# FIRST-EPISODE SCHIZOPHRENIA

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## Introduction

Clinicians treating patients with first-episode (FE) schizophrenia can draw upon the vast literature on the treatment of patients with multiple-episode schizophrenia. Studies with multi-episode patients, however, may not fully generalize to the treatment of FE patients. Studies with multi-episode patients typically recruit from hospitals or other acute care units, settings where patients usually have been either non-responsive or non-adherent to previous treatment, or mixtures of both. Studies of multi-episode patients therefore tend to include patients who are not fully responsive to treatment. Without the filter of prior treatment history, FE compared with multi-episode patients may show a broader range of treatment patterns, ranging from extremely good to very poor. Further, studies of FE patients may be very instructive about side effects, as the confounding effect of prior medication use is particularly important with side effects. Finally, data suggest that much of the deterioration (eg, more severe negative symptoms) associated with schizophrenia may occur during the 5 years following illness onset. Providing patients with better treatment at illness onset offers the hope of improving their long-term outcome.

FE studies do have limitations. Relatively few new cases of schizophrenia occur each year. The typically chronic course of schizophrenia results in a large number of patients with multi-episode schizophrenia for every FE patient at any one time. Recruitment for studies of FE schizophrenia compared with those of multi-episode schizophrenia is often more difficult given the smaller number of available patients. We systematically know less about the treatment of FE patients than we do about the treatment of multi-episode patients.

## Treatment of the Initial Episode of Schizophrenia

Five major contemporary studies[1-5] of FE schizophrenia with strict, albeit varied, response criteria all found higher response rates (primarily based upon positive symptom improvement) than the rates typically found in studies of multi-episode schizophrenia. This is especially remarkable, because response criteria are usually more stringent in FE compared with multi-episode studies. No antipsychotic has shown superior efficacy for the treatment of an initial psychotic episode, which may be due to the overall high rate of response by FE patients. For example, chloropramazine and clozapine showed equal efficacy after 1 year in a study[2] comparing them as the initial treatment for FE schizophrenia. This outcome differs from the results with treatment-resistant multi-episode patients, where clozapine shows superior efficacy.[6,7]

Another notable feature about FE treatment is that the average doses of medication are usually lower than those used with multi-episode patients. Quetiapine, and possibly ziprasidone, dosing may be an exception.[8,9]

## Cognitive Outcomes

Studies with FE patients comparing scores on cognitive tests longitudinally have found modest improvements with treatment with a variety of antipsychotics.[10-13] However, these improvements in test scores may not be due solely to improvement in cognitive ability.

Effect sizes allow assessment of the magnitude of improvement with a treatment. An effect size of 0.2 is consistent with a small effect, 0.5 with a medium effect, and 0.8 with a large effect. Goldberg and colleagues[14] assessed cognition at baseline and at weeks 6 and 16 in a group of FE patients being treated with olanzapine or risperidone and a matched sample of healthy control subjects. Cognition improved in all groups to a small to moderate degree (effect size for cognitive change was 0.33 in the healthy control group and 0.36 in the FE patients). We would not anticipate that the actual cognitive ability of the health control group would improve over time, as they were receiving no treatment. The very similar improvement between patient and control subjects suggests that cognitive test score improvement was likely due to practice effects, ie, patients and controls did better on subsequent tests because they had seen the tests before. In contrast to the small effect size for cognitive change, the effect size for positive symptom improvement in the same study was extremely large—between 1.25 and 1.5. Available treatments have the ability to improve positive symptoms greatly, but, unfortunately, may have very little effect on cognitive symptoms.

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## Adverse Events in First-Episode Schizophrenia

Even with low dose medication strategies, patients with FE schizophrenia often experience substantial side effects. Typical of side effect patterns with FE patients are results from the CAFE trial comparing olanzapine, quetiapine, and risperidone.[8] Side effects across multiple domains were frequent for all the medications (Slide 1). Clinicians treating early-phase patients must be particularly vigilant about assessing for potential side effects. Metabolic side effects have important implications for long-term health outcomes. Unfortunately, early-phase patients tend to be more susceptible to antipsychotic metabolic side effects than older patients.[3,5,8]

## Maintenance Treatment of Early-Phase Schizophrenia

Although the initial psychotic episode typically is very responsive to treatment, relapse rates are high during the first years of the illness, with as many as 81.9% of early-phase patients suffering relapse within the first five years of treatment (Slide 2).[15]

Given the frequency of relapse, a critical question is how to minimize relapse risk. Placebo-controlled studies have demonstrated a significant advantage for maintenance antipsychotic treatment for relapse prevention with FE patients.[16-19]

Medication adherence is by far the most powerful predictor of relapse.[15] Patients who stop maintenance medication have a relapse rate ~5 times greater than those who continue on their antipsychotic medications.[15]

Although no particular agents are superior to others for treatment of the initial episode of schizophrenia, second-generation agents (SGAs) may be more effective as maintenance treatment for first-episode patients, at least in comparison with haloperidol (Slide 3).[4,20]

A randomized, placebo-controlled comparison of risperidone (mean modal dose 3.3 mg) and haloperidol (mean modal dose 2.9 mg) found equal efficacy for acute treatment of the initial episode but a better chance of remaining relapse-free on risperidone.[4] The

**SLIDE 1**
*CAFE: Percentage of Subjects Experiencing the Most Common Adverse Events*[8]

| Adverse Event | Olanzapine n=133 | Quetiapine n=134 | Risperidone n=133 | All Subjects N=400 |
|---|---|---|---|---|
| Daytime drowsiness | 53.4% | 57.5% | 49.6% | 53.5% |
| Weight gain | 51.1% | 40.3% | 41.4% | 44.3% |
| Increased sleep hours | 33.8% | 41.8% | 27.1% | 34.3% |
| Insomnia | 38.4% | 29.1% | 33.8% | 33.8% |
| Menstrual irregularities | 31.3% | 23.8% | 47.1% | 33.3% |
| Sex drive | 27.8% | 26.1% | 27.1% | 27.0% |
| Akinesia | 24.1% | 24.6% | 27.1% | 25.3% |
| Dry mouth | 21.8% | 34.3% | 15.8% | 24.0% |
| Akathisia | 20.3% | 18.7% | 22.6% | 20.5% |
| Sexual arousal | 21.8% | 16.4% | 18.1% | 18.8% |
| Sexual orgasm | 16.5% | 15.7% | 18.8% | 17.0% |
| Orthostatic faintness | 11.3% | 19.4% | 12.8% | 14.5% |
| Constipation | 8.3% | 11.9% | 13.5% | 11.3% |
| Sialorrhea | 5.3% | 6.0% | 13.5% | 8.3% |

**SLIDE 2**
*The Risk for Psychotic Relapse is High*[15]

| Year* | Relapse rate (%) | 95% limit (%) Lower | Upper |
|---|---|---|---|
| 1 | 16.2 | 8.9 | 23.4 |
| 2 | 53.7 | 43.4 | 64.0 |
| 3 | 63.1 | 52.7 | 73.4 |
| 4 | 74.7 | 64.2 | 85.2 |
| 5 | 81.9 | 70.6 | 93.2 |

n=104 first-episode schizophrenia patients
*Year(s) since previous episode

**SLIDE 3**
*FGAs vs. SGAs for Maintenance Treatment*

| Study | FGAs | SGAs |
|---|---|---|
| Schooler[4] | Relapse rate of haloperidol treated subjects (n=203): 54.7% | Relapse rate of risperidone treated subjects (n=197): 42.1% |
| Green[20] | Mean days until discontinuation of haloperidol: 230 | Mean days until discontinuation of olanzapine: 322 |

median time to relapse was 466 days for patients given risperidone and 205 days for those given haloperidol.

A recent maintenance study comparing haloperidol with amisulpride (not approved for use in the United States), olanzapine, quetiapine, and ziprasidone found that patients maintained on haloperidol discontinued their medication significantly sooner than patients on the SGAs.[9] There was no statistically significant difference between the three SGAs. These results suggest that SGAs as a group may be more beneficial than haloperidol for maintenance treatment. Whether SGAs are more beneficial for maintenance treatment than first-generation agents, other than haloperidol, has not been studied.

FE patients have, unfortunately, a strong tendency to become non-adherent with treatment. Rates of non-adherence range from 40% to 60% (Slide 4).[21-26] Some of the factors common to non-adherence in multi-episode patients—lack of income, substance use, Parkinsonian side effects—are also associated with non-adherence by FE patients. In addition, FE patients with poor executive function, and other cognitive deficits, have been shown to be less likely to continue their medication.[23]

**SLIDE 4**
*Retention and Adherence: Pharmacological Treatment*

- Approximately 40% of FE patients are non-adherent[22]
- Approximately 60% have intermittent periods of non-adherence[27,28]
- Predictors of medication nonadherence[21-26]
  - Lack of insight
  - Negative attitudes towards medication
  - Substance misuse
  - Severe positive symptoms
  - Parkinsonism
  - Executive dysfunction

## Recovery

Proposed recovery criteria for schizophrenia[29] require that patients do well in four separate domains (symptoms remission, appropriate role functioning, performing day-to-day living tasks, and social interactions outside the family) continuously for a 2-year period. An investigation[30] of 118 FE patients found that by 5-year follow-up 47.2% of subjects had symptom remission for 2 years or longer and 25.5% had adequate social functioning for ≥2 years. Only 13.7% of patients had, however, a ≥2 year period of full recovery. The low rate of full recovery highlights the need for further efforts to improve outcomes for FE patients.

## Psychosocial Interventions for Individuals at the First Episode of Psychosis

Psychosocial interventions are an important part of improving outcomes for patients with FE psychosis. Some of the modalities studied individually include psychoeducation with patients and families, cognitive behavioral therapy for symptom control, vocational and educational programs, and family work. Substance misuse is very common with FE patients and requires its own intervention.

The efficacy of treatment programs offering several psychosocial modalities provided by specialized teams, along with medication treatment, is an area of active research. Two large studies, one in the United Kingdom and one in Denmark, have evaluated integrated treatment programs. The LEO trial[31] demonstrated a reduced risk of relapse over an 18-month follow-up for patients in an integrated treatment program. The OPUS trial[32] found that patients in an integrated program, compared with care as usual, showed positive symptom improvement and better treatment adherence at two years. At 5-year follow-up, however, the differences between patients given integrated treatment versus usual care were marginal. The National Institute of Mental Health has recently initiated the RAISE (Recovery After an Initial Schizophrenia Episode) study, which will evaluate the efficacy of integrated treatments in the United States. RAISE is in the start-up phase, with the study projected to begin in 2010.

## Case Report

Ms. A was a 17-year-old high school student who had been doing well academically and socially. She began to believe that people outside her home were conspiring to harm her and her family and began hearing noises from the conspirators. Ms. A's family brought her to the hospital after repeated unsuccessful attempts to persuade her that no one was conspiring to harm them. Her medical and psychiatric history before the current episode was unremarkable. She was started on a low dose of risperidone, eventually reaching a dose of 2 mg/day. After four weeks of treatment Ms. A had no hallucinations and no specific delusions, but remained globally suspicious. These symptoms, too, resolved after 10 weeks. Despite being on a very low dose, she experienced sedation and extrapyramidal symptoms.

Ms. A did not want her peers to know about her psychiatric hospitalization. With the support of her therapist, she resumed her education at a different high school. After 9 months of successful treatment, Ms. A decided to stop treatment, because she did not want her new boyfriend to know that she had a problem. Four months after treatment cessation, her hallucinations and delusions returned. The content was similar, but the hallucinations and delusions were more intense than during her first episode. She resumed treatment and responded well, but it took longer the second time for her to experience a full resolution of her illness.

Ms. A illustrates some of the points we have discussed. Her response to treatment in terms of positive symptom improvement was very good. Despite the low dose of medication, she had side effects. She also shows that even patients who do very well are at great risk for relapse when they stop maintenance treatment. Even though she responded well to medication treatment, she benefited by psychosocial support to maximize her potential for recovery.

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