Importance of Gender in the Treatment of Schizophrenia

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ABSTRACT

Objective: To compare male and female patients participating in e-STAR (electronic Schizophrenia Treatment Adherence Registry), an international, prospective, observational study assessing use of risperidone long-acting injection in patients with schizophrenia or schizoaffective disorder in both the Czech and Slovak Republics.

Method: The demographic, clinical, and treatment-related data were collected at baseline and then prospectively for 24 months. We focused on gender differences in demographic and clinical data (hospitalizations, concomitant medication, and clinical improvement using Clinical Global Impressions-severity of illness [CGI-S], Global Assessment of Functioning [GAF], and Personal and Social Performance [PSP] scales). All psychiatric diagnoses were made according to *International Classification of Diseases*, *Tenth Revision* criteria. Data were collected from September 2006 through September 2009.

Results: A total of 868 patients (488 men and 380 women) were included in the assessment. At baseline, the women were significantly older than the men (42.1 ± 12.8 vs 34.8 ± 11.1 years, respectively; $P < .0001$). The women were also significantly more frequently diagnosed with schizoaffective disorder ($P = .0048$). There was no difference between men and women in the proportion of patients hospitalized in the retrospective and prospective period (including length of stay). At 24 months, the men were taking fewer antidepressants and benzodiazepines than the women (controlled for baseline values). In men and women, a significant decrease in the CGI-S score ($P < .001$) and a significant increase in the GAF and PSP scores ($P < .001$) from baseline were observed. The improvements in CGI-S and PSP scores were similar in both groups (no significant difference between male and female patients). The improvement (increase) in the mean GAF score was significantly higher in women than in men ($P = .0317$).

Conclusions: The treatment with risperidone long-acting injection was associated with clinically significant improvement in both male and female patients with schizophrenia with comparable severity of illness. There were no significant differences in most outcome measures. Gender differences, especially concerning treatment response to individual antipsychotics and their different forms, should be more intensively studied.

Prim Care Companion CNS Disord 2012;14(6):doi:10.4088/PCC.12m01407

Submitted: *May 3, 2012; accepted August 13, 2012.*
Published online: *November 15, 2012.*
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Differences between male and female patients with schizophrenia have been frequently reported in psychopathology and course of illness.[1] Gender-related effects may play a role in antipsychotic treatment.[2] However, there is little information about gender differences in schizophrenia and its treatment.

Risperidone long-acting injection is the first injectable atypical antipsychotic. The efficacy and safety of risperidone long-acting injection have been demonstrated in clinical trials. The electronic Schizophrenia Treatment Adherence Registry (e-STAR) is an international, prospective, observational registry that assesses use of risperidone long-acting injection in patients with schizophrenia or schizoaffective disorder in a normal clinical practice setting. The methodology of this international registry has been described by Olivares et al.[3] The aim of the present study was to compare male and female patients participating in e-STAR in both the Czech and Slovak Republics.

METHOD

Patient Population

Participating physicians with a primary specialty in psychiatry enrolled patients in e-STAR after they started treatment with risperidone long-acting injection or were switched from their current antipsychotic therapy to risperidone long-acting injection. All patients who are prescribed risperidone long-acting injection have this medication supplied by pharmacies and administered by psychiatric nurses every 2 weeks.

Patients were ≥ 18 years of age. All psychiatric diagnoses were made according to *International Classification of Diseases*, *Tenth Revision* criteria.

Study Design

The international, multicenter, prospective, observational registry e-STAR was designed to evaluate clinical outcomes in patients who had started risperidone long-acting injection as a part of their continuing therapy in routine clinical practice. Data were collected from September 2006 through September 2009.

Assessment Instruments

The clinical parameters included severity of illness (Clinical Global Impressions–severity of illness [CGI-S] scale),[4] global functioning (Global Assessment of Functioning [GAF] scale),[5] social performance (Personal and Social Performance [PSP] scale),[6] remission achievement,[7] and the number of rehospitalizations and the length of stay.

Data Analysis

The demographic, clinical, and treatment-related data (risperidone long-acting injection doses, dose changes, and concomitant medication) were collected at baseline and then prospectively for 24 months. The primary analysis was restricted to those patients with 24 months of follow-up data; patients with less than 24 months of data were excluded.

Clinical Points

- Long-acting injections of second-generation antipsychotics are a valuable option for patients with schizophrenia with poor adherence to treatment.
- Gender may be a predictor of clinical response to antipsychotic treatment, but its influence is not the same for all antipsychotics.
- Treatment with risperidone long-acting injections was associated with clinically significant improvement in both male and female patients with comparable severity of schizophrenia; there were no significant differences between men and women on most outcome measures.

Hospitalization parameters were compared over the 12-month period prior to the initiation of risperidone long-acting injection (retrospective assessment) and the first and second 12-month periods following the initiation (prospective assessment). Both descriptive (mean ± SD values) and nonparametric methods were used (Wilcoxon rank sum test and Fisher exact test). Comparison between the male and female groups of psychiatric comedication use at 24 months was done by means of a logistic model, controlling for comedication use at baseline. Logistic regression models were employed to determine the odds ratio (OR) associated with higher levels of comedication.

The CGI-S, GAF, and PSP scores were expressed as mean values per time point, and the statistical significance of score change over time with treatment was calculated using a paired *t* test. The CGI-S, GAF, and PSP score changes from baseline for male and female patients were compared using an analysis of covariance model, with baseline CGI-S, GAF, and PSP scores included in the model as covariates.

RESULTS

Sample Characteristics

A total of 868 patients were included in the study: 488 men and 380 women. The baseline characteristics of the men and women who completed the study with 24 months of follow-up and a comparison of their demographic and baseline characteristics are presented in Table 1.

Female patients were significantly older ($P < .0001$), with a longer duration of illness ($P < .0001$), and were more often diagnosed with schizoaffective disorder ($P = .0048$). Fewer female patients were employed full time. More male patients (91.2%) than female patients (89.7%) started the treatment as outpatients.

Hospitalization

Comparison between men and women in the 12-month retrospective period. There were no significant differences in the proportion of patients fully hospitalized at least once during the 12-month retrospective period (46.7% of men [228/488] vs 47.4% of women [180/380]; $P = .8910$), mean ± SD length of stay in days (25.2 ± 44.8 in men vs 24.1 ± 39.3 in women; $P = .7078$), or mean ± SD number of stays (0.56 ± 0.68 in men vs 0.58 ± 0.70 in women; $P = .7075$).

Table 1. Comparison of Male and Female Demographic and Baseline Characteristics

Parameter	Men (n = 488)	Women (n = 380)	*P* Value
Age at baseline, mean ± SD, y	34.8 ± 11.1	42.1 ± 12.8	< .0001*
Time since diagnosis, mean ± SD, y	7.7 ± 7.7	11.2 ± 9.4	< .0001*
Diagnosis, n (%)			
Schizoaffective disorder	46 (9.4)	60 (15.8)	.0048*
Schizophrenia	442 (90.6)	320 (84.2)	NS
Employment status, n (%)			
Full-time	58 (11.9)	23 (6.1)	.0018*
Not working	411 (84.2)	326 (85.8)	NS
Part-time	9 (1.8)	9 (2.4)	NS
Student	7 (1.4)	17 (4.5)	NS
Volunteer	3 (0.6)	5 (1.3)	NS
Outpatient	445 (91.2)	341 (89.7)	NS
Inpatient	43 (8.8)	39 (10.3)	NS

*Significant difference between male and female patients.
Abbreviation: NS = not significant.

Comparison between men and women in the 12-month prospective period. There were no significant differences in the proportion of patients fully hospitalized at least once during the 12-month prospective period (18.4% of men [90/488] vs 18.4% of women [70/380]; $P = 1.0000$), mean ± SD length of stay in days (7.0 ± 22.4 in men vs 6.6 ± 18.5 in women; $P = .9858$), or mean ± SD number of stays (0.21 ± 0.48 in men vs 0.23 ± 0.53 in women; $P = .9195$).

Changes (prospective—retrospective) in the mean ± SD length of stay in days (−18.2 ± 47.7 in men vs −17.5 ± 40.2 in women; $P = .3429$) and mean ± SD number of stays (−0.34 ± 0.70 in men vs −0.35 ± 0.69 in women; $P = .8275$) were not significantly different between men and women.

In both groups, a significant difference between the retrospective and prospective periods in the percentage of hospitalizations, mean length of stay, and mean number of stays was observed ($P < .001$).

Medication

Risperidone long-acting injection. The mean ± SD initial risperidone long-acting injection dose for men was 28.2± 6.7 mg every second week; the dose was 35.0 ± 10.2 mg at the end of the study. The values were approximately the same for women: 27.8 ± 6.1 mg initially and 35.0 ± 10.0 mg at the end of the study. In 79.3% of men and 81.1% of women, the initial risperidone long-acting injection dose was 25 mg every second week. In 54.1% of men and 51.8% of women, there was no dosage change during the study. In these parameters, no statistically significant differences between men and women were found.

Comedication. The comedications included anticholinergics, antidepressants, benzodiazepines, mood stabilizers, and somatic medications. Each patient could have more than 1 medication per time point.

Women were given significantly more antidepressants ($P = .0218$) and mood stabilizers ($P = .0134$) at baseline. The female group was given significantly more antidepressants

(OR = 0.664, $P = .0499$) and fewer anticholinergics (OR = 1.807, $P = .0317$) than the male group (controlled for baseline values) when concomitant medication at 24 months was compared.

Assessment Instruments (CGI-S, GAF, and PSP)

In men and women, a significant decrease in the CGI-S score ($P < .001$) and a significant increase in the GAF and PSP scores ($P < .001$) from baseline were observed.

The improvements in CGI-S and PSP scores were similar in both groups (no significant difference between male and female patients). The improvement (increase) in the mean GAF score was significantly higher in women than in men ($P = .0317$; Table 2).

Table 2. Comparison of Male and Female CGI-S, GAF, and PSP Scores at Baseline and 24 Months[a]

Parameter	Men (n = 452)	Women (n = 341)	Significant Difference Between Men and Women *P* Value
CGI-S			
Score at baseline	4.5 ± 1.0	4.6 ± 1.1	NS
Score at 24 mo	2.9 ± 1.0	2.9 ± 1.0	NS
Change from baseline	−1.5 ± 1.3*	−1.7 ± 1.2*	NS
GAF			
Score at baseline	52.9 ± 14.5	51.0 ± 15.5	NS
Score at 24 mo	72.0 ± 14.9	73.6 ± 14.5	NS
Change from baseline	19.1 ± 16.7*	22.5 ± 18.2*	.0317
PSP			
Score at baseline	50.6 ± 16.3	49.9 ± 17.5	NS
Score at 24 mo	70.7 ± 13.2	71.9 ± 12.5	NS
Change from baseline	20.1 ± 17.8*	22.0 ± 18.4*	NS

[a]All values are presented as mean ± SD.
*Significant change from baseline, $P < .001$.
Abbreviations: CGI-S = Clinical Global Impressions–severity of illness scale, GAF = Global Assessment of Functioning scale, NS = not significant, PSP = Personal and Social Performance scale.

DISCUSSION

Our sample included 488 men and 380 women. This ratio is common in observational studies. The earlier onset of schizophrenia in men has been reported in the recent literature.[1,8,9] At baseline, the men in the present study were significantly younger, with a shorter duration of illness ($P < .0001$). Our data show that the comparable severity of illness is achieved in women later than in men. With this later onset of illness, we can speculate that most women were married and taking care of children. Fewer of the women in our study had full-time employment. Unfortunately, neither the marital nor parental status was separately evaluated.

Risperidone long-acting injection is the first second-generation antipsychotic available in this formulation. In our sample, the mean initial and final risperidone long-acting injection doses were not significantly different between men and women. However, the dose per kilogram of bodyweight was not calculated. Raedler et al[10] reported that high-dose treatment with risperidone may be more beneficial in men for the treatment of acute schizophrenia. Our results concern only risperidone long-acting injection; however, there may be gender differences in schizophrenia in response to different antipsychotics. The Schizophrenia Outpatient Health Outcomes study,[11] a 3-year, prospective, observational study in 10 European countries, showed that gender was a significant predictor for CGI-S response, with women having a better response. The highest gender differences were found in typical antipsychotics and clozapine, and no differences were found for risperidone.[11]

At baseline, the female patients were given significantly more antidepressants and mood stabilizers. When concomitant medication at 24 months was compared, the female group took significantly more antidepressants and fewer anticholinergics than the male group (controlled for baseline values). These differences could be partially explained by a higher proportion of schizoaffective disorders in women. Further, according to the literature, women have more depressive symptoms than men.[8]

There was no difference between men and women in the proportion of patients hospitalized, mean number of hospitalizations, or mean length of stay in the retrospective and prospective periods. The improvement in CGI-S and PSP scores was similar in both groups. Only the improvement (increase) in the mean GAF score was significantly higher in women than in men. This finding partially corresponds with the literature. Galderisi and colleagues[1] did not find any significant effect of gender on any index of social functioning. The study described by Segarra et al[9] explored whether gender determines clinical and functional outcome 2 years after the initiation of treatment with risperidone in patients with first-episode psychosis. At 24-month follow-up, both groups had achieved significant improvements in outcome measures including PANSS, CGI-S, and GAF scores.[9`]

Our findings are limited by the fact that the study was an open, nonrandomized study performed under routine clinical conditions. Strengths of the study are length of follow-up and relative homogeneity of the sample. Our data show a similar severity of illness in both men and women, and the main reasons for switching to risperidone long-acting injection were noncompliance and insufficient response.[12,13]

Our findings bring some new knowledge on gender-dependent response on risperidone long-acting injection, which is a form of risperidone avoiding first-pass effect. Therefore, some gender differences in bioavailability might be diminished.

Drug names: clozapine (Clozaril, FazaClo, and others), risperidone (Risperdal and others).

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Potential conflicts of interest: **Dr Ceskova** is a consultant to Janssen-Cilag for the e-STAR project in the Czech Republic. **Dr Prikryl** reports no conflicts of interest related to the subject of this article.

Funding/support: Supported by a research grant from Janssen CR and the project CEITEC (Central European Institute of Technology; CZ.1.05/1.1.00/02.0068) from European Regional Development Fund.

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