Schizophrenia Bulletin vol. 31 no. 3 pp. 705–722, 2005
doi:10.1093/schbul/sbi032
Advance Access publication on July 8, 2005

Pharmacological Treatments for First-Episode Schizophrenia

Delbert G. Robinson[1–4], Margaret G. Woerner[3–4], Howard M. Delman[3], and John M. Kane[3–4]

[2]Research Department, The Zucker Hillside Hospital, Glen Oaks, NY 11004; [3]Department of Psychiatry, The Zucker Hillside Hospital of the North Shore–Long Island Jewish Health System, Glen Oaks, New York 11004; [4]Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, New York 10461

Studies with first-episode populations offer the unique opportunity to examine the effectiveness and side effects of medications without the confounding effects of prior medication use. This review focuses upon studies of (1) treatment of the initial episode, (2) maintenance treatment issues, (3) recovery, and (4) side effects. Response rates for the initial episode are high with both conventional and new-generation antipsychotics. However, we lack data directly comparing the new-generation agents with one another for treatment of the initial episode, and data about options for patients with treatment resistance at illness onset are very limited. With the most commonly used pharmacological therapies, the course of early-phase schizophrenia is characterized by repeated relapses and a low rate of recovery. Medication treatment is also associated with a variety of side effects. Of particular concern for treatment of first-episode patients are the metabolic side effects with the new-generation antipsychotics because they occur rapidly, are very distressful to adolescents and young adults, and have long-term medical consequences. Available data support maintenance treatment to prevent relapse, but questions remain about the optimal duration of maintenance treatment, whether there are differences among the new-generation agents for maintenance treatment, and balancing the benefits of maintenance antipsychotics with their long-term side effects.

Key words: treatment response/maintenance treatment/relapse/recovery/adherence/side effects

Introduction

Studies with first-episode populations offer the unique opportunity to examine the effectiveness and side effects of medications without the confounding effects of prior medication use. Most treatment study samples include a high proportion of chronic patients who have had multiple episodes of illness. These study samples may systematically overrepresent patients who are not fully responsive to treatment or are nonadherent to treatment (or both). Results from these studies may underestimate response to medication. First-episode samples may be less biased on these factors and therefore may be more informative about the spectrum of outcomes with medication treatments.

First-episode studies and interventions derived from them are also important from several clinical perspectives. By definition, first-episode patients do not have a known response to treatment. Treatment recommendations for them must be based upon research findings rather than upon past individual response to treatment. In addition, successful treatment of the initial psychotic episode is crucial for minimizing the cascading effects of social and vocational deterioration. Controlling the unusual behavior associated with positive symptoms is key to allowing subjects to return to mainstream activities.

The focus of this article is an exploration of the knowledge already gained from studies of pharmacological interventions with subjects with first-episode schizophrenia as well as the limitations of our current understanding. Our review will cover (1) treatment of the initial episode, (2) maintenance treatment issues, (3) recovery, and (4) side effects.

Response to Treatment of the Initial Episode

Table 1 summarizes the findings from studies of the treatment of the initial episode of illness.

Treatment With Conventional Antipsychotics

As initially shown by the pioneering study of May and colleagues[1] and replicated in subsequent studies, the response rates with conventional antipsychotics in studies specifically designed to examine treatment of the initial episode are high, ranging from 46 to 96%. Only 1 study[2] has found a low rate (29%) of response (based on a 40% or greater reduction in Brief Psychiatric Rating Scale[3] total score from baseline) to treatment with haloperidol. Possible reasons for this divergent finding include that the study was a secondary analysis of a large international study with 1,996 subjects that was not designed to study first-episode patients, the number of

[1]To whom correspondence should be addressed; e-mail: robinson@lij.edu

Table 1. Treatment of the Initial Episode

Study	Population	Inclusion Criteria	Design/Protocol	Response Criteria	Response Rate	Other Comments
May, Tuma, Yale, Potepan, & Dixon, 1976[1]	228 first-admission schizophrenia patients admitted to a state psychiatric hospital between 1959 and 1962	diagnosis of schizophrenia; no significant prior treatment for schizophrenia; very good and very poor prognosis patients were excluded	6- to 12-month randomized trial comparing individual psychotherapy alone, trifluoperazine alone, individual psychotherapy + trifluoperazine, ECT alone, and milieu therapy alone	discharge from the hospital	individual psychotherapy—65%; trifluoperazine—96%; combined therapy and trifluoperazine—95%; ECT—79% milieu therapy alone—58%	trend indicating less time in the hospital following initial discharge for trifluoperazine and ECT groups
Scottish Schizophrenia Research Group, 1987[58]	46 first-episode schizophrenia (ICD-9) patients admitted to the hospital	none stated	5-week randomized, double-blind trial of pimozide (10–40 mg) versus flupenthixol (10–50 mg); adjunctive medications allowed	responder: switched to maintenance therapy on assigned medication; nonresponder: requires other treatment (ECT or another neuroleptic); noncompleter: not proceeding to maintenance therapy and not clearly nonresponder	overall 63%	positive symptoms responded to treatment, while negative symptoms did not (for both groups); data on longer-term follow-up are provided in [17, 20]
Kopala, Frederikson, Good, & Honer, 1996[59]	22 antipsychotic-naive schizophrenia (DSM) patients	no substance abuse, previous head injury, organic pathology, uncertain diagnosis, or inadequate source of collateral history	risperidone, titrated over 2 weeks to 2–8 mg daily; mean length of treatment: 7.1 weeks; adjunctive medications allowed	20% or greater reduction in total PANSS score compared to baseline	59%; significant improvements found on all 5 factors but less so on negative symptoms	CGI severity and GAF scores also improved
Emsley, 1999[6]	183 first-episode schizophrenia or schizophreniform (DSM-III-R) disorder patients	age 15–45; requires treatment with oral antipsychotic; no more than 3 days of prior treatment; no neurological, electrocardiographic, or laboratory test abnormalities	6-week randomized, double-blind comparison of risperidone with haloperidol; initial dose 2 mg twice daily, titrated to range of 2–16 mg/day; adjunctive medications allowed on very limited basis	50% or more reduction in total PANSS scores at end point	risperidone: 63%; haloperidol: 56%; between-treatment differences were not statistically significant	PANSS total and subscale scores significantly improved compared with baseline at all time points in both groups

Table 1. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Response Criteria	Response Rate	Other Comments
Robinson, Woerner, Alvir, et al., 1999[4]; interim results in Lieberman, Jody, Geisler, et al., 1993[60]	118 first-episode schizophrenia and schizoaffective disorder (RDC) patients	less than 12 weeks of prior antipsychotic exposure; at least 1 psychotic symptom of moderate severity; no medical conditions that could affect diagnosis or the biological variables in the study or contraindicate antipsychotic treatment	standardized algorithm—subjects proceeded to the next level if no improvement: fluphenazine hcl up to 20 mg/day for 6 weeks; fluphenazine hcl 40 mg/day for 4 weeks; switch to haloperidol 20mg/day for 6 weeks; haloperidol 40mg/day for 6 weeks; switch to antipsychotic from different biochemical class (e.g., molindone, up to 300 mg/day); if still treatment resistant, considered for clozapine trial	CGI improvement ratings of 2 or 1 and ratings no greater than 3 on SADS-C+PD psychosis items maintained for 8 weeks	the cumulative percentage of patients responding by 1 year: 87%; median time to response: 9 weeks	higher response rates for woman; serious obstetric complications, prolonged DUP (trend), more severe positive symptoms, and worse performance on attention and motor tests associated with lower response rates
Sanger, Lieberman, Tohen, Grundy, Beasley, & Tollefson, 1999[2]	83 first-episode schizophrenia, schizophreniform, or schizoaffective disorder (DSM-III-R) patients; a subset of participants in a multicenter study with 1,996 subjects	actively symptomatic; length of current episode no greater than 5 years; age of onset of episode no greater than 45 years old	6-week double-blind randomized trial (2:1 ratio) comparing olanzapine and haloperidol; initial dosage of 5 mg/day could be increased or decreased by 5 mg after each 7-day period, within 5–20 mg/day range; adjunctive medications allowed	a 40% reduction from baseline in PANSS-derived BPRS total score	olanzapine: 67%; haloperidol: 29%	reduction of 20% or more on BPRS total: olanzapine—83%, haloperidol—58%; olanzapine superior in reduction of BPRS total and negative scores and PANSS total and positive scores
Yap, Mahendran, Lim, et al., 2001[61]	24 treatment-naive first-episode schizophrenia and schizophreniform disorder (DSM-IV) patients	duration of episode no greater than 12 months; age 18–65 years old	8-week open label trial of risperidone	20% or more reduction in total PANSS scores at end point	87% (54% had a reduction of at least 50%)	significant reductions on all PANSS items except mannerisms and posturing; all patients improved on CGI

Table 1. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Response Criteria	Response Rate	Other Comments
Lieberman, Phillips, Gu, et al., 2003[5]	160 patients with schizophrenia or schizophreniform disorder (DSM-IV)	duration of symptoms no more than 60 months; prior antipsychotic use no more than 14 days; age 16–40 years; current psychotic symptoms of moderate severity or greater	52-week double-blind randomized trial of clozapine + benztropine placebo and chlorpromazine + benztropine; titrated over first 28 days, up to 400 mg/day of clozapine or 600 mg/day of chlorpromazine; benztropine dose 2 mg twice daily	50% or more reduction in total BPRS with no score greater than mild psychosis items and CGI severity item	chlorpromazine: 79% by 1 year (median 12 weeks); clozapine: 81% by 1 year (median 8 weeks); difference not statistically significant	after 12 weeks of treatment, clozapine patients had significantly more improvement on total BPRS, BPRS anergia, total SANS, SANS affective, poverty of speech, avolition, anhedonia, CGI severity, and GAF
Lieberman, Tollefson, Tohen, et al., 2003[8]	263 patients with schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV)	age 16–40; onset by age 35; psychotic symptoms for 1 to 60 months; score of at least 4 on at least 2 PANSS psychosis items or at least 5 on 1 item; CGI severity score of at least 4	double-blind randomized trial of olanzapine and haloperidol; olanzapine doses 5–10 mg/day for 6 weeks, then 5–20 mg/day; haloperidol doses 2–6 mg/day, then 2–20 mg/day; acute treatment phase 12 weeks; follow-up for up to 2 years; certain adjunctive medications allowed	no ratings greater than 3 on PANSS psychosis items; at least a 30% reduction in total PANSS score; CGI severity score no greater than 4	by end of 12 weeks: olanzapine—55% (median 7.9 weeks), haloperidol—46% (median 8.4 weeks); the difference was not significant	olanzapine patients improved more on PANSS total, negative, and general scales and Montgomery-Asberg Depression scores; no differences on the PANSS positive scale or the CGI severity ratings
Woerner, Robinson, Alvir, Sheitman, Lieberman, & Kane, 2003[13]	34 first-episode schizophrenia or schizoaffective disorder (RDC) patients	age 16–45; at least 1 SADS-C psychotic symptom of moderate or worse severity; no more than 12 weeks of prior antipsychotic treatment; no medical conditions that might affect diagnosis, assessment, or contraindicate treatment with clozapine	open clozapine treatment with follow-up for up to 4 years; standard titration with increases of 25 mg every other day for first 9 days (to 100 mg), then in increments of 50 mg every other day until treatment response or occurrence of dose-related side effects	no psychotic symptoms rated more than mild on the SADS-C and being rated much improved or very much improved on the CGI; the improvement had to be maintained for at least 2 months	cumulative response rate was 66.4% (95% CI 48.3%, 84.5%); all response occurred by week 13; mean dose at time of response was 206 mg (SD = 133)	of the patients who relapsed, only 1 was still taking clozapine at the time of relapse; long-term, there was a high rate of discontinuation of clozapine (71% by year 1)

Table 1. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Response Criteria	Response Rate	Other Comments
Schooler, Rabinowitz, Davidson, et al., 2005[7]	555 schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV) patients	age 16–45; ill for 12 months or less; no more than 2 hospitalizations for psychosis; no more than 12 weeks of prior antipsychotic treatment	international 12-week double-blind randomized comparison of risperidone and haloperidol; identical dosing scheme: titrated from 1 mg/day to a maximum of 4 mg/day; certain adjunctive medications allowed	20% or more reduction in PANSS total score	risperidone: 74%; haloperidol: 76%	

Note: ECT = electroconvulsive therapy, PANSS = Positive and Negative Syndrome Scales, CGI = Clinical Global Impression, GAF = Global Assessment of Functioning, SADS-C+PD = Schedule for Affective Disorders and Schizophrenia–Change version + Psychosis and disorganization items, DUP = duration of untreated psychosis, BPRS = Brief Psychiatric Rating Scale.

haloperidol-treated first-episode subjects identified was small (n = 24) and only 5 were antipsychotic naïve, and only 9 of the haloperidol-treated subjects finished the 6-week-long trial.

The response rates for the primary first-episode studies are especially notable in comparison with the usual response rates reported for treatment of multiepisode subjects. Response criteria differ across studies. Many investigators have used more stringent response criteria in first-episode studies than those usually employed in studies of multiepisode subjects. It seems appropriate to aim for a substantial improvement in symptoms, if not a return to premorbid condition, with subjects who are young and just beginning treatment. For example, in our treatment algorithm study using conventional antipsychotics with clozapine for treatment-resistant subjects,[4] response criteria required the absence of delusions, hallucinations, and substantial thought disorder for at least 8 consecutive weeks. The stringency of response criteria in many first-episode studies makes the high response rates reported particularly striking.

Treatment With New-Generation Versus Conventional Antipsychotics

Four large-sample-size studies comparing first- and second-generation antipsychotics in first-episode samples have been published: clozapine versus chlorpromazine (n = 160),[5] risperidone versus haloperidol (n = 183,[6] n = 555),[7] and olanzapine versus haloperidol (n = 263).[8] None has found statistically significant differences in response rates between first- and second-generation agents.

The studies comparing olanzapine and risperidone with haloperidol, given their frequent use with first-episode subjects, are of particular interest. The largest study with olanzapine is that of Lieberman and colleagues.[8] Two hundred sixty-three patients were randomly assigned to treatment under double-blind conditions. Although these patients were early in their illness course, prior treatment with antipsychotics for up to 16 cumulative weeks was allowed; 26% had no prior treatment, and the remaining 74% had a mean of 6 (and a median of 3) weeks of prior treatment. Fifty-nine percent of patients had a diagnosis of schizophrenia; 31%, schizophreniform disorder; and 10%, schizoaffective disorder. Mean age was 24 years, and 82% were male. The mean modal doses were 9.1 mg olanzapine per day and 4.4 mg haloperidol per day. Sixty-eight percent of the olanzapine- and 54% of the haloperidol-treated patients completed the 12-week acute phase (p = .03). Response was defined as a rating of 3 or less on items P1, P2, P3, P5, and P6 of the Positive and Negative Syndrome Scale (PANSS),[9] a 30% or greater reduction from baseline of the PANSS total score, and a Clinical Global Impression (CGI)[10] severity score of moderately ill or better. Response rates (55% with olanzapine

and 46% with haloperidol) did not differ ($p = .19$). Analyses of psychopathology scale scores were also performed. Significant reductions in symptoms were found with both medications in last-observation-carried-forward and also mixed-model analyses. No significant differences between the medications in symptom reduction were found with the last-observation-carried-forward analyses, but the mixed-model analyses showed that olanzapine compared with haloperidol treatment is associated with significantly greater decrease in symptom severity on the PANSS total, negative, and general scale scores and on the Montgomery-Asberg Depression Rating Scale score[11] (but not on the PANSS positive scale or on the CGI severity score).

The largest study of risperidone is the trial of Schooler and colleagues.[7] Patients were eligible if they met DSM criteria for schizophrenia, schizophreniform, or schizoaffective disorder for 1 year or less; had no more than 2 psychiatric hospitalizations for psychosis; and had less than 12 weeks cumulative exposure to antipsychotics. Five hundred fifty-five first-episode patients were randomly assigned to double-blind treatment with risperidone (mean modal daily dose 3.3 mg) or haloperidol (mean modal daily dose 2.9 mg). Sixty-nine percent of subjects had some prior use of antipsychotics, 70% were male, the mean age was 25 years, and 48% had a diagnosis of schizophrenia; 44%, schizophreniform disorder; and 8%, schizoaffective disorder. At 3 months both groups showed significant clinical improvement; 74% of those on risperidone and 76% of those on haloperidol met response criteria. Response criteria (20% reduction in total PANSS scores) in this study were less stringent than in many first-episode studies.

Future Questions

Although the response rates from published studies are encouraging, there remain important gaps in our knowledge about treatment of the initial episode of illness. The most conspicuous is the lack of data directly comparing the new-generation agents with each other for the treatment of first-episode subjects. This is partially the result of the difficulty of recruiting a sufficient number of first-episode subjects for comparative trials. Thus early knowledge about new agents is based upon studies of multiepisode patients; studies with first-episode patients are reported later. Data from our group and others comparing the new-generation agents in first-episode subjects will be available shortly.

Some patients do not respond to their initial treatment trial. How to manage these patients is an important clinical question. In addition, these subjects offer an opportunity to study the biological basis of treatment resistance without the confounds of prolonged medication effects and other factors related to chronicity present in studies of treatment resistance with multiepisode patients.

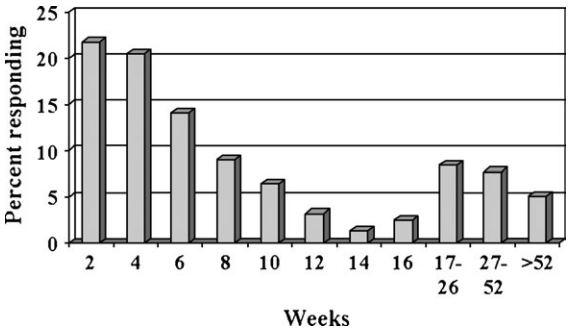

Fig. 1. Time to Response: 156 First-Episode Subjects Who Met Response Criteria in Medication Algorithm Studies. Medications, dose, and duration of treatment before medication changes varied across studies.

In discussions with patients who do not respond to their initial treatment, one can fortunately assure them and their family members that some subjects do respond only after a long period of treatment. We examined the time to response for all subjects who had been in medication algorithm studies at our institution. The initial medications in the different algorithms were conventional agents, clozapine or risperidone. One hundred fifty-six subjects met response criteria based upon 2 consecutive Schedule for Affective Disorders and Schizophrenia–Change version with psychosis and disorganization items (SADS-C+PD)[12] ratings, with 3 (mild) or less on severity of delusions, severity of hallucinations, and impaired understandability items. As shown in figure 1, many subjects responded rapidly, but a substantial number took 6 months or longer to respond. The medications taken up to (and at) the time of response for subjects who responded late in treatment varied considerably. Determining the basis for delayed treatment response is an unanswered question with important clinical implications.

Given that some first-episode patients do not respond to initial treatment, the question arises about the use of clozapine with first-episode patients. Two studies[5, 13] have used clozapine as the initial treatment for a first episode. Neither has found advantages for clozapine that would warrant its use as a first-line treatment. The data, although limited, do support its use with patients who fail trials with other antipsychotics. Szymanski et al. have found a 30% response rate to clozapine treatment among 10 first-episode subjects who had failed to respond to trials with 3 conventional antipsychotics.[14]

Maintenance Treatment

Is Pharmacological Maintenance Treatment Indicated?

It is important to recognize that there are no clear-cut demarcations between treatment for the acute episode and that for maintenance phases. In schizophrenia some aspects of the illness are more amenable to treatment than others (e.g., positive versus negative or

cognitive symptoms), making the demarcation among acute, continuation, and maintenance treatment difficult. Maintenance treatment studies have used different criteria for treatment response and for duration of response required before subjects begin maintenance trials. This limits the ability to compare results across studies. In addition, the interpretation of maintenance treatment studies is complicated by the lack of a standard definition of relapse. Relapse criteria employed have included the return of positive symptoms, the return of various nonpsychotic symptoms, or rehospitalization.

Placebo-Controlled Trials. Maintenance treatment studies with first-episode samples are summarized in table 2. As shown in the table, there have been several placebo-controlled trials with conventional antipsychotics. As has been found in studies with multiepisode patients, all the trials show a substantial advantage for active medication compared with placebo for prevention of relapse. The reported rates of relapse vary substantially across studies. Relapse rates on placebo versus active medication were 41 versus 0%,[15] 62 versus 46%,[16] 57 versus 0%,[17] and 64 versus 43%.[18] These differences in relapse rates across studies may be attributable to variations in key aspects of study design (e.g., stability of response before randomization, definition of relapse). In addition, the confidence intervals around these estimates may be large in some of the studies due to small sample sizes.

Naturalistic Studies. Placebo-controlled trials have lasted a maximum of 2 years. The results of naturalistic studies are useful to provide data on relapse risk over longer time frames. Long-term follow-up of 26 of the Kane et al. sample (mean follow-up 3.5 years) showed that 69% had 1 relapse and 54% had 2 relapses.[15] Follow-up[19] of the Crow et al.[16] sample has found that of the 44 patients traced, 2 had died, and 79% of the remaining 42 subjects had been hospitalized at least once within 5 years. The Scottish Schizophrenia Research Group reports that 70% of its sample of 44 patients had relapsed over a 5-year period.[20] Gitlin et al. followed 53 subjects with recent-onset schizophrenia who had been clinically stabilized on a maintenance regimen of fluphenazine decanoate for a mean of 16.7 months and then had their antipsychotic medication withdrawn under clinical supervision.[21] Patients initially entered a 24-week, double-blind crossover trial in which fluphenazine and placebo were administered for 12 weeks each. For those individuals who did not experience symptom exacerbation or relapse during this period, fluphenazine was openly withdrawn. Participants were then followed for up to 18 months. When a low threshold was used for defining symptom reemergence 78% of 50 subjects experienced an exacerbation within 1 year, and 96%, within 2 years. Only 13% of subjects who relapsed were rehospitalized.

The primary outcome for most studies of maintenance treatment has been the first relapse following response to treatment of the initial episode. The study by Robinson and colleagues provides data showing that most subjects experience multiple relapses during the first years of illness.[22] By 5 years of follow-up, 82% of subjects had experienced 1 relapse, 78% of subjects who had recovered from their first relapse had a second relapse, and 86% of subjects who recovered from their second relapse had a third relapse episode. A survival analysis using medication status as a covariate has found a 5-times higher relapse rate for patients who discontinued medication compared to those who continued medication.

Continuous Versus Intermittent Maintenance Medication

If maintenance antipsychotic medications are effective, how should they be administered? Gaebel et al. report results involving a subsample of first-episode patients participating in a 2-year randomized open treatment study comparing 3 medication strategies: continuous maintenance treatment, prodrome-based intervention, and crisis intervention.[23] Prodrome-based intervention involved the reintroduction of antipsychotic medication as soon as prodromal symptoms (suspected predictors of impending relapse, e.g., restlessness, trouble sleeping, trouble concentrating, tension and nervousness, loss of interest or depression) occurred. Once restabilization was attained the antipsychotic drugs were again discontinued. Crisis intervention provided for the reintroduction of antipsychotic medication only in the case of a full relapse. Relapse rates during the 2-year period for first-episode subjects who completed the study were as follows: maintenance treatment, 38%; prodrome-based intervention, 42%; crisis intervention, 67%.

The authors suggest that, in contrast to their results with multiepisode patients, prodromal intervention may be an alternative to continuous maintenance treatment for first-episode patients. For those first-episode patients who insist on discontinuing medication, certainly a prodromal intervention strategy would be preferable to no treatment at all or a crisis intervention approach. However, the study findings need to be interpreted with caution. First, antipsychotic treatment was not controlled and was left to clinician discretion. Second, 21% of subjects assigned to prodrome-based and 20% of subjects assigned to crisis intervention either could not be withdrawn from their antipsychotic treatment or could be maintained for at least 4 weeks off antipsychotics. Including these subjects and dropouts for other causes, over half (55.6% with maintenance treatment, 51.3% with prodrome-based intervention, and 62.5% with crisis intervention) of the first-episode subjects did not complete the study. Third, during the first year of treatment the average numbers of relapses per subject for first-episode subjects assigned to maintenance treatment

Table 2. Maintenance Treatment

Study	Population	Inclusion Criteria	Design/Protocol	Relapse Criteria	Relapse Rate	Other Comments
Kane, Rifkin, Quitkin, Nayak, & Ramos-Lorenzi, 1982[15]	28 first-episode patients with RDC-defined diagnoses of schizophrenia (n = 19) or another disorder with psychotic features (n = 9)	no serious psychopathology or treatment prior to 3 months before hospitalization; stable remission of at least 4 weeks within 1 year of hospital admission; no drug abuse, alcoholism, or important medical illness	double-blind, 1-year randomized comparison of oral fluphenazine (5–20 mg/day) or fluphenazine decanoate (12.5–50 mg/2 weeks), with placebo (n = 17)	substantial clinical deterioration with a potential for marked social impairment	fluphenazine: 0%; placebo: 41%	18 of 26 (69%) of those available for follow-up had a second relapse, and 14 of these 18 experienced a third episode
Crow, MacMillan, Johnson, & Johnstone, 1986[16]	120 first-episode patients with nonaffective psychosis	age 15–70	randomized, placebo-controlled comparison of maintenance medication, either IM flupenthixol, chlorpromazine, haloperidol, pimozide, or trifluoperazine, with placebo	readmission to a psychiatric hospital, or readmission considered necessary but not possible, or any antipsychotic medication change considered necessary because of features indicating imminent relapse	active medication: 46%; placebo: 62%	relapse rates consistently lower at 6-, 12-, 18-, and 24-month follow-up for patients on active medications; the strongest predictor of relapse was time between onset of illness and first trial prescription; data on longer-term follow-up are provided in Geddes el al.[19]
Rabiner, Wegner, & Kane, 1986[62]	36 first-episode patients with schizophrenia (RDC; a subset of participants in a study of first-episode psychosis)	hospitalization for a first episode of psychosis	naturalistic follow-up design; assessments at baseline and 3, 6, and 12 months	criteria for remission of the first episode: absence of delusions, hallucinations, and formal thought disorder for 3 months; relapse defined as the reoccurrence of these symptoms after remission	8 (22%) did not achieve remission during the 1-year study; 8 (29%) of the 28 subjects who achieved remission relapsed during the follow-up period	longer duration of illness and premorbid asociality were associated with poorer outcome

Table 2. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Relapse Criteria	Relapse Rate	Other Comments
Scottish Schizophrenia Research Group, 1989[17]	15 schizophrenia patients who participated in a randomized acute treatment trial	successful completion of the first year's double-blind study comparing once weekly IM flupenthixol with pimozide	1-year randomized, double-blind comparison of active treatment, either pimozide or IM flupenthixol (n = 8), with placebo (n = 7)	rehospitalization	active medication: 0%; placebo: 57%	
Hogarty & Ulrich, 1998[18]	75 first-episode schizophrenia (DSM-II) patients (a subset of a larger study)	discharge from hospital within past 21 days; duration of most recent hospital stay 2 years or less	double-blind randomized comparison of chlorpromazine with placebo	clinical deterioration to point of imminent rehospitalization	chlorpromazine: 27% at 1 year, 43% at 2 years placebo: 61% at 1 year, 64% at 2 years	
Robinson, Woerner, Alvir, et al., 1999[22]	118 schizophrenia and schizoaffective disorder (RDC) patients began treatment within the study for their first episode (see [4]); the sample for the relapse analyses includes 104 subjects who responded to treatment of their initial episode and were followed up for at least 2 months after fulfilling response criteria	at study entry: less than 12 weeks of prior antipsychotic treatment, rating of 4 or more on at least 1 psychotic symptom item on the SADS-C+PD, no medical contraindications to treatment with neuroleptics, no neurologic or endocrine disorder or neuromedical illness that could affect diagnosis or the biological variables in the study	standardized algorithm—subjects proceeded to the next level if no improvement: fluphenazine up to 20 mg/day for 6 weeks, fluphenazine 40 mg/day for 4 weeks, switch to haloperidol 20 mg/day for 6 weeks, haloperidol 40 mg/day for 6 weeks, switch to antipsychotic from different biochemical class (e.g., molindone, up to 300 mg/day); if still treatment resistant, considered for clozapine trial	at least "moderately ill" on CGI severity scale; "much worse" or "very much worse" on CGI improvement scale, and at least "moderate" on 1 or more of the SADS-C+PD psychosis items sustained for a minimum of 1 week	82% relapsed within 5 years; 78% had a second and 86% had a third relapse	discontinuing antipsychotic medication increased the risk of relapse by almost 5 times; early adolescent premorbid adjustment significantly predicted first relapse; late adolescent premorbid adjustment and hippocampal volume were trend-level predictors

Table 2. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Relapse Criteria	Relapse Rate	Other Comments
Gitlin, Nuechterlein, Subotnik, et al., 2001[21]	53 patients with schizophrenia or schizoaffective disorder, mainly schizophrenic (RDC); a subset of a larger cohort of patients	first onset of a psychotic episode no more than 2 years before study entry; age 18–45 years; no evidence of neurological disorder or history of significant substance use in the 6 months prior to study entry; clinically stable on fluphenazine decanoate for at least 1 year	24-week double-blind crossover study in which fluphenazine decanoate and placebo were each given for 12 weeks; those who remained stable had open discontinuation of fluphenazine decanoate and were followed up for up to 18 months	exacerbation: 2-point change on any of the 3 BPRS psychotic items; relapse: a rating of 6 or 7 on any of the 3 BPRS psychotic items or a worsening of clinical condition warranting change in treatment regardless of BPRS ratings	crossover relapse or exacerbation: medication—6%, placebo—13%; withdrawal phase, relapse, or exacerbation: by 1 year—78%, by 2 years—96%	only 13% of 45 patients required hospitalization following exacerbation or relapse
Malla, Norman, Scholten, Zirul, & Kotteda, 2001[63]	38 schizophrenia (DSM-III-R or DSM-IV) patients receiving initial treatment between 1991 and 1997 (typical) or 1993 and 1997 (risperidone)	treatment with either risperidone alone for >1 year or a single typical antipsychotic for the entire course of illness	cohorts derived from chart review were matched on age, gender, length of illness, and length of treatment; follow-up data 1 to 8 years after initial treatment included case record reviews, interviews, and rating scales	readmission within the first year following discharge from index admission	within 1 year: typical antipsychotic—32% (6 patients), risperidone—5% (1 patient)	
Gaebel, Janner, Frommann, et al., 2002[23]	115 schizophrenia or schizoaffective disorder (fulfilling both ICD-9 and RDC criteria) patients; a subset of a larger study	age 18–55; stable for 3 months following inpatient treatment; no organic illness, substance abuse, mental retardation, pregnancy, suicide attempts, serious legal problems	2-year randomized trial comparing 3 open treatment strategies 1. maintenance—continued neuroleptic treatment, any drug, minimally 100mg chlorpromazine equivalents per day 2. prodrome-based intervention—gradual neuroleptic discontinuation medication reintroduced upon emergence of prodromal symptoms; 3. crisis intervention—medication discontinuation, as above, medication reintroduced only upon relapse	psychotic deterioration of maximum intensity usually demanding hospitalization, plus BPRS psychosis factor sum of at least 10, GAS no greater than 20, and CGI of at least 6	the dropout rate was more than 50%; for completers: maintenance—38%, prodrome based—42%, crisis intervention—67%	treatment adherence was best with the prodrome-based intervention; cumulative neuroleptic dosage was lowest with intermittent treatment; no differences among groups in psychopathology, social adjustment, subjective well-being, or side effects; the average number of relapses per subject was the same in years 1 and 2 with maintenance therapy but increased from year 1 to year 2 with the prodrome intervention

Table 2. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Relapse Criteria	Relapse Rate	Other Comments
Schooler, Rabinowitz, Davidson, et al., 2005[7]	555 patients with a diagnosis of schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV) began the study; 203 haloperidol-treated and 197 risperidone-treated subjects met response criteria and were included in the analyses of relapse	age 16–45; illness duration no more than 12 months; no more than 2 hospitalizations for psychosis; no more than 12 weeks of prior antipsychotic treatment	international 12-week double-blind randomized comparison of risperidone and haloperidol; identical dosing scheme: titrated from 1 mg/day to a maximum of 4 mg/day; certain adjunctive medications allowed	following clinical improvement, a 25% or more increase in PANSS score, CGI score of "much worse" or "very much worse," deliberate self-injury, emergence of clinically significant suicidal or homicidal ideation or completed suicide, or violent behavior resulting in significant injury to another person or significant property damage	risperidone: 42% haloperidol: 55% (the difference is statistically significant)	median time to relapse: 466 days for risperidone and 205 days for haloperidol

Note: CGI = Clinical Global Impression, SADS-C+PD = Schedule for Affective Disorders and Schizophrenia–Change version + Psychosis and disorganization items, BPRS = Brief Psychiatric Rating Scale, GAS = Global Assessment Scale, PANSS = Positive and Negative Syndrome Scales.

and for first-episode subjects assigned to prodrome-based interventions were very similar (0.25 and 0.21, respectively) and substantially lower than the 0.60 average for crisis intervention subjects. The average number of relapses per subject during the second year of follow-up for the maintenance intervention (0.25) was no different from the average during the first year. However, the average number of relapses per subject for the prodrome intervention was higher during the second compared to the first year of follow-up (0.42 versus 0.21). Most maintenance treatment studies have found a relatively low rate of relapse during the first year of follow-up and substantially higher rates in the second year. The higher rate of relapse during the second year with prodrome interventions in the Gaebel et al. study suggests that prodrome-based interventions may become less effective as subjects enter a period of greater relapse risk.

Comparison of Antipsychotics for Relapse Prevention

The primary source of data comparing different antipsychotics for maintenance treatment with first-episode patients is the study by Schooler and colleagues described previously.[7] Median length of follow-up was 206 days; the longest length of study participation was 1,514 days. Rates of response (defined as a 20% or greater reduction of total PANSS scores) were similar for treatment with risperidone and haloperidol. Among subjects meeting response criteria (haloperidol, $n = 203$; risperidone, $n = 197$), there were fewer relapses during longitudinal follow-up among risperidone-treated subjects (42.1%) than among haloperidol-treated subjects (54.7%). Median time to relapse was 466 days with risperidone and 205 days with haloperidol. These differences are clinically relevant. As with all studies, there are limitations in the interpretation of the results. The study used the relapse criteria employed in the Csernansky et al. study of relapse with multiepisode subjects.[24] These criteria define relapse broadly (e.g., 25% increase in PANSS score, self-injury, or violent behavior). It is therefore unclear how the results relate to more circumscribed definitions of relapse (e.g., return of positive symptoms). In addition, the criteria for treatment response were less stringent than those often employed in other first-episode studies. Whether similar results would be found if a more rigorous standard of response were required for subjects to enter into the relapse analyses is an important unanswered question.

Adherence

A treatment regimen can, of course, only be effective if patients are willing to adhere to it. There have been many studies of adherence with multiepisode patients but very few with first-episode patients. Numerous factors suggest the need to study recent-onset patients. Due to their younger age, treatment decisions are

more likely to involve both patients and their family members than is the case with multiepisode patients. Further, recent-onset patients and their families lack experience with antipsychotics and with the chronic and relapsing course of schizophrenia. Their assessment of the benefits versus liabilities of antipsychotics may differ from those of multiepisode patients who have experienced the adverse consequences associated with repeated relapses. In an analysis of data from our first-episode algorithm study using conventional antipsychotics,[25] we found that parkinsonian side effects increased the likelihood of medication discontinuation and better executive functioning decreased the likelihood of discontinuation. These data suggest that efforts to minimize side effects, as well as efforts to improve cognitive deficits or teach patients strategies to improve their functioning despite deficits, may enhance adherence.

Recovery

Schizophrenia affects many aspects of patients' lives. Ideally, assessments of outcome should include all domains that are impaired by the disease. Most treatment studies employ global improvement measures or measure a limited number of specific areas (e.g., positive or negative symptoms). Although these methods have been very useful for evaluating treatment effects, they do not assess patients in important areas that may remain impaired despite symptomatic improvement and which seriously affect the quality of life of patients and their family members. Recently, criteria for recovery have been proposed that require sustained improvement in symptoms, role functioning, and social adjustment. Although not all-encompassing, these recovery criteria identify a level of improvement that more closely approximates the state of recovery desired by patients and their families than traditional outcome criteria do.

The primary sources of data on recovery in schizophrenia have been long-term follow-up studies (reviewed in [26]). These studies have examined subjects 2 to 3 decades after an index admission and found that a substantial number of subjects recover after prolonged periods of illness. Although these studies have provided valuable information about recovery, they all have similar methodological limitations: reliance upon retrospective information, an inability to address many biological and clinical measures of current interest because the samples were obtained decades ago, and no data about recovery during the crucial early phase of the illness.

Studies of recovery during the early phase of schizophrenia are of interest to complement the data from the long-term studies. There are several ongoing studies in this area, and work by our group has demonstrated the potential importance of such studies.[27] We have analyzed data from the sample of 118 subjects with first-episode schizophrenia who were treated according to a medication algorithm employing conventional antipsychotics or clozapine for subjects who failed treatment with conventional agents. Subjects were followed for up to 5 years. Our recovery measures were derived from the University of California at Los Angeles recovery criteria.[28] Symptom remission criteria are a rating of mild (3) or less on all the SADS-C+PD psychosis items and a rating of moderate (3) or less on the global ratings on the Scale for the Assessment of Negative Symptoms.[29] Adequate social vocational functioning has 3 components, and all 3 had to be fulfilled simultaneously to meet criteria. These components are (1) *appropriate role function*—in paid employment, attending school at least half-time, or if a homemaker, performing that role adequately or better; (2) *ability to perform day-to-day living tasks without supervision*—personal appearance and grooming are "reasonable, neat, clean and appropriate"[30] or better and functioning at least adequately as a homemaker or performs household chores as appropriate for age; and (3) *social interactions*—with a peer outside of the family once a week or more frequently.

By 5 years of follow-up, 47.2% of subjects met symptom remission criteria for a continuous period of 2 years or more, and 25.2% met adequate social vocational functioning criteria for a continuous period of 2 years or more. However, only 13.7% of subjects had a period of 2 years or longer during which they simultaneously meet criteria for both symptom remission and adequate social vocational functioning (i.e., fulfilled the recovery criteria). This low rate of recovery highlights the need to develop better treatments for first-episode schizophrenia.

Side Effects

Second-generation antipsychotics replaced the first-generation agents as the standard treatments for schizophrenia in part because of their decreased risk of causing motor side effects. Ironically, clinicians and the field now struggle to balance the benefits of second-generation antipsychotics with the consequences of other side effects, especially weight gain and other metabolic changes. Medication-naive first-episode samples have been very informative for studies of treatment outcome and biological investigations. Their utility for studying side effects will probably become more widely appreciated in the future.

The Mount Sinai Consensus Guidelines for Physical Health Monitoring of Patients With Schizophrenia identifies 4 classes of second-generation antipsychotic side effects with medical consequences that are relevant to the treatment of first-episode patients: metabolic side effects, elevated prolactin levels, motor side effects, and QT prolongation (of importance with ziprasidone).[31] The metabolic side effects are of prime importance: they occur rapidly, are of particular concern to adolescents and young adults, have well-established long-term

medical consequences, and, unlike extrapyramidal motor side effects, have no well-established treatments.

Health Consequences of Antipsychotic-Associated Metabolic Side Effects

Cardiovascular disease[32] is the most common cause of mortality among patients with schizophrenia, accounting for 34% of deaths among male patients and 31% among female patients. Mortality from cardiovascular disease is significantly higher in patients with schizophrenia than in the general population. Patients with schizophrenia frequently have risk factors for cardiovascular disease such as cigarette smoking and sedentary lifestyles. In addition, the disease process of schizophrenia may directly affect some risk factors. Ryan and associates have found that medication-naive first-episode subjects ($n = 16$) had more intra-abdominal fat than healthy control subjects matched for age and body mass index ($116.8 \pm 20.2\ cm^2$ versus $38.0 \pm 4.8\ cm^2$, respectively; $p < .0001$).[33] This suggests that schizophrenia may be associated with changes in fat distribution that could increase the risk for insulin resistance, hyperglycemia, and dyslipidemia. Given the difficulty of reversing weight gain after it occurs[34–42] and the adverse effects of obesity on health,[43–45] one must consider long-term health risks when deciding upon medication treatment for first-episode patients.

Weight Gain and Metabolic Side Effects From Studies of Second-Generation Antipsychotics With First-Episode Populations

Published data on side effects in first-episode populations are summarized in table 3. Two large-sample-size industry-sponsored first-episode studies have reported on weight gain with risperidone and olanzapine treatment. In the Schooler et al. trial, risperidone-treated subjects gained a mean of 4.6 (SD 4.96) kg at 3 months and a mean of 7.5 (SD 9.29) kg at end point.[7] Moderate hyperglycemia was reported in 1 risperidone-treated subject. Lieberman and colleagues used a last-observation-carried-forward analysis, which would tend to underestimate the amount of weight gain associated with treatment.[8] Nonetheless, over 12 weeks, olanzapine-treated subjects gained a mean of 7.3 (SD 6.1) kg and 2.39 body mass index units, and 61% gained more than 7% of their baseline weight. Mean changes were 4.9 (SD 34.2) U/l in nonfasting glucose and 17.3 (SD 27.4) mg/dl for cholesterol.

Prolactin Elevation. Treatment of multiepisode patients with first-generation antipsychotics or with risperidone is associated with prolactin elevation.[46–51] In the Schooler et al. trial with first-episode subjects, abnormal prolactin levels (males >18 ng/mL, females >25 ng/mL) occurred in 73.8% of the 256 risperidone-treated subjects.[7] The medical consequences of the degree of prolactin elevation associated with antipsychotic treatment are not clear. Some studies[52–53] have suggested an increased risk of breast cancer, but this has been contradicted by other studies.[54] Menstrual disturbance and galactorrhea have been reported with antipsychotic-induced hyperprolactinemia (reviewed in [55]). However, in the Schooler et al. trial, only 14 risperidone-treated subjects reported prolactin-related side effects (gynecomastia, galactorrhea).[7] These data are based on an unstructured inquiry that may have underestimated the effects of prolactin elevation. Decreased sexual interest or impaired sexual performance occurs frequently in patients with schizophrenia. Prolactin level elevation may increase the prevalence of sexual dysfunction (although a recent nocturnal penile tumescence study of 14 men treated with risperidone for 3 months or longer found a correlation between higher prolactin levels and better erectile function).[56] In summary, antipsychotic-induced prolactin elevation is a potential cause of medical concern and patient distress, but its long-term risk is much less clear than the risks associated with metabolic side effects.

Motor Side Effects. Treatment of first-episode patients with conventional antipsychotics is associated with a risk of developing persistent tardive dyskinesia (TD) of 5% per year of treatment.[57] Fortunately, the second-generation antipsychotic agents probably convey a lower risk of TD. First-episode patients have fewer extrapyramidal side effects when treated with second-generation antipsychotics, compared with conventional agents, as do multiepisode patients. However, extrapyramidal side effects remain relatively common with the second-generation agents. For example, in the study by Lieberman and colleagues comparing treatment with olanzapine and haloperidol, treatment-emergent parkinsonism and akathisia were both more common among subjects treated with haloperidol than with olanzapine, but 26.1% of olanzapine-treated subjects developed parkinsonism and 11.9% developed akathisia.[8] Although treatable by antipsychotic dose reduction or the addition of medications for side effects, extrapyramidal symptoms are distressing to patients and are associated with antipsychotic discontinuation by first-episode subjects even when present at low levels of severity.[25]

Summary

With the most commonly used pharmacologic therapies, the course of early-phase schizophrenia is characterized by initial improvement in symptoms followed by repeated relapses and a low rate of sustained recovery. In addition, schizophrenia and the medications commonly used in its treatment are associated with important long-term health risks.

For the acute treatment phase, we lack data directly comparing the new-generation agents with one another.

Table 3. Side Effects

Study	Population	Inclusion Criteria	Design/Protocol	Side Effects	Other Comments
Chakos, Alvir, Woerner, et al., 1996[57]	118 first-episode schizophrenia, schizophreniform, or schizoaffective disorder (RDC) patients	age 16–40; no more than 12 weeks of prior antipsychotic drug exposure; no current substance abuse; no neuromedical illness that could influence diagnosis	standardized algorithm—subjects proceeded to the next level if no improvement: fluphenazine up to 20 mg/day for 6 weeks, fluphenazine 40 mg/day for 4 weeks, switch to haloperidol 20 mg/day for 6 weeks, haloperidol 40 mg/day for 6 weeks, switch to antipsychotic from different biochemical class (e.g., molindone, up to 300 mg/day); if still treatment resistant, considered for clozapine trial	cumulative incidence of presumptive TD was 6.3% after 1 year of follow-up, 11.5% after 2 years, 13.7% after 3 years, and 17.5% after 4 years; cumulative incidence of persistent TD was 4.8% after 1 year, 7.2% after 2 years, and 15.6% after 4 years	risk factors for development of TD include poor treatment response, greater impairment on childhood premorbid adjustment, and antipsychotic drug dose
Sanger, Lieberman, Tohen, Grundy, Beasley, & Tollefson, 1999[2]	83 first-episode schizophrenia, schizophreniform, or schizoaffective disorder (DSM-III-R) patients; a subset of participants in a multicenter trial with 1,996 subjects	actively symptomatic; length of current episode no greater than 5 years; age at onset of episode no greater than 45 years old	double-blind randomization (2:1 ratio) comparing olanzapine and haloperidol; initial dosage of 5 mg/day could then be increased or decreased by 5 mg after each 7-day period, with 5–20 mg/day range; adjunctive medications allowed	olanzapine: less akathesia, parkinsonism, hypertonia, and hyperkinesias and early transient increases in alanine aminotransferase serum glutamic-pyruvic transaminase; haloperidol: less somnolence, asthenia, headache, and weight gain and higher prolactin levels	dropout rates due to adverse events were 4 times higher among haloperidol patients
Malla, Norman, Scholten, Zirul, & Kotteda, 2001[63]	38 first-episode schizophrenia (DSM-III-R or DSM-IV) patients with a diagnosis receiving initial treatment between 1991 and 1997 (typical) or 1993 and 1997 (risperidone)	treatment with either risperidone alone for >1 year or a single typical antipsychotic for the entire course of illness	cohorts derived from chart review were matched on age, gender, length of illness, and length of treatment; follow-up data 1 to 8 years after initial treatment included case record reviews, interviews, and rating scales	parkinsonism: higher for typical group (not significant); anticholinergic use significantly lower for risperidone group	no patients in either treatment group showed akathisia, dystonia, or dyskinesia at the time of follow-up assessment

Table 3. Continued

Study	Population	Inclusion Criteria	Design/Protocol	Side Effects	Other Comments
Lieberman, Phillips, Gu, et al., 2003[5]	160 schizophrenia or schizophreniform (DSM-IV) patients	duration of symptoms 60 months or less; prior antipsychotic use no more than 14 days; age 16–40; current psychotic symptoms of moderate severity or greater	52-week double-blind randomized trial of clozapine + benztropine placebo and chlorpromazine + benztropine; titrated over first 28 days, up to 400 mg/day of clozapine or 600 mg/day of chlorpromazine; benztropine dose 2 mg twice daily	chlorpromazine + benztropine: significantly more extrapyramidal symptoms, parkinsonism, dystonia, akathisia, blurry vision, depressed affect, dry mouth, tense muscles, and decreased urinary production at 12 weeks clozapine: more sweating and higher heart rate at 52 weeks; both groups had significant weight gain	more chlorpromazine patients left the study because of adverse effects; women had more parkinsonism at 12 weeks
Lieberman, Tollefson, Tohen, et al., 2003[8]	263 schizophrenia, schizophreniform, or schizoaffective (DSM-IV) disorder patients	age 16–40; onset by age 35; psychotic symptoms for 1 to 60 months; score of at least 4 on at least 2 PANSS psychosis items or at least 5 on 1 item; CGI severity score at least 4	double-blind randomized trial of olanzapine and haloperidol; olanzapine doses 5–10 mg/day for 6 weeks and then 5–20 mg/day; haloperidol doses 2–6 mg/day and then 2–20 mg/day; acute treatment phase 12 weeks; follow-up for up to 2 years; certain adjunctive medications allowed	haloperidol: significantly more frequent and severe extrapyramidal symptoms, higher incidence of akathisia, parkinsonism, and prolactin elevation; olanzapine: greater weight gain (mean of 7.3 kg in 12 weeks) and increased body mass index scores	7 patients receiving haloperidol withdrew due to extrapyramidal symptoms (versus none receiving olanzapine); 2 olanzapine patients withdrew due to weight gain (versus none on haloperidol)
Schooler, Rabinowitz, Davidson, et al., 2005[7]	555 schizophrenia, schizophreniform, or schizoaffective disorder (DSM-IV) patients	age 16–45; ill for 12 months or less; no more than 2 hospitalizations for psychosis; no more than 12 weeks of prior antipsychotic treatment	international 12-week double-blind randomized comparison of risperidone and haloperidol; identical dosing scheme: titrated from 1 mg/day to a maximum of 4 mg/day; certain adjunctive medication allowed	haloperidol: more frequent and severe extrapyramidal symptoms (emergent dyskinesia, parkinsonism, and dystonia); risperidone: higher prolactin levels; more weight gain early in study but no difference at the end	

Note: TD = tardive dyskinesia, PANSS = Positive and Negative Syndrome Scales, CGI = Clinical Global Impression.

Data from large studies comparing haloperidol with olanzapine and with risperidone are available. Newer agents with a potentially lower risk of metabolic side effects are now on hand, but studies of these agents with first-episode patients are lacking. A crucial question is how much, if any, trade-off in effectiveness would result if a second-generation antipsychotic with a lower propensity to cause metabolic side effects were used in place of the older second-generation agents.

Concerns about balancing risks and benefits are more pressing with maintenance treatment. The preponderance of currently available data supports a recommendation of continuous maintenance treatment for first-episode patients. For patients who refuse continued medication, an ''intermittent'' or ''targeted'' strategy can be recommended. Debate persists about whether continuation pharmacotherapy should be indefinite or time limited. Unfortunately, there are no empirically based guidelines concerning who, when, and under what circumstances the benefit-to-risk assessment favors medication discontinuation.

Decisions about maintenance treatment are critical given the potential adverse impact of a single psychotic relapse on the psychosocial, educational, and vocational opportunities available to a young person. While the data suggesting a possible increase in relapse prevention efficacy for second-generation agents compared with conventional antipsychotics are encouraging, various questions remain, including, Are there differences among the second-generation agents for relapse prevention? What is the ideal dosing with the new agents for relapse prevention? and What are the long-term benefits versus risks of continued treatment?

Just as knowledge gained from studies with multiepisode subjects is often then applied in studies with first-episode subjects, studies of treatment response, relapse prevention, and recovery in first-episode subjects can inform studies of the prodrome. Successful strategies developed with first-episode subjects can guide studies designed to develop and evaluate the benefits and risks of interventions whose ultimate goal is the prevention of the first episode.

Acknowledgments

Supported by grants MH60004 and MH41960 (the Zucker Hillside Center for Intervention Research in Schizophrenia) from the National Institute of Mental Health, Bethesda, MD. Lior Aronoff and Craig Kimmelblatt provided assistance with manuscript preparation.

References

1. May PRA, Tuma AH, Yale C, Potepan P, Dixon WJ. Schizophrenia—a follow-up study of results of treatment. II. hospital stay over two to five years. *Arch Gen Psychiat* 1976;33:481–486.
2. Sanger TM, Lieberman JA, Tohen M, Grundy S, Beasley C, Jr., Tollefson GD. Olanzapine versus haloperidol treatment in first-episode psychosis. *Am J Psychiat* 1999; 156:79–87.
3. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *Psychol Rep* 1962;10:799–812.
4. Robinson DG, Woerner MG, Alvir JMJ, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiat* 1999;156:544–549.
5. Lieberman JA, Phillips M, Gu H, et al. Atypical and conventional antipsychotic drugs in treatment-naïve first-episode schizophrenia: a 52-week randomized trial of clozapine vs chlorpromazine. *Neuropsychopharmacol* 2003;28:995–1003.
6. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. *Schizophrenia Bull* 1999;25:721–729.
7. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first episode psychosis: a long-term randomized trial. *Am J Psychiat* 2005;162:947–953.
8. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized double-blind trial of olanzapine versus haloperidol. *Am J Psychiat* 2003; 160:1396–1404.
9. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophrenia Bull* 1987;13:261–276.
10. Guy W, ed.*ECDEU assessment for psychopharmacology*. Rev. ed. Rockville, Md: National Institute of Mental Health; 1976.
11. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. *Brit J Psychiat* 1979; 134:382–389.
12. Spitzer RL, Endicott J. *Schedule for Affective Disorders and Schizophrenia—Change Version*. 3rd ed. New York: New York State Psychiatric Institute; 1978.
13. Woerner MG, Robinson DG, Alvir JMJ, Sheitman BB, Lieberman JA, Kane JM. Clozapine as a first treatment for schizophrenia. *Am J Psychiat* 2003;160:1514–1516.
14. Szymanski S, Masiar S, Mayerhoff D, et al. Clozapine response in treatment-refractory first-episode schizophrenia. *Biol Psychiat* 1994;35:278–280.
15. Kane JM, Rifkin A, Quitkin F, Nayak D, Ramos-Lorenzi J. Fluphenazine vs placebo in patients with remitted, acute first-episode schizophrenia. *Arch Gen Psychiat* 1982;39:70–73.
16. Crow TJ, MacMillan JF, Johnson AL, Johnstone EC. A randomized controlled trial of prophylactic neuroleptic treatment. *Brit J Psychiat* 1986;148:120–127.
17. Scottish Schizophrenia Research Group. The Scottish first episode schizophrenia study. VII. two-year follow-up. Acta Psychiat Scand 1989;80:597–602.
18. Hogarty GE, Ulrich RF. The limitations of antipsychotic medication on schizophrenia relapse and adjustment and the contributions of psychosocial treatment. *J Psychiat Res* 1998;32:243–250.
19. Geddes J, Mercer G, Frith CD, et al. Prediction of outcome following a first episode of schizophrenia: a follow-up study of Northwick Park first episode study subjects. *Brit J Psychiat* 1994;165:664–668.
20. Scottish Schizophrenia Research Group. The Scottish first episode schizophrenia study. VIII. five-year follow-up:

clinical and psychosocial findings. *Brit J Psychiat* 1992; 161:496–500.

21. Gitlin M, Nuechterlein K, Subotnik KL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. *Am J Psychiat* 2001;158:1835–1842.
22. Robinson D, Woerner MG, Alvir JMJ, et al. Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiat* 1999; 56:241–247.
23. Gaebel W, Janner M, Frommann N, et al. First vs multiple episode schizophrenia: two-year outcome of intermittent and maintenance medication strategies. *Schizophr Res* 2002;53:145–159.
24. Cernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. *N Engl J Med* 2002;346:16–22.
25. Robinson DG, Woerner MG, Alvir JMJ, Bilder RM, Hinrichsen GA, Lieberman JA. Predictors of medication discontinuation by patients with first-episode schizophrenia and schizoaffective disorder. *Schizophr Res* 2002;57:209–219.
26. Harding CM. Course types in schizophrenia: an analysis of European and American studies. *Schizophrenia Bull* 1988;14:633–643.
27. Robinson DG, Woerner MG, McMeniman M, Mendelowitz A, Bilder RM. Symptomatic and functional recovery from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiat* 2004;161:473–479.
28. Liberman RP, Kopelowicz A, Ventura J, Gutkind D. Operational criteria and factors related to recovery from schizophrenia. *Int Rev Psychiatr* 2002;14:256–272.
29. Andreasen NC, Olsen S. Negative v positive schizophrenia: definition and validation. *Arch Gen Psychiat* 1982;39:789–794.
30. Schooler NR, Hogarty GE, Weissman MM. Social Adjustment Scale II. In: Hargreaves WP, Attkisson CC, Sorenson JE, eds. *Resource Materials For Community Health Program Evaluations, 2nd ed.* Rockville, MD: US Department of Health, Education, and Welfare. 1979:290–302.
31. Marder SR, Essock SM, Miller AL, et al. Physical health monitoring of patients with schizophrenia. *Am J Psychiat* 2004;161:1334–1349.
32. Brown S. Excess mortality of schizophrenia: a meta-analysis. *Brit J Psychiat* 1997;171:502–508.
33. Ryan MCM, Flanagan S, Kinsella U, Keeling F, Thakore JH. The effects of atypical antipsychotics on visceral fat distribution in first episode, drug-naive patients with schizophrenia. *Life Sci* 2004;74:1999–2008.
34. Ball MP, Coons VB, Buchanan RW. A program for treating olanzapine-related weight gain. *Psychiatr Serv* 2001; 52:967–969.
35. Cohen S, Glazewski R, Khan S, Khan A. Weight gain with risperidone among patients with mental retardation: effect of calorie restriction. *J Clin Psychiat* 2001;62:114–116.
36. Gracious BL, Krysiak TE, Youngstrom EA. Amantadine treatment of psychotropic-induced weight gain in children and adolescents: case series. *J Child Adol Psychop* 2002;12:249–257.
37. Morrison JA, Cottingham EM, Barton BA. Metformin for weight loss in pediatric patients taking psychotropic drugs. *Am J Psychiat* 2002;159:655–657.
38. Yanovski SZ, Yanovski JA. Obesity. *N Engl J Med* 2002;346:591–602.
39. Vreeland B, Minsky S, Menza M, Rigassio Radler D, Roemheld-Hamm B, Stern R. A program for managing weight gain associated with atypical antipsychotics. *Psychiatr Serv* 2003;54:1155–1157.
40. Nemeroff CB. Safety of available agents used to treat bipolar disorder: focus on weight gain. *J Clin Psychiat* 2003;64: 532–539.
41. Birt J. Management of weight gain associated with antipsychotics. *Ann Clin Psychiat* 2003;15:49–58.
42. Bray GA, Hollander P, Klein S, et al. A 6-month randomized, placebo-controlled, dose-ranging trial of topiramate for weight loss in obesity. *Obes Res* 2003;11:722–733.
43. National Task Force on the Prevention and Treatment of Obesity. Overweight, obesity, and health risk. *Arch Intern Med* 2000;160:898–904.
44. American Diabetes Association. Report of the expert committee on the diagnosis and classification of diabetes mellitus. Diabetes Care 2001;24(suppl 1):S5–S20.
45. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. *N Engl J Med* 2003;348: 1625–1638.
46. David SR, Taylor CC, Kinon BJ, Breier A. The effects of olanzapine, risperidone, and haloperidol on plasma prolactin levels in patients with schizophrenia. *Clin Ther* 2000;22:1085–1096.
47. Kasper S, Muller-Spahn F. Review of quetiapine and its clinical applications in schizophrenia. *Expert Opin Pharmaco* 2000;1:783–801.
48. Goodnick PJ. Ziprasidone: profile on safety. *Expert Opin Pharmaco* 2001;2:1655–1662.
49. Esel E, Basturk M, Saffet Gonul A, et al. Effects of olanzapine and haloperidol on serum prolactin levels in male schizophrenic patients. *Psychoneuroendocrino* 2001;26:641–647.
50. Turrone P, Kapur S, Seeman MV, Flint AJ. Elevation of prolactin levels by atypical antipsychotics. *Am J Psychiat* 2002;159:133–135.
51. Volavka J, Czobor P, Cooper TB, et al. Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol. *J Clin Psychiat* 2004;65:57–61.
52. Schyve PM, Smithline F, Meltzer HY. Neuroleptic-induced prolactin elevation and breast cancer: an emerging clinical issue. *Arch Gen Psychiat* 1978;35:1291–1301.
53. Mortensen PB. Neuroleptic treatment and other factors modifying cancer risk in schizophrenic patients. *Acta Psychiat Scand* 1987;75:585–590.
54. Wang PS, Walker AM, Tsuang MT, et al. Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiat* 2002;59:1147–1154.
55. Dickerson RA, Glazer WM. Neuroleptic-induced hyperprolactinemis. *Schizophr Res* 1999;35:S75–S86.
56. Spollen JJ, Wooten RG, Cargile C, Bartztokis G. Prolactin levels and erectile function in patients treated with risperidone. *J Clin Psychopharm* 2004;24:161–166.
57. Chakos MH, Alvir JM, Woerner MG, et al. Incidence and correlates of tardive dyskinesia in first episode of schizophrenia. *Arch Gen Psychiat* 1996;53:313–319.
58. Scottish Schizophrenia Research Group. The Scottish first episode schizophrenia study. II. treatment: pimozide versus flupenthixol. *Brit J Psychiat* 1987;150:334–338.
59. Kopala LC, Frederikson D, Good KP, Honer WG. Symptoms in neuroleptic-naïve, first-episode schizophrenia: response to risperidone. *Biol Psychiat* 1996;39:296–298.

60. Lieberman J, Jody D, Geisler S, et al. Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiat* 1993;50:369–376.
61. Yap HL, Mahendran R, Lim D, et al. Risperidone in the treatment of first episode psychosis. *Singapore Med J* 2001; 42:170–173.
62. Rabiner CJ, Wegner JT, Kane JM. Outcome study of first-episode psychosis. I: relapse rates after 1 year. *Am J Psychiat* 1986;143:1155–1158.
63. Malla AK, Norman RMG, Scholten DJ, Zirul S, Kotteda V. A comparison of long-term outcome in first-episode schizophrenia following treatment with risperidone or a typical antipsychotic. *J Clin Psychiat* 2001;62:179–184.