliance. *Doctor noncompliance* is a term used to indicate that not all physicians see the necessity of long-term treatment of the patient with chronic schizophrenia. One of the reasons patients do not necessarily achieve a successful long-term maintenance is that the doctor did not prescribe it at all or did not clearly understand the necessity and explain this to the patient. We will discuss (1) the choice of which antipsychotic to prescribe, (2) the issues of the long-acting injectable versus the oral form of administration, and (3) the issue of doctor noncompliance and the overall stakes to the patient of maintenance medication in preventing relapse.

Since there are many antipsychotics on the market, the physician has a choice of which drug to prescribe. Shortly after chlorpromazine was discovered, many conventional antipsychotic drugs were developed. Klein and Davis³ reviewed the evidence for efficacy and safety in detail at that time and concluded that all conventional antipsychotics were equally efficacious, and there are marginal differences in side effects.

Since the many conventional drugs are very similar, psychiatrists have tended to think that all antipsychotics are relatively similar. We feel this generalization is no longer true for the newer-generation antipsychotics. At the present time, most guidelines discuss the newer-generation antipsychotics as if they were a homogeneous group.⁴⁻⁶ (We would hasten to add that a few of these guidelines will differentiate the drugs in the text.) We feel that the newer-generation antipsychotics are quite hetero-

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geneous, and we are more impressed with their differences than their similarities.

There are very few double-blind, random-assignment studies comparing newer-generation antipsychotics for maintenance treatment. Almost all of the controlled clinical trials are on acute treatment. To evaluate the risks and benefits of different antipsychotics, we must rely in large part on the acute trials. This article focuses on interpretation from these existing data, which have implications for the drug of choice for long-term antipsychotic maintenance medication.

EFFICACY OF NEWER-GENERATION ANTIPSYCHOTICS

Risperidone and Olanzapine

Our meta-analyses of the double-blind random-assignment studies on risperidone and olanzapine concluded that both newer-generation antipsychotics are more efficacious than conventional antipsychotics for acute episodes.⁷⁻¹⁰ Geddes et al.¹¹ found both of these drugs superior in efficacy to conventional antipsychotics, although they reached a different conclusion, which we will discuss below. Our updated meta-analysis (references 12 and 13 and J.M.D.; N.C.; I. D. Glick, M.D., unpublished data) based on 22 studies¹⁴⁻³⁵ found risperidone markedly more efficacious than conventional antipsychotics (usually haloperidol), with an effect size of 0.25 (95% CI = 0.18 to 0.33, $t = 7.10$, $p = 10^{-12}$). Fifteen of these studies reported the results on the Positive and Negative Syndrome Scale (PANSS).³⁶ The effect size for positive symptoms was 0.16 (95% CI = 0.09 to 0.24, $t = 4.37$, $p = 10^{-5}$), and for negative symptoms the effect size was 0.20 (95% CI = 0.13 to 0.28, $t = 5.45$, $p = 10^{-7}$). Our meta-analysis (references 12 and 13 and J.M.D.; N.C.; I. D. Glick, M.D., unpublished data) of olanzapine^{17-19,37-47} showed that it produces greater efficacy over conventional antipsychotics as measured by the Brief Psychiatric Rating Scale (BPRS)⁴⁸ or PANSS total, similar to that of risperidone, with a similar degree of significance.

We have recently analyzed the U.S. database on the acute treatment of schizophrenia with risperidone combining the 2 pivotal studies, the United States study performed by Marder and Meibach³¹ and the Canadian study performed by Chouinard and collaborators.²⁶ In collaboration with Marder and Chouinard, we conducted a meta-analysis on the original data.¹⁰ We also obtained the registrational database for olanzapine and conducted a meta-analysis on the original data.⁸ Both of these large data sets were collected in random-assignment double-blind studies. We factor analyzed both the risperidone data set and the olanzapine data set and found that both the BPRS and the PANSS clustered in 5 distinct factors. Our results verified the pioneering work of a number of factor analysts in a variety of different countries who have found the PANSS items loaded on 5 factors.¹⁰

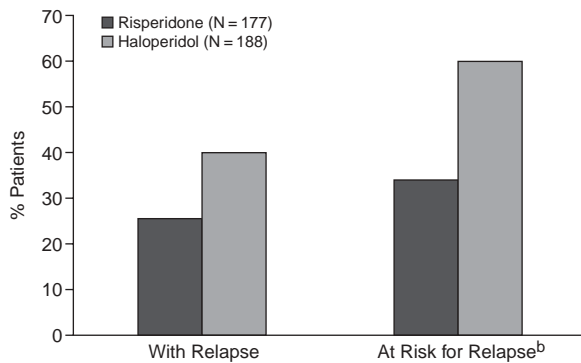
There is remarkable agreement within this body of statistical analysis, even among diverse cultures and languages. The factor structure of the BPRS is not as unambiguous as the PANSS. Because the BPRS has substantially fewer items—18 versus the 30 items in the PANSS—the results with the BPRS are less clear-cut. That said, we are able to extract 5 factors from the BPRS data consistent with the factor analysis of the PANSS. In comparison with haloperidol, olanzapine and risperidone in their respective databases produce greater improvement to a statistically significant degree on each of these 5 factors (positive symptoms, negative symptoms, thought disorder, impulsivity/hostility, and anxiety/depression).^{8,9}

The original division of the PANSS into positive symptoms and negative symptoms was made on theoretical grounds prior to collection of empirical data. Our factor loadings are close enough to verify that 2 original subscales are positive and negative symptoms, but the classical divisions were not optimal. The general symptom subscale of the PANSS is not informative since it does not distinguish between the impulsivity/hostility, thought disorder, and anxiety/depression factors. Indeed, haloperidol has little effect on negative symptoms, impulsivity/hostility, and anxiety/depression, while haloperidol has some minor efficacy on the thought disorder factor. Olanzapine and risperidone produce a substantial improvement over and above that of haloperidol on all factors.

The degree of symptom reduction as measured by the PANSS or BPRS was normally distributed in the response to all of the different drug groups in the pivotal studies of both olanzapine and risperidone.^{8,9} There was no evidence of a bimodal curve that would allow patients to be classified as responders or nonresponders on the basis of how much they responded. This division is widely made. The 20% criterion (of PANSS or BPRS score reduction) is frequently used as a definition of responders. An important problem with an arbitrary definition of responders is that a given manufacturer can choose the optimal cutoff point for its drug, creating a systematic bias. If all studies use the 20% criteria, then the bias is avoided. A better method of measuring improvement is the covariate-adjusted change from baseline (with baseline as covariate). When the underlying distribution is continuous, information is lost by setting an arbitrary dichotomy. Fifty percent of information is lost when both continuous variables of a correlation are dichotomized.

In both of these meta-analyses,^{8,9} the major difference between risperidone and olanzapine in comparison with haloperidol was that both of these newer-generation antipsychotics produced improvement in all of the dimensions of schizophrenic behavior during acute treatment. It is noteworthy that they produced more improvement on positive symptoms than haloperidol, although haloperidol had a good effect on positive symptoms. In both of these studies, the placebo group experienced substantial de-

Figure 1. Relapse Rates With Oral Risperidone or Haloperidol at Study Endpoint^a



^aData from Csernansky et al.²⁸ The median length of treatment was significantly ($p = .02$) longer with risperidone (364 days, range: 3–799) than with haloperidol (238 days, range: 4–794).

^b $p < .001$ for between-group difference.

terioration on impulsivity/hostility. This dimension may be an important part of schizophrenic symptomatology. The impulsivity/hostility factor deteriorates most rapidly in the absence of drug treatment. Impulsively threatening or striking out against family members or others may be an important reason for hospitalization. Haloperidol appears to hold this factor in check but does not improve it over baseline. Both olanzapine and risperidone substantially reduce the symptoms on this dimension. While haloperidol produces a minor degree of improvement in the thought disorder dimension, both olanzapine and risperidone produce a much more substantial effect in this dimension.

It is possible that the observed better effect on positive symptoms of risperidone and olanzapine over that of conventional antipsychotics is a consequence of a carryover effect from better improvement on the other 4 factors. It is also possible that risperidone and olanzapine have some additional beneficial effect on positive symptoms per se. The most important finding is not this modest extra benefit but rather that there is no trade-off between improvement of positive symptoms and improvement of the other 4 factors. Examining the sertindole registration studies indicates that sertindole shows about the same overall improvement as haloperidol, but improvement on positive symptoms is not as good as that seen with haloperidol, although the improvement in negative symptoms may be a little better. With sertindole, there was a trade-off between positive and negative symptoms. With risperidone and olanzapine, no trade-off exists during acute treatment. There is some improvement in positive symptoms with these drugs greater than that found with haloperidol, but the improved efficacy on the other 4 dimensions is not at the expense of positive symptoms.

Csernansky et al.²⁸ report a particularly important large-sample maintenance study of risperidone versus haloperi-

dol. In their study, risperidone reduced the relapse rate of schizophrenia substantially more than did haloperidol (Figure 1). Additionally, it produced more symptom improvement on each of the 5 factors of schizophrenic behavior. The risperidone-versus-haloperidol pattern of long-term (more than a year) improvement is identical to the short-term results. The clear implication of this result is that long-term risperidone produces progressive improvement over time and is better on all 5 factors at the end of 1 year. This study provides strong evidence that at least one newer-generation antipsychotic is indicated over conventional antipsychotics for maintenance. It also strengthens the generalization based on acute studies to long-term maintenance.

We examined the effect of risperidone versus haloperidol or olanzapine versus haloperidol and placebo on each individual symptom.^{8,9} These 2 newer-generation antipsychotics produce more improvement than haloperidol on almost every symptom of schizophrenia. While haloperidol produces more improvement than placebo on some of the positive items and an occasional item in the other 4 clusters, both olanzapine and risperidone are better than haloperidol for most of the symptoms of schizophrenia. This difference between the newer-generation antipsychotics and haloperidol is not clearly seen in individual data from single studies. It is unusual for authors of a single study to report the data because individual items are not sensitive enough to show a difference between a new drug and a standard drug. With the pooled data set, one can see that almost every item is improved more with these 2 newer-generation antipsychotics. Our item analysis shows that many symptoms that are left untouched by the conventional antipsychotics are substantially benefited by olanzapine and risperidone. The symptoms cluster into the negative symptoms, anxiety/depression, and impulsivity/hostility factors. These symptoms are characteristic of schizophrenia and interfere with function in schizophrenia.

Using both the olanzapine and risperidone data sets, we constructed a scale that we called the haloperidol-nonresponsive scale, which is composed of symptoms that did not seem to improve with haloperidol in comparison with placebo.^{8,9} The magnitude of the changes with both drugs is about the same. We also divided the individual symptoms into symptoms that were responsive to haloperidol. Both olanzapine and risperidone were more effective than haloperidol on both the haloperidol-responsive and the haloperidol-nonresponsive items. The size of this superiority over haloperidol was larger for the haloperidol-nonresponsive items. We feel it is clear that both olanzapine and risperidone improve a number of symptoms not helped by haloperidol. This difference accounts for almost two thirds of the difference between risperidone or olanzapine and haloperidol. Again, we note that risperidone and olanzapine are clearly superior (highly statistically significant) on the haloperidol-responsive items. It is possible

that some sort of a carryover effect from the haloperidol-nonresponsive items affected the haloperidol-responsive items.

The pattern of response on the 5 dimensions of schizophrenia is very similar between risperidone and haloperidol and between olanzapine and haloperidol. Both risperidone and olanzapine produce much more improvement on negative symptoms than does haloperidol. Both olanzapine and risperidone are moderately superior on positive symptoms and on the thought disorder (cognitive) factor. They differ very slightly, although both improved, on the impulsivity/hostility factor. Risperidone is clearly moderately superior to haloperidol on this factor, while olanzapine is slightly but statistically significantly superior. In contrast, olanzapine is moderately superior to haloperidol on the anxiety/depression factor, but risperidone also produced slightly (but statistically significantly) greater improvement than haloperidol with this factor. We emphasize, however, that both drugs are statistically significantly better than haloperidol on both dimensions. Whether this modest difference in profile can be replicated remains to be determined. We feel that the most striking thing about the pattern of response of these 2 newer-generation antipsychotics is their similarity. There have been a number of studies comparing olanzapine and risperidone, and our meta-analyses of these studies found no significant difference between the 2 newer-generation antipsychotics.

There is a saying that "one should use new drugs while they are still effective and while they are still safe." Most of the large controlled studies are done for registrational purposes. They constitute the best evidence on efficacy and on common side effects. Our appreciation of rare side effects must await widespread use.

Ziprasidone

Ziprasidone is available in a short-acting intramuscular formulation for acute agitation and in capsules for treatment of acute or chronic schizophrenia. It has been a difficult drug to evaluate because until recently few of the well-controlled registrational studies, upon which an evaluation should be based, had been published.⁴⁹⁻⁵³ The most comprehensive collection of data has been available on the U.S. Food and Drug Administration (FDA) Web site.⁵⁴ On the basis of the data, there is no doubt that ziprasidone is more effective than placebo. The data presented on the FDA Web site show ziprasidone to be a little less effective than the conventional antipsychotics for acute treatment, but this difference may not be statistically significant. In a 28-week study⁵⁰ in patients with stable schizophrenia, oral ziprasidone and haloperidol had comparable efficacy. It is important that the data be inspected for their implications on dose response. The low doses of ziprasidone are not more effective than placebo in acute schizophrenia or schizoaffective disorder. Doses in the range of 120 to 200 mg are clearly statistically signifi-

cantly more efficacious than placebo, although doses of 40 to 80 mg might also be effective for patients with stable schizophrenia. The real question is how ziprasidone compares to conventional antipsychotics.

One side effect of ziprasidone, prolongation of the QT interval corrected for heart rate (QTc), makes this antipsychotic contraindicated for patients who have cardiovascular dysfunctions or take another medication that might prolong QTc. Also, it is not uncommon for side effects to surface after the registrational studies, particularly rare side effects. Because ziprasidone was recently released, it is appropriate to have some caution about final evaluation.

Aripiprazole

Aripiprazole was recently approved and released by the FDA for general marketing. Results of some of the published registrational studies⁵⁵⁻⁵⁷ demonstrate that aripiprazole appears to be more effective than placebo and similar in efficacy to the conventional antipsychotics for acute treatment. Doses of 10 to 30 mg are statistically significantly more effective than placebo, without increased efficacy for doses above 15 mg. Because aripiprazole has been on the market for only a short time, some caution should be used in making final evaluations of its safety and marketability.

Quetiapine

The principal evidence for the efficacy of quetiapine for acute treatment comes from 4 large double-blind studies.⁵⁸⁻⁶¹ All 4 studies show that quetiapine has about the same efficacy as conventional antipsychotics. Two studies^{58,61} show exactly the same efficacy, while 1 study⁵⁹ shows a conventional antipsychotic to be very slightly superior to quetiapine (not statistically significant). Another study⁶⁰ shows the conventional antipsychotic to be very slightly less effective (not statistically significant). Since quetiapine is neither significantly superior to nor significantly inferior to the conventional antipsychotics, we would conclude that the efficacy of quetiapine for acute treatment is equal to that of conventional antipsychotics.

Clozapine

Most guidelines, narrative reviews, and meta-analyses find clozapine to be the most effective antipsychotic. The only exception is that Geddes et al.¹¹ feel that there is insufficient evidence to establish clozapine as superior to other newer-generation antipsychotics. Although the data from their own meta-analysis¹¹ find these differences to be highly statistically significant, Geddes and colleagues reject this finding.

Clozapine has the potential of producing agranulocytosis. Weekly white blood cell counts have almost eliminated death from agranulocytosis related to clozapine use. The assessment of weekly white blood cell counts is an inconvenience. Clozapine has a large number of other side

effects, which places it in a special category. In short, although clozapine may be more efficacious than other newer-generation antipsychotics, its unfavorable side effect profile necessitates that it be considered to be a drug of last resort.

SIDE EFFECTS

In choice of drug, we think it is important to weigh side effects by severity and frequency. One must weigh the medical seriousness of the side effect and its reversibility. Certainly, agranulocytosis leading to death, even though rare, is very serious. Tardive dyskinesia, which is a persistent drug-induced movement disorder with a progressive incidence of 3% to 5% per year and the potential to become severe and irreversible, has considerable importance to the patient. Reversible drug-induced movement disorders such as acute extrapyramidal side effects (EPS), although not permanent, certainly can be painful and frightening. Some patients have a dysphoric reaction to conventional antipsychotics.

Both risperidone and olanzapine result in much fewer reversible motor side effects, e.g., EPS, and hence have an advantage over standard antipsychotics. The safety of risperidone clearly has endured the test of time. It does produce a low incidence of reversible motor side effects at the therapeutic dose range of around 4 to 6 mg. Dystonia is very rare with risperidone. Since patients taking placebo show some elevated ratings of reversible motor side effects above zero, we do not know whether this lack of specificity is due to rating, persistence of reversible motor side effects from previous conventional antipsychotics, or other factors such as the presence of other neurologic diseases. We found that both olanzapine- and placebo-treated patients in the double-blind controlled study of olanzapine versus placebo experienced a decrease in ratings of reversible motor side effects such as EPS and akathisia from those measured at baseline.⁸ The incidence of reversible motor side effects was the same with olanzapine as with placebo, suggesting that the data could not show that olanzapine produced a higher rate of reversible motor side effects than was found in placebo-treated patients. Indeed, the reversible motor side effects scores on rating scales for reversible motor side effects decreased below baseline for both drugs. The possibility exists that risperidone and olanzapine will not, or will only rarely, cause tardive dyskinesia. We would make the inference that since these drugs are more efficacious and safer than conventional antipsychotics for acute treatment, they would also be both more efficacious and safer for maintenance treatment. Hence, they are the drugs of choice in both acute and maintenance treatment. Clozapine should be used for patients unresponsive to other antipsychotics.

Csernansky and coworkers⁶² found substantially fewer movement disorders with risperidone than with haloperi-

dol in their maintenance study. They report that 5 patients assigned to haloperidol experienced new onset of tardive dyskinesia compared with only 1 assigned to risperidone. We feel that somnolence is a particularly important side effect because it interferes with mental functioning and hence quality of life. The rate of somnolence with risperidone was 14% compared with 25% with haloperidol. We feel this somnolence rate is an important difference between risperidone and haloperidol. It is not merely a nuisance or nonspecific side effect. Sedation is often reported in placebo patients. Unfortunately, sedation cannot be evaluated in the long-term maintenance studies of risperidone versus haloperidol since no placebo group was present.

Weight gain and new-onset diabetes have proved to be important side effects of the newer-generation antipsychotic drugs. Substantial weight gain is observed with clozapine and olanzapine, but some weight gain is observed with other newer-generation antipsychotics as well. Weight gain is medically and socially significant and can be functionally irreversible, since it is very difficult to lose weight. Weight gain plateaus with time. The long-term maintenance study by Csernansky and coworkers⁶² comparing risperidone and haloperidol found that risperidone produced weight gain of 2.3 kg (5.0 lb) in this trial with an average length of about a year. This was similar in magnitude to the weight gain seen in acute trials, suggesting that the weight had plateaued and did not progress. Medical and family history is important in evaluating choice of drug to avoid side effects that may be particularly problematic for a particular patient.

It is difficult to make a precise evaluation of the side effects of ziprasidone. The most important question with ziprasidone is its effect on the QT interval and consequently the propensity for causing sudden death. The issue is complex. We would like to draw the reader's attention to an excellent review article on this question by Glassman.⁶³ Although time will tell, to our knowledge, sudden death has not been documented with ziprasidone. Other than this, ziprasidone appears to have a favorable side effect profile. The problem of interpreting side effects with ziprasidone is that few fixed-dose studies have been published. The FDA Web site⁵⁴ has group data on ziprasidone and side effects that primarily reflect pooled studies including lower, ineffective doses. Because many pharmacologic effects are dose related, the inclusion of low-dose studies might underestimate the side effects occurring at an adequate dosage. However, a 1-year fixed-dose study⁴⁹ of 40 mg, 80 mg, and 160 mg of ziprasidone found that most adverse events occurred in similar percentages of patients in all ziprasidone groups and in the placebo group. There are patients who cannot tolerate the weight gain seen with at least some other newer-generation antipsychotics, and there may be clear indications for ziprasidone or aripiprazole in patients with chronic schizophrenia in

relative remission. Aripiprazole has a very favorable side effect profile, causing few if any reversible motor side effects and little if any sedation, weight gain, or prolactin elevation.

GENERAL PRINCIPLES OF MAINTENANCE AND DOCTOR NONCOMPLIANCE

What then is the relevance of the large body of literature on the use of conventional antipsychotics in maintenance treatment, if newer-generation antipsychotics are better? We feel that this body of data gives general principles for maintenance drug use, even though we recommend switching patients to risperidone or olanzapine. The use of maintenance antipsychotics has come under fire recently, with several authors advocating slow tapering of dose followed by the complete withdrawal of treatment. Gilbert and colleagues review maintenance medication and conclude that their results “show that nearly half of the patients do not relapse when kept off neuroleptic therapy over a 10-month period. Maintaining medication would seem unnecessary. . . . The optimal solution in a substantial proportion of cases would probably be to slowly taper the neuroleptic therapy to the lowest dose that would control the symptoms of schizophrenia to a satisfactory degree. In some patients, the lowest dose may be zero—stopping neuroleptic therapy.”^{64(p186)}

We disagree with their inference. Indeed, the 1975 meta-analysis by Davis⁶⁵ covered almost all of the same material that Gilbert et al. used. Specifically, we reviewed this literature and did a meta-analysis of the double-blind, random-assignment, controlled studies of maintenance medication and found that 52% of patients relapsed on placebo treatment in contrast to 20% on maintenance neuroleptic treatment. This analysis was massively statistically significant at that time ($p = 10^{-84}$). The 1995 article by Gilbert et al. reviewed only a partial sample of the relevant articles, and their results are essentially the same as those of our 1975 article. Meltzer⁶⁶ has criticized the Gilbert et al. methodology. We have updated the meta-analysis on several occasions, most recently in 1994,⁶⁷ when we found that of 3720 patients, 55% relapsed on placebo treatment and only 21% relapsed on maintenance medication treatment, a difference that yields a chi-square value of 483 ($df = 1, p < 10^{-107}$).

We also disagree with the inference by Gilbert et al. that because “nearly half of the patients do not relapse when kept off neuroleptic therapy. . . . Maintenance medication would seem unnecessary.”^{64(p186)} These studies were usually conducted over 6 months or less in duration, a relatively brief period of time, although there were a few 1- or 2-year studies. In our 1975 article,⁶⁵ we calculated the rate of relapse over time (about 10% per month) with respect to making inferences about the kinetics of relapse. We were drawing an analogy between half time with the

drug’s half-life. This was the first time that survival methodologies were applied to antipsychotic drugs. Most survival analyses focus on the statistical significance of drug versus placebo or new drug versus old drug. We think the survival plots are also of interest in the kinetics of relapse.

Mathematically, if the relapse is constant over time, then a plot of patients not yet relapsed on a log scale (i.e., a semi-log plot) versus time on a linear scale will show a straight line. In our original meta-analysis, we plotted the time course of relapse, plotting number of patients not yet relapsed versus time in a semi-log plot. With the passage of every month, more patients relapsed at about the same rate. Gilbert and coworkers⁶⁴ make a fallacious assumption about what will happen after the studies are over. The most logical extension of the data is that patients will relapse at about the same rate after the study is over as they did during the study. In our first approximation of this, we plotted out data from a number of studies that present rate of relapse over time and found that the rate of relapse is about the same early in the study as later in the study.⁶⁷ There are studies over 2 to 4 years. Hogarty and Ulrich⁶⁸ and Hogarty et al.⁶⁹ performed survival analyses on their data, finding that, in longer studies, patients taking placebo relapse at about the same rate after 6 months as they did before. In some of the longer studies, the rate of relapse seems to decrease somewhat, but this occurred in studies that generally were over a year and a half in length. Since the percentage of patients relapsing increases month after month, there is no reason to suppose that once a given study is ended, the progressive relapses stop.

For our argument, it does not matter a great deal whether the rate of relapse is constant or whether the rate of relapse decreases somewhat with time because in either case, with the passage of more time, more patients will relapse. After a long enough period of time, all the patients at risk for relapse would have relapsed. While this is true for most patients, we would expect that an unknown number of patients do not have the relapsing type of schizophrenia and will never relapse. We think this percentage is perhaps 10% of schizophrenic patients. This is an approximation; we really do not know. The conclusion of Gilbert et al. that “nearly half of patients do not relapse when kept off neuroleptics” and therefore “maintenance medication would seem unnecessary” is incorrect. In summary, to say that 50% do not relapse is a true statement, but it refers to relapsing in the time period of the study. We suggest that many of the 50% of patients would have gone on to relapse had the studies been longer. Greden and Tandon⁷⁰ argue that “since we cannot pinpoint which patients will not relapse despite being neuroleptic-free, the conventional practice of taking all patients off medications in an effort to see if they might belong to the small minority of schizophrenic patients (approximately 10%) who may not relapse despite being neuroleptic-free is highly questionable.”^{70(p199)}

Gilbert et al.⁶⁴ then advocate slow tapering of neuroleptic dose and indicate that this should be done for most patients and that the slow taper should go to zero. They report only 2 studies that support this strategy. One study is an unpublished study on which we are unable to comment, and in the other study, by Smith,⁷¹ dosage was reduced by one fifth to one third every 1 to 2 months in 16 chronically ill hospitalized schizophrenic patients continuously hospitalized for a mean of 12 years on a neuroleptic dose of approximately 1300 mg chlorpromazine equivalence. With this slow taper, Smith was able to reduce the dose to 437 mg chlorpromazine equivalence. In a meta-analysis of dose-response studies, Bollini et al.⁷² found this to be a more-than-adequate dose. We would surmise that Smith studied treatment-resistant inpatients on very high doses at some time in the past with the hope that the high doses might produce enough benefit so that the patients could be discharged. Consequently, the study by Smith represents a comparison of massive doses against medium doses. It is a fallacy to conclude from these data that patients can be slowly tapered to zero without relapse. The Smith study is completely irrelevant to that question; it is relevant to the question of whether or not continuously hospitalized patients now receiving massive doses really need such high doses. This is an important study in its context, but this finding has nothing to do with outpatient maintenance medications.

The conclusion by Gilbert et al. that patients should be slowly tapered down to zero, stopping neuroleptic therapy, is fallacious. Greenberg and Roth⁷³ found no significant difference between randomly assigned abrupt versus gradual discontinuation in about 40 psychotic long-stay inpatients. If we restrict the analyses to patients who made it to an abrupt withdrawal phase or to complete discontinuation following gradual withdrawal, 55% of patients in the former group relapsed by 3 months in comparison with 63% of the patients in the latter group. Branchey et al.⁷⁴ found that 50% of patients had relapsed by 2½ months despite gradual withdrawal. Crow et al.⁷⁵ studied patients after a 1-month (of half dose) neuroleptic withdrawal period, but many were in the first psychotic episode: 91 of 120 patients were rated as being well, 13 were noted to have residual psychotic features, 10 were rated to be in a deficit state, and 6 were said to have nonspecific symptoms. This is a different population of patients from the great majority of patients in investigated medication maintenance studies. The lower rate of relapse may have been due to the fact that the majority of these patients were well at the start of the study. Levine and coworkers,⁷⁶ in a non-random continuation study, found a nonsignificant (.05 level) trend for fewer relapses after discontinuation from depot than from oral conventional antipsychotics, a trend possibly explained by depot neuroleptic drugs persisting in the brain months after depot conventional antipsychotic is stopped. Gilbert et al.⁶⁴ and Baldessarini and Viguera⁷⁷

performed analyses of length of study versus relapse rate, but the lower relapse rate associated with these studies' longer length may actually be attributable to the fact that patients in the targeted group of long-duration studies received some conventional antipsychotics whereas patients in the shorter-length studies used in the Gilbert et al. analysis received placebo. In short, all the evidence that Gilbert et al. use to support their assertion is flawed.

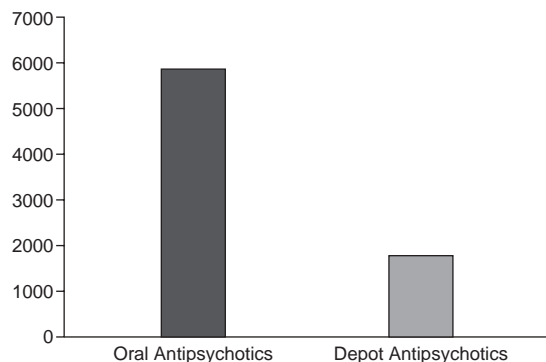
Viguera et al.⁷⁸ and Baldessarini and Viguera⁷⁷ have suggested that abrupt withdrawal may produce a higher relapse rate than gradual withdrawal, and indeed this is observed over a number of analyses with a number of different drugs. If true, it might explain why patients relapse while still receiving medication. If there were a supersensitivity psychosis or other withdrawal phenomena that would put patients at special risk after abrupt withdrawal, then a few days of noncompliance might lead to more relapses than expected. In that case, continuous medication might be particularly important. We feel that long-term continuous medication is required to prevent relapse. We would recommend that oral olanzapine or risperidone be used except when compliance is in doubt, in which case a long-acting injectable newer-generation antipsychotic should be used.

Davis and Andriukaitis⁷⁹ and Wyatt⁸⁰ suggest that untreated psychotic episodes may have deleterious effects on the natural course of schizophrenia. We feel that dose reduction to zero will result in unnecessary relapses and that consistent maintenance medication is still required. We feel that it is important that physicians appreciate the need for maintenance antipsychotics and explain it clearly to patients to eliminate a form of noncompliance that has been called "doctor noncompliance." We want to argue against what we believe are myths about long-term maintenance medications often perpetuated by some articles that we feel do not have real insight into the underlying evidence and create misleading impressions.

LONG-ACTING INJECTABLE VERSUS ORAL ANTIPSYCHOTICS

One of the classic studies of maintenance antipsychotic medication is a Veterans Administration (VA) study of schizophrenia inpatients randomly assigned to placebo or continuous medication.^{67,79} The relapse rate following discontinuation was 15% per month. The relapse rate with continued oral medication was 1.5% per month. This was a study of long-term inpatients with schizophrenia in a VA hospital who were required to take the medication. The great majority of outpatient studies of schizophrenia patients found a high rate of relapse—about 10% per month with placebo.⁷⁹ Antipsychotic drug can reduce this rate, often by 3% to 5% per month, suggesting that noncompliance is a major factor in relapse.⁷⁹ The most likely explanation is noncompliance, often simply forgetfulness.

Figure 2. Number of Days in Hospital for Patients Receiving Oral Medication Who Were Later Switched to Depot Conventional Antipsychotics: Data From 5 Mirror-Image Studies^a



^aData from Davis et al.⁶⁷

The issue of long-acting injectable medication is discussed by others in this supplement; we will not deal with it at this point at length except to note that, in our opinion, high technology research for subjects who volunteer for complicated protocols with invasive tests tends to attract cooperative patients. The patients are likely to take their oral medication as prescribed, and this population may not be fully representative with regard to noncompliant patients. The so-called “mirror-image” study, a subtype of case-control study, investigates days in hospital and similar variables in patients receiving oral medication and the same patients later receiving long-acting injectable, or depot, medication. Since the same patients are studied, many variables are held constant. One variable not held constant is the enthusiasm of the investigator. In Figure 2, we have summarized mirror-image studies on depot conventional antipsychotics. It shows that depot medication very dramatically prevents much rehospitalization, whether measured by number of readmissions either before or after depot medication or by days in hospital on treatment with oral medication and later days in hospital after depot medication.

SUMMARY

Unmedicated schizophrenia patients relapse at a rate of about 10% per month. Maintenance conventional antipsychotics can reduce this rate by about two thirds. Long-acting injectable medication can reduce the relapse rate even further. Data from Csernansky et al.²⁸ suggest that use of risperidone can reduce the relapse rate by about an additional one third. Some newer-generation antipsychotics (risperidone, olanzapine) produce a wider range of improvement than conventional antipsychotics, improving negative symptoms, thought disorder, impulsivity/hostility, and anxiety/depression.

Drug names: aripiprazole (Abilify), chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented in this article that is outside U.S. Food and Drug Administration–approved labeling.

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