# Switching to Olanzapine After Unsuccessful Treatment With Risperidone During the First Episode of Schizophrenia: An Open-Label Trial

Hitoshi Takahashi, M.D., Ph.D.; Mitsuhiro Kamata, M.D., Ph.D.; Keizo Yoshida, M.D., Ph.D.; Jun Ishigooka, M.D., Ph.D.; and Hisashi Higuchi, M.D., Ph.D.

***Background:*** The efficacy and safety of switching to olanzapine were investigated in patients with first-episode schizophrenia who failed to attain an adequate clinical response to an initial therapeutic trial of risperidone (2–6 mg/day for 12 weeks).

***Method:*** A total of 58 first-episode patients with DSM-IV schizophrenia who had residual symptoms following treatment with risperidone were enrolled in an open-label, 12-week study of olanzapine. Dosing was determined by clinical judgment. The main efficacy measure was the Brief Psychiatric Rating Scale (BPRS). Patients with a 20% or greater decrease in BPRS total score plus a final Clinical Global Impressions-Severity of Illness scale score of ≤ 3 (mildly ill) were considered responders. The study was conducted from April 2001 to March 2005.

***Results:*** Fifty-one patients completed the study, and 7 discontinued due to side effects and medication noncompliance. The mean dosage of olanzapine was 15.3 (SD 4.2) mg/day at study endpoint. Total BPRS scores significantly decreased (12.3%) during olanzapine treatment ($p < .001$). In addition, BPRS subscales of anxiety/depression and excitement significantly decreased (19.1% and 29.5%, respectively; $p < .001$). The responder rate was 29.3% (17/58). BPRS positive symptom subscale score at baseline was significantly higher in nonresponders compared to responders ($p < .001$). Comparison of percentage change in BPRS total scores between responders and nonresponders revealed a significant difference at week 4 that continued until study endpoint ($p < .001$). Of 58 patients, 27 (46.6%) showed clinically significant weight gain (≥ 7%) from baseline.

***Conclusion:*** Although we cannot draw any conclusion from a study without a control group, favorable outcomes and good tolerance were observed after switching to olanzapine from risperidone in our population. In addition, factors that predicted a good overall response included a relative absence of positive symptoms at baseline and the percentage reduction in total BPRS score at 4 weeks of treatment. Double-blind, crossover trials are needed to confirm these observations.

*(J Clin Psychiatry 2006;67:1577–1582)*

*Received March 26, 2006; accepted May 10, 2006.* *From the Yuri Kumiai General Hospital, Honjoh, Akita (Drs. Takahashi and Kamata); the Department of Psychiatry, Nagoya University School of Medicine, Nagoya, Aichi (Dr. Yoshida); the Department of Psychiatry, Tokyo Women's Medical University, Tokyo (Dr. Ishigooka); and Omagari City Hospital, Daisen, Akita (Dr. Higuchi), Japan.*

*This study did not receive any financial or material support.*

*The authors report no financial or other relationship relevant to the subject of this article.*

*The authors thank Andrew H. Miller, M.D., and Charles L. Raison, M.D., for their assistance with manuscript preparation.*

*Corresponding author and reprints: Hitoshi Takahashi, M.D., Yuri Kumiai General Hospital, 38 yago, kawaguchi, Honjoh, Akita, 015-8511, Japan (e-mail: takahashi_h1969@yahoo.co.jp).*

Several reports have shown a beneficial effect of atypical antipsychotic agents in the treatment of first-episode schizophrenia. Risperidone and olanzapine are 2 examples of atypical antipsychotics reported to have high efficacy and a reduced side effect burden in this population.[1–4] Symptom reduction during antipsychotic treatment in the early phases of the disease has been reported to result in an enhanced clinical outcome as reflected by shorter time to remission, improved quality of life, and reduced risk of relapse.[5,6] Some patients with first-episode schizophrenia, however, fail to respond to an initially prescribed atypical antipsychotic. It is, therefore, important to address the pharmacologic management of patients in the acute phase of first-episode schizophrenia who have failed to adequately respond to an initially prescribed atypical antipsychotic medication. However, limited information is currently available regarding options in the first episode of schizophrenia when an initially prescribed atypical antipsychotic has failed.

Using an open-label design, in this study, we investigated the efficacy and safety of switching to olanzapine in patients with first-episode schizophrenia who failed to attain an adequate clinical response to risperidone.

## METHOD

### Study Group

Study participants were male and female patients between the ages of 14 and 40 years who met DSM-IV crite-

Table 1. Patients' Characteristics at Baseline (N = 58)

| Characteristic | Value |
|---|---|
| Age, mean (SD), y | 20.5 (2.7) |
| Duration of illness, mean (SD), d | 328.4 (280.2) |
| Male, N (%) | 24 (41.4) |
| Risperidone dose, mean (SD), mg/d | 3.2 (1.4) |
| Concomitant medication, N (%) | |
| Anticholinergics | 18 (31.0) |
| Benzodiazepines | 30 (51.7) |
| Laxatives | 11 (19.0) |
| Schizophrenia diagnosis, N (%) | |
| Paranoid | 47 (81.0) |
| Disorganized | 4 (6.9) |
| Residual | 0 (0) |
| Undifferentiated | 7 (12.1) |

ria for schizophrenia and had a disease duration including prodrome of not more than 5 years. Additional inclusion requirements were a failure to respond (as defined by a less than 40% decrease in Brief Psychiatric Rating Scale [BPRS] score)[4,7] to a 12-week open-label trial of risperidone (2–6 mg/day) for the treatment of first-episode active psychosis, with residual symptoms needed for treatment. Patients with laboratory or electrocardiogram abnormalities were excluded from participation, as were patients with a history of a neurologic illness (i.e., epilepsy, dementia) or any psychiatric disorder other than schizophrenia (i.e., substance abuse). Patients with a history of previous exposure to antipsychotic drugs before risperidone treatment were also excluded from this study. Written informed consent was obtained from patients or their families prior to study entry. The study was approved by the Institutional Review Board of the Yuri Kumiai General Hospital (Honjoh, Akita, Japan). The study was conducted from April 2001 to March 2005.

### Study Design and Medication

Study duration was 12 weeks. Patients were tapered off risperidone during the first 2 weeks of the study, while simultaneously being titrated onto olanzapine to a dosage dictated by the clinical judgment of the treating physician. Following this cross-titration, olanzapine was continued at a fixed dose for an additional 10 weeks until study conclusion. Concomitant medications such as anticholinergics and benzodiazepines, which had been prescribed at baseline (prior to study entry), were used continuously without change during the study period. No additional medications were allowed unless otherwise required for exacerbation of extrapyramidal symptoms (EPS) (biperiden 1–2 mg/day), agitation or insomnia (brotizolam 0.25–0.5 mg/day), or constipation (sennoside 12–24 mg/day).

### Assessment

Clinical assessments were conducted at study weeks 2, 4, 6, 8, and 12. In addition, plasma prolactin concentrations were obtained at baseline and study week 12. To assess changes in the severity of psychotic symptoms during the study, the BPRS was employed as the main outcome measure.[8] In addition to BPRS total score, scores were obtained from each of 5 BPRS subscales. As classified by Lindenmayer et al.,[9] these subscales include positive symptoms (exaggerated self-esteem, suspiciousness, hallucinations, and unusual thought content), negative symptoms (emotional withdrawal, psychomotor retardation, and blunted affect), cognitive symptoms (conceptual disorganization, specific motor disturbance, and disorientation), anxiety/depression symptoms (somatic concern, psychic anxiety, somatic anxiety, self-deprecation, and depressed mood), and excitement (hostility, uncooperativeness, and psychomotor agitation). The Clinical Global Impressions-Severity of Illness scale (CGI-S) was also used to assess the patients' overall clinical condition during the study. Medication-induced EPS were evaluated with the CGI-Extrapyramidal Symptom Rating Scale (CGI-ESRS).[10] Other spontaneously reported adverse events were recorded by study physicians at each visit.

### Data Analysis

Data were analyzed using intent-to-treat methodology, with last observations carried forward. Patients with a 20% or greater decrease in BPRS total score plus a final CGI-S score of ≤ 3 (mildly ill) were considered responders. Previous studies have used this 20% reduction in symptom scores as evidence of response to treatment in patients after partial response to prior antipsychotic therapy.[11,12] Percentage change in BPRS total score, as well as changes in plasma concentrations of prolactin from baseline to study endpoint, were analyzed using the Wilcoxon signed rank test. The time course of the percentage change in BPRS total score from baseline to each measurement occasion was analyzed using a Friedman test followed by a Wilcoxon signed rank test. Differences in clinical characteristics between responders and nonresponders were analyzed using the Mann-Whitney U test or Fisher exact test as appropriate. The difference between responders and nonresponders in the percentage change in BPRS scores from baseline to each scaling point was analyzed using the Mann-Whitney U test. A p value of .05 or less was regarded as significant.

## RESULTS

### Patient Characteristics and Medication Status at Baseline

Baseline characteristics of the study population are presented in Table 1. A total of 58 subjects (34 women and 24 men) were enrolled in the study. Of these, 51 completed the full 12-week trial, and 7 dropped out. Three patients dropped out due to medication noncompliance, and 3 dropped out secondary to medication side effects (2 due to somnolence and 1 due to weight gain). One subject dis-

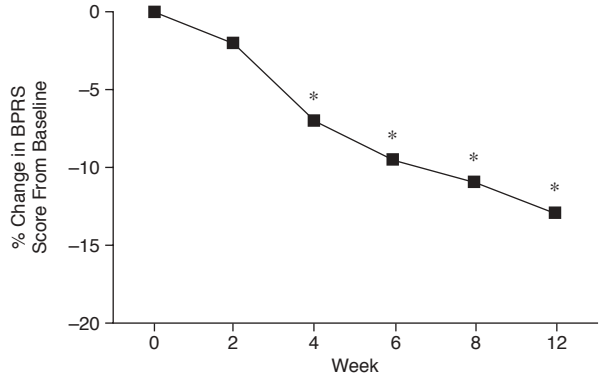
  

Table 2. Brief Psychiatric Rating Scale (BPRS) Scores at Baseline and Endpoint and Percentage Change in BPRS Scores in Each Symptom Category During the Study (N = 58)

| BPRS Score | Baseline, Mean (SD) | Endpoint, Mean (SD) | % Change in BPRS Scores, Mean (SD) |
|---|---|---|---|
| Total | 23.5 (1.9) | 20.6 (3.6) | –12.3 (13.8)* |
| Positive | 6.3 (1.2) | 6.3 (1.4) | –1.2 (19.2) |
| Excitement | 4.2 (0.7) | 2.9 (1.0) | –29.5 (27.8)* |
| Negative | 4.3 (1.0) | 4.2 (0.9) | –3.4 (17.7) |
| Cognitive | 1.9 (0.5) | 1.8 (0.6) | –8.3 (19.4) |
| Anxiety/depression | 6.7 (1.0) | 5.4 (1.8) | –19.1 (28.2)* |

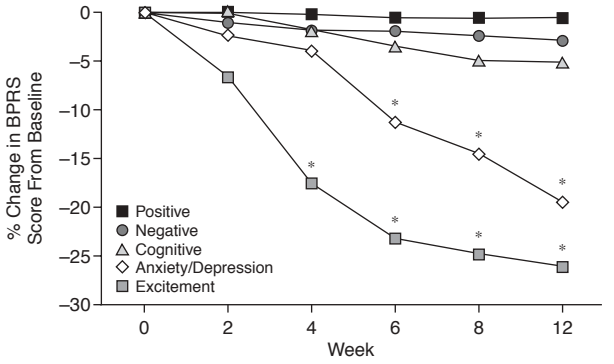
*p < .001 vs. baseline (Wilcoxon signed rank test).

Figure 1. Time Course of the Percentage Change in Brief Psychiatric Rating Scale (BPRS) Total Score From Baseline (N = 58)




*p < .001 vs. baseline (Friedman test followed by Wilcoxon signed rank test).

Figure 2. Time Course of the Percentage Change in 5 Brief Psychiatric Rating Scale (BPRS) Subscale Scores From Baseline (N = 58)




*p < .001 vs. baseline (Friedman test followed by Wilcoxon signed rank test).

continued the study for unknown reasons. There were no differences in age, sex, duration of illness, or schizophrenia diagnosis between those who remained in the study and those who dropped out. The mean (SD) dose of risperidone prior to study entry was 3.2 (1.4) mg/day.

### Medication at Endpoint

The mean (SD) dose of olanzapine at study endpoint was 15.3 (4.2) mg/day. No patient required initiation of an anticholinergic agent during the study. Five patients initiated benzodiazepine treatment, and 2 patients who entered the study on treatment with a benzodiazepine required a dosage increase during the study period.

### Overall Response

Table 2 shows mean BPRS scores at baseline and the study endpoint, as well as mean percentage change in BPRS scores from baseline to endpoint in each symptom category. Total BPRS score and scores on the excitement and anxiety-depression scales decreased significantly from baseline to endpoint ($p < .001$). Scores on the positive, negative, and cognitive symptoms subscales did not change during the study. Figure 1 shows the time course of the percentage change in BPRS total score from baseline to study endpoint. Significant symptom reduction was found after 4 weeks of treatment with olanzapine that continued until the study endpoint ($p < .001$). Figure 2 shows the time course of the percentage change in scores for each of the 5 BPRS subscales over the course of the study. Significant symptom reductions that persisted until the study endpoint were observed in the anxiety/depression subscale starting at study week 6 and in the excitement subscale starting at week 4 ($p < .001$).

### Differences Between Responders and Nonresponders

Table 3 shows the scores on BPRS at baseline and also indicates the percentage change in BPRS scores during the study in responders and nonresponders. Of the 58 patients who enrolled in the study, 17 (29.3%) were considered as responders and 41 (70.7%) were considered as nonresponders. BPRS positive symptom scores at baseline were significantly higher in nonresponders compared to responders ($p < .001$). No significant differences were observed between responders and nonresponders in percentage change in BPRS scores on positive, negative, or cognitive symptoms. When we analyzed differences in the time course of the percentage change in BPRS total score between responders and nonresponders, a difference between groups was found at week 4 that continued until the study endpoint ($p < .001$). There were no significant differences between responders and nonresponders in age, duration of illness, or gender balance.

### Safety and Tolerance

Eleven patients demonstrated parkinsonian symptoms at baseline (7 were rated "very mild" and 4 were rated as

Table 3. Differences Between Responders and Nonresponders in Brief Psychiatric Rating Scale (BPRS) Scores at Baseline and Percentage Change From Baseline in Each Symptom Category

| BPRS Score | Responders (N = 17), Mean (SD) | Nonresponders (N = 41), Mean (SD) |
|---|---|---|
| Total | | |
| Baseline | 22.7 (2.0) | 23.9 (2.0) |
| % Change | –33.2 (3.9) | –6.6 (8.2)* |
| Positive | | |
| Baseline | 5.0 (0.7) | 6.9 (0.9)* |
| % Change | –7.7 (15.3) | 0.8 (18.8) |
| Excitement | | |
| Baseline | 4.3 (0.9) | 4.1 (0.7) |
| % Change | –62.0 (10.7) | –15.4 (20.5)* |
| Negative | | |
| Baseline | 4.3 (1.0) | 4.3 (0.9) |
| % Change | –9.8 (11.4) | –0.7 (19.0) |
| Cognitive | | |
| Baseline | 2.0 (0.4) | 1.9 (0.5) |
| % Change | –7.9 (24.0) | –8.5 (31.0) |
| Anxiety/depression | | |
| Baseline | 7.0 (0.9) | 6.6 (1.0) |
| % Change | –61.0 (16.5) | –0.7 (19.0)* |

*$p < .001$ vs. responders (Mann-Whitney U test).

Table 4. Adverse Events During the Study (N = 58)

| Adverse Event | Value |
|---|---|
| Events at any time during the study, N (%) | |
| Weight gain[a] | 27 (46.6) |
| Excessive appetite | 22 (37.9) |
| Headache | 15 (25.9) |
| Somnolence | 10 (17.2) |
| Dry mouth | 10 (17.2) |
| Insomnia | 7 (12.1) |
| Constipation | 7 (12.1) |
| Blurred vision | 6 (10.3) |
| Dizziness | 6 (10.3) |
| Nausea | 5 (8.6) |
| Extrapyramidal symptoms at baseline/endpoint, N[b] | |
| Parkinsonism | 11/3 |
| Dyskinesia | 0/0 |
| Dystonia | 0/0 |
| Akathisia | 4/2 |

[a]Clinically significant weight gain (≥ 7%).
[b]No patients experienced new development or worsening of extrapyramidal symptoms.

"mild" severity with the CGI-ESRS). By study endpoint, these symptoms had resolved in all but 3 patients, and in these patients severity ratings had decreased from mild to very mild. Four patients endorsed mild akathisia at baseline. By the study endpoint, akathisia had resolved in 2 of these patients and had diminished from mild to very mild in the other 2 patients. No patients experienced new-onset EPS or worsening of preexisting EPS after switching from risperidone to olanzapine (Table 4). Table 4 also shows adverse events that developed or worsened over the study period. Three patients withdrew from the study due to these side effects (2 because of somnolence and 1 because of weight gain). During the study period, mean (SD) plasma concentrations of prolactin decreased significantly from 18.2 (10.2) ng/L to 6.3 (6.5) ng/L in men ($p < .001$) and from 50.4 (34.2) ng/L to 16.2 (20.2) ng/L in women ($p < .001$). Mean (SD) body weight significantly increased from 62.2 (8.5) kg to 65.5 (9.2) kg, or 5.3% from baseline. Of 58 patients who enrolled in the study, 27 (46.6%) developed clinically significant weight gain (≥ 7%) from baseline.

## DISCUSSION

To our knowledge, this is the first report describing the effect of switching to olanzapine after an insufficient response to risperidone in the treatment of first-episode schizophrenia. We found a significant improvement in BPRS total score after patients were switched (Table 2). When separate domains of psychopathology were examined, significant improvement was found in the scores on the BPRS excitement and anxiety/depression subscales (Table 2). In addition, responders had a significantly higher percentage of improvement in these 2 subscales than nonresponders (Table 3). These results suggest that excitement and anxiety/depression symptoms might be appropriate target symptoms likely to improve with a switch from risperidone to olanzapine in risperidone nonresponders.

Recent reports have emphasized the beneficial effects of olanzapine in the treatment of bipolar disorder with manic, depressed, or mixed states.[13] The efficacy of olanzapine on these unstable mood states might explain the improvement seen in both excitement and anxiety/depression in our patients. The symptom improvements were in the excitement and anxiety/depression factors only, without response on psychotic, negative, or cognitive symptoms. Therefore, we cannot rule out the possibility that symptom reductions are due to nonspecific effects of a more sedative antipsychotic. Significant symptom reduction beginning 4 weeks after the initiation of switching from risperidone to olanzapine was found in this study. This suggests that clinicians need to treat with olanzapine for at least 4 weeks prior to evaluating its benefit as an alternative to risperidone in this population.

Of note, the dose range of risperidone (2–6 mg/day) in the lead-in trial (before the switch to olanzapine) is consistent with a previous report suggesting a favorable effect of risperidone at this dosage range in patients with a first episode of schizophrenia. An open-label study in 22 patients (later extended to 41) showed that low doses of risperidone (2–4 mg/day) were associated with a superior outcome in terms of ameliorating positive and negative symptoms when compared to higher doses (5–8 mg/day),[14,15] a finding also suggested by another study that divided patients into those taking ≤ 6 mg/day (N = 34) and those taking > 6 mg/day (N = 62).[1] Moreover, the mean (SD) dose of risperidone, 3.2 (1.4) mg/day,

prior to study entry was compatible with risperidone dosages that have been reported to be effective for not only first-episode[16] but also chronic schizophrenia.[17]

To date, 2 studies comparing risperidone to olanzapine in patients with a first episode of schizophrenia have been published, with inconsistent results. Malla et al.[18] reported no differences between the 2 medications in positive or negative symptoms or in cognitive functioning following 1 year of treatment. In that study, treatment was initiated with risperidone for 50 and olanzapine for 28 patients. Analyses were carried out on 17 and 15 subjects, respectively, for the risperidone and the olanzapine groups who remained on treatment with the initial drug 1 year after the treatment. Gasquet et al.,[19] on the other hand, suggested that olanzapine was more effective than risperidone in promoting a clinical response and improving quality of life, based on a 6-month trial in the subgroup of previously untreated patients with schizophrenia selected from the European Schizophrenia Outpatient Health Outcomes (SOHO) study,[20] a prospective, observational investigation. The analysis of the study by Gasquet et al. used 650 and 224 patients, respectively, in the olanzapine and risperidone groups. Results from our study are consistent with the outcomes reported by Gasquet et al.

In the current study, nonresponders had a higher BPRS positive symptom score at baseline than responders. This finding may suggest a need to be especially attentive to the presence of these types of symptoms in determining whether a given subject in the early phases of schizophrenia with an inadequate response to risperidone might be likely to benefit from a switch to olanzapine.

The most important concern in this study is that its design lacked a control group. Patients are known to respond slowly to pharmacotherapy after a first episode of psychosis. For example, the mean time to response has been reported as 9 weeks,[21] and a recent study has highlighted the slow response in some first-episode patients.[22] Therefore, without a control group, one cannot predict how many subjects would have spontaneously improved if kept on risperidone treatment in this study. Results from trials with control groups are needed to resolve this issue.

In conclusion, olanzapine was effective and well tolerated in the treatment of patients with a first episode of schizophrenia who failed to adequately respond to risperidone. The improved response to olanzapine appears to be accounted for by an enhanced effect of this medication on excitement and anxiety/depression symptom dimensions of the BPRS. In addition, factors that might predict a good response with switching from risperidone to olanzapine include a relative absence of positive symptoms at baseline and the percentage reduction in BPRS total symptom scores following 4 weeks of treatment. Significant weight gain was observed after switching to olanzapine, and clinicians need to closely monitor this side effect during olanzapine treatment. Results from this study should be considered preliminary due to the small sample size, limited duration of the study period, and open-label design. Double-blind, crossover trials with larger sample sizes are needed to confirm preliminary findings of this study.

*Drug names:* biperiden (Akineton), olanzapine (Zyprexa), risperidone (Risperdal).

## REFERENCES


1. Emsley RA. Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Risperidone Working Group. Schizophr Bull 1999;25:721–729
2. Zalsman G, Carmon E, Martin A, et al. Effectiveness, safety, and tolerability of risperidone in adolescents with schizophrenia: an open-label study. J Child Adolesc Psychopharmacol 2003;13:319–327
3. Keefe RS, Seidman LJ, Christensen BK, et al. Comparative effect of atypical and conventional antipsychotic drugs on neurocognition in first-episode psychosis: a randomized, double-blind trial of olanzapine versus low doses of haloperidol. Am J Psychiatry 2004;161:985–995
4. Bobes J, Gibert J, Ciudad A, et al. Safety and effectiveness of olanzapine versus conventional antipsychotics in the acute treatment of first-episode schizophrenic inpatients. Prog Neuropsychopharmacol Biol Psychiatry 2003;27:473–481
5. McGlashan TH. A selective review of recent North American long-term follow-up studies of schizophrenia. Schizophr Bull 1988;14:515–542
6. Waddington JL, Quinn JF. From first to second generation antipsychotics. In: Ellenbroek BA, Cools AR. Atypical Antipsychotics (Milestones in Drug Therapy). Nijmegen, the Netherlands: Birkhauser; 2000:19–33
7. Dellva MA, Tran P, Tollefson GD, et al. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. Psychiatr Serv 1997;48:1571–1577
8. Bech P, Kastrup M, Rafaelsen OJ. Mini-compendium of rating scales for states of anxiety depression mania schizophrenia with corresponding DSM-III syndromes. Acta Psychiatr Scand Suppl 1986;326:1–37
9. Lindenmayer JP, Bernstein-Hyman R, Grochowski S, et al. Psychopathology of schizophrenia: initial validation of a 5-factor model. Psychopathology 1995;28:22–31
10. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res 2005;76:247–265
11. Emsley RA, Raniwalla J, Bailey PJ, et al. A comparison of the effects of quetiapine ("Seroquel") and haloperidol in schizophrenic patients with a history of and a demonstrated, partial response to conventional antipsychotic treatment. PRIZE Study Group. Int Clin Psychopharmacol 2000;15:121–131
12. Larmo I, de Nayer A, Windhager E, et al. Efficacy and tolerability of quetiapine in patients with schizophrenia who switched from haloperidol, olanzapine or risperidone. Hum Psychopharmacol 2005;20: 573–581
13. McCormack PL, Wiseman LR. Olanzapine: a review of its use in the management of bipolar disorder. Drugs 2004;64:2709–2726
14. Kopala L, Fredrikson D, Good KP, et al. Symptoms in neuroleptic-naive, first-episode schizophrenia: response to risperidone. Biol Psychiatry 1996;39:296–298
15. Kopala L, Good KP, Fredrikson D, et al. Risperidone in first-episode schizophrenia: improvement in symptoms and pre-existing extrapyramidal signs. Int J Psychiatry Clin Pract 1998;2(suppl):19–25
16. Huq ZU, RIS-GBR-32 Investigators. A trial of low doses of risperidone in the treatment of patients with first-episode schizophrenia, schizophreniform disorder, or schizoaffective disorder. J Clin Psychopharmacol 2004;24:220–224
17. Lieberman JA, Stroup TS, McEvoy JP, et al. Effectiveness of antipsychotic drug in patients with chronic schizophrenia. N Engl J Med 2005; 353:1209–1223
18. Malla A, Norman R, Scholten D, et al. A comparison of two novel antipsychotics in first episode non-affective psychosis: one year outcome on symptoms, motor side effects and cognition. Psychiatry Res 2004; 129:159–169

19. Gasquet I, Haro JM, Novick D, et al. Pharmacological treatment and other predictors of treatment outcomes in previously untreated patients with schizophrenia: results from the European Schizophrenia Outpatient Health Outcomes (SOHO) study. Int Clin Psychopharmacol 2005;20: 199–205
20. Haro JM, Edgell ET, Jones PB, et al. The European Schizophrenia Outpatient Health Outcomes (SOHO) study: rationale, methods and recruitment. Acta Psychiatr Scand 2003;107:222–232
21. Robinson DG, Woerner MG, Alvir JM, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 1999;156:544–549
22. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first-episode schizophrenia. Am J Psychiatry 2006; 163:743–745