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Gender differences in the treatment of first-episode schizophrenia: Results from the European First Episode Schizophrenia Trial

Eva Ceskova [a,b,c,d,*], Radovan Prikryl [a,b], Jan Libiger [e], Jan Svancara [f], Jiri Jarkovsky [f]

[a] Department of Psychiatry, Faculty Hospital Brno, Czech Republic
[b] Central European Institute of Technology, Masaryk University (CEITEC MU), Brno, Czech Republic
[c] Department of Clinical Studies Medical Faculty, University Ostrava, Czech Republic
[d] Department of Psychiatry, Faculty Hospital Ostrava, Czech Republic
[e] Department of Psychiatry, University Hospital Hradec Kralove, Czech Republic
[f] Institute of Biostatistics and Analyses, Faculty of Medicine, Masaryk University, Brno, Czech Republic

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ABSTRACT

Gender differences in the response to antipsychotic treatment have been detected in the past, but not studied in great detail. The results of the European First-Episode Schizophrenia Trial (EUFEST) were analyzed with a focus on gender differences in the response to randomized treatment of first-episode schizophrenia. A total of 498 patients (298 men and 200 women) were randomly assigned by a web-based online system to open-label treatment with haloperidol, amisulpride, olanzapine, quetiapine, and ziprasidone. Treatment response was evaluated using the positive and negative syndrome scale (PANSS). Data were collected at baseline and then prospectively for one year. Baseline characteristics (age and proportion of patients assigned to individual antipsychotics) were the same between the male and female patients with the exception of ziprasidone: significantly fewer men, proportionately, were prescribed ziprasidone. There was no significant difference between genders between the initial total PANSS and subscale scores. A significant interaction between time and gender was found, with more robust PPANSS and TPANSS score improvement in women during the course of treatment. Of all of the antipsychotics used, only olanzapine led to significantly greater improvement in the total PANSS score in women during the follow-up period. Gender differences should be given more attention in research and clinical practice. Their causes require clarification, and future strategies for dealing with them may be considered in early intervention programs and guidelines.

1. Introduction

Gender differences in psychotic disorders have been observed in terms of illness onset and course. Clinical studies that examine outcomes separately for men and women can help determine whether treatment has differential effectiveness or distinct side effects according to gender. The issue of gender-specific responses to medication interventions addresses an understudied area. For many years, researchers omitted women from clinical trials to avoid the difficulty of assessing the potentially interfering effects of female hormones and the bias menstrual cycles might mean for study results.

Many studies have tried to determine the role of gender in schizophrenia, but mainly in terms of epidemiology, clinical symptoms, and course of illness. Gender differences in antipsychotic responses have been less systematically pursued. However, gender-related effects may play a role in antipsychotic treatment (Seeman, 2004). It has been hypothesized that estrogen, with effects on both neurodevelopment and neurotransmission, may play a protective role in women with schizophrenia and account for some of the gender differences observed in the disorder (Canuso and Pandini, 2007; Groleger and Novak-Grubic, 2010). Gender differences in response to individual antipsychotics have been observed (Usall et al., 2007; Raedler et al., 2006; Segarra et al., 2011; Xiang et al., 2010; Müller et al., 2006).

Fifty sites in 14 countries, including three Czech centers, participated in the European First-Episode Schizophrenia Trial (EUFEST), a one-year pragmatic, multicenter, randomized trial focused on the prospective evaluation of treatment effectiveness under circumstances similar to routine clinical practice (Kahn et al., 2008). The aim of this paper is to use the EUFEST data to evaluate gender differences in schizophrenia in response to typical (low dose of haloperidol) and atypical antipsychotics. We hypothesized that there would be gender differences in the response to individual antipsychotics and between typical and atypical antipsychotics. We expected greater improvement of psychopathology in women than in men.

* Corresponding author at: Department of Psychiatry, Faculty Hospital Brno, Jihlavska 102, Brno-Bohunice 625 00, Czech Republic.
E-mail address: eva.ceskova@gmail.com (E. Ceskova).

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2. Methods

2.1. Study design

Data from EUFEST were used for the present study. The EUFEST rationale, design, and methods were published elsewhere (Fleischhacker et al., 2005; Kahn et al., 2008). The subjects were 18–40 years of age, met the Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM IV) criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. The first episode of schizophrenia in a partially antipsychotic-naive study population must not have lasted more than two years since the first onset of symptoms. The use of any antipsychotic drug had to be shorter than two weeks in the previous year and must not have exceeded six weeks cumulatively. All participants, or their legal representatives, provided written informed consent. The trial complied with the Declaration of Helsinki and was approved by the ethics committees at the participating centers. The study is registered as an International Standard Randomized Controlled Trial, number ISRCTN68736636.

2.2. Treatment

Patients were randomly assigned by a dedicated web-based online system to a daily regimen of haloperidol (1–4 mg), amisulpride (200–800 mg), olanzapine (5–20 mg), quetiapine (200–750 mg), or ziprasidone (40–160 mg). Patients and their treating physicians were not blinded to the assigned treatment. All study drugs were given orally, within the above dose ranges, at the treating psychiatrist's discretion. The use of mood stabilizers, benzodiazepines, antidepressants, and anticholinergic drugs was allowed, and documented (Kahn et al., 2008).

2.3. Assessment

To evaluate gender differences in response to antipsychotics, positive and negative syndrome scale (PANSS, Kay et al., 1987) scores were applied. For a more detailed analysis, the total PANSS and all subscales (positive PPANSS, negative NPANSS, and general GPANSS) scores were used.

2.4. Data analysis

Demographic, clinical, and treatment-related data were collected at baseline and then prospectively for 12 months. We analyzed the baseline data and data collected after 1, 3, 6, 9, and 12 months. We compared the men and women in terms of mean PANSS total and all subscales scores.

Standard descriptive statistics were applied in the analysis: absolute and relative frequencies for categorical variables and mean supplemented by a 95% confidence interval for continuous variables and scores.

The statistical significance of differences between men and women was tested using Fisher's exact test for categorical variables and an unpaired t-test for continuous variables and scores. The statistical significance of gender, treatment, and their overall interaction was computed using generalized estimating equations (GEE) with time as a within-subject variable. Bonferroni correction was applied for multiple testing; $\alpha = 0.05$ was taken as the level of statistical significance in all analyses. Statistical analysis was computed using SPSS 22 (IBM Corporation, 2013).

3. Results

3.1. Demographic data

Descriptive data for patients in the EUFEST trial have been published. The data can be summarized as follows: The study was performed at 50 sites in 14 countries. A total of 498 patients (298 men and 200 women) were randomly assigned by a web-based online system to haloperidol (1–4 mg per day, n 103: 64 men, 39 women), amisulpride (200–800 mg per day, n 104: 58 men, 46 women), olanzapine (5–20 mg per day, n 105: 67 men, 38 women), quetiapine (200–750 mg per day, n 104. 68 men, 36 women), or ziprasidone (40–160 mg per day, n 82: 41 men, 41 women); follow-up visits were continued for one year (Kahn et al., 2008).

3.2. Baseline characteristics — comparison between men and women

Baseline characteristics (age and proportion of patients assigned to individual antipsychotics) were the same between men and women with the exception of ziprasidone: significantly fewer men, proportionately, were randomly assigned to ziprasidone. The initial total PANSS and all PANSS subscales scores did not differ between groups (Table 1).

3.3. Psychopathology change — comparison between men and women

After three months of treatment, a significantly greater improvement in the total PANSS and all PANSS subscales scores, was seen in women. However, after Bonferroni correction was applied, only PPANS and total PANSS score remained significant. After six months, the women had improved significantly more in the total PANSS and the PPANSS subscale, but only in the PPANSS subscale after Bonferroni correction. After nine months, significantly more pronounced improvement was seen in women in the total PANSS and all the PANSS subscale scores, with the exception of the NPANSS. After Bonferroni correction only PPANSS subscale and the total PANSS scores in women was significant— see Table 2.

Using GEE, a significant interaction between time and gender was found, with a more robust PPANSS and TPANSS score improvement in women over the course of treatment — see Table 4, model 1, and Table 2.

3.4. Psychopathology change — comparison between men and women in response to all given antipsychotics

Among all antipsychotics randomized to EUFEST participants at the admission to the trial, only olanzapine led to significantly greater improvement in all domains of psychopathology, e.g. the total PANSS

Table 1
Comparison of male and female baseline characteristics.

Results	Whole sample N = 498	Men N = 298	Women N = 200	P value
Age in years at study entry (95% CI)	26.0 (25.5–26.5)	25.6 (25.0–26.2)	26.5 (25.7–27.3)	0.069
Antipsychotic randomized at study entry				
Haloperidol	103 (20.7%)	64 (21.5%)	39 (19.5%)	0.652
Amisulpride	104 (20.9%)	58 (19.5%)	46 (23.0%)	0.369
Olanzapine	105 (21.1%)	67 (22.5%)	38 (19.0%)	0.372
Quetiapine	104 (20.9%)	68 (22.8%)	36 (18.0%)	0.217
Ziprasidone	82 (16.5%)	41 (13.8%)	41 (20.5%)	**0.050**
Psychopathology (PANSS)				
PPANSS	23.1 (22.6–23.7)	22.9 (22.2–23.6)	23.5 (22.6–24.3)	0.346
NPANSS	21.2 (20.6–21.9)	21.3 (20.4–22.2)	21.2 (20.1–22.2)	0.870
GPANSS	44.1 (43.2–45.1)	43.6 (42.4–44.8)	44.9 (43.4–46.5)	0.179
TPANSS	88.5 (86.7–90.4)	87.8 (85.4–90.2)	89.6 (86.7–92.5)	0.344
GAF score	40.0 (38.8–41.2)	40.1 (38.5–41.7)	40.0 (38.2–41.8)	0.941

PPANSS: positive PANSS subscale score; NPANSS: negative PANSS subscale score; GPANSS: general PANSS: subscale score; TPANSS: total PANSS score; CI: confidence interval; significant results are shown in bold.