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ORIGINAL PAPER

Similarities in early course among men and women with a first episode of schizophrenia and schizophreniform disorder

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Abstract The aims of this study were to analyze the presence of gender differences in the phenotypic expression of schizophrenia at the onset of illness and to explore whether these differences determine clinical and functional outcome 2 years after the initiation of treatment. Data from 231 first-episode-psychosis non-substance-dependent patients (156 men and 75 women) participating in a large-scale naturalistic open-label trial with risperidone were recorded at inclusion and months 1, 6, 12, and 24. Men presented a significant earlier age of onset (24.89 years vs. 29.01 years in women), poorer premorbid functioning, and a higher presence of prodromal and baseline negative symptoms. Women were more frequently married or lived with their partner and children and more frequently presented acute stress during the year previous to onset than men. No other significant clinical or functional differences were detected at baseline. The mean dose of antipsychotic treatment was similar for both genders during the study, and no significant differences in UKU scores were found. The number of hospitalizations was similar between groups, and adherence was more frequent among women. At the 2-year follow-up, both groups obtained significant improvements in outcome measures: PANSS, CGI severity, and GAF scores. Significant gender * time interactions were detected for negative and general PANSS subscales, with the improvement being more pronounced for men. However, no differences were detected for the mean scores obtained during the study in any outcome measure, and the final profile was similar for men and women. Our results suggest that although the initial presentation of schizophrenia can differ according to gender, these differences are not sufficient enough to determine differentiated outcome 2 years after the initiation of treatment in non-substance-dependent patients. The influence of gender on the early course of schizophrenia does not seem to be clinically or functionally decisive in this population.

Keywords Schizophrenia · Psychosis · First episode · Gender

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Introduction

Gender has been considered to be one of the factors that contribute to the heterogeneity of psychotic disorders. Murray et al. (1985) suggested the possibility of "female

psychosis" versus "male psychosis", pointing out not the existence of two clinical subtypes of the illness, but underlying differences in the expression of clinical variables depending on the gender of the patient [53]. Accordingly, many authors support the notion that gender modifies the phenotypic expression of schizophrenia and underline the subsequent prognostic and therapeutic implications of these differences [6, 15, 16, 28, 38, 39, 48, 51, 61, 63, 64, 66, 71].

Male gender has been associated with higher prevalence and incidence of schizophrenia [14, 30], earlier age of onset, worse social premorbid adjustment, poorer social networks (patients are frequently unemployed and live alone), and more severe negative symptoms at onset [21, 31, 39, 42]. In contrast, estrogens are believed to have a protective effect against the development of illness. Consequently, women become ill later in life than men, with the most noticeable symptoms observed during the menopause [31, 32, 38]. Women are reported to present more affective symptoms and a better course and outcome characterized with a shorter duration of the acute phase of the illness, a lower and shorter rehospitalization rate, and a longer time to relapse [16, 38, 39, 59].

Unfortunately, there is no real consensus on gender-related differences; some authors do not support a higher incidence of schizophrenia in men [27, 30, 33] or differences in the age of onset [39, 63], and others have failed to find significant differences in the clinical expression of symptoms or disease course [1, 6, 8, 29, 31, 37, 45, 52, 65].

As for medication, women have been reported to respond significantly better to treatment after diagnosis [62]. This faster and better response is probably due to a potentially protective antidopaminergic effect of estrogens in relation to antipsychotic drugs [67] and to an increased self-awareness apparently derived from a better adequacy of introspection in women [9, 40]. Additionally, general recommendations for antipsychotic drugs prescription stress that most females require lower doses to repair symptoms and well-being [60]. Some authors have tried to analyze gender differences in the antipsychotic dose necessary for stabilization; however, findings on pharmacokinetics or pharmacodynamics are inconsistent. Whereas some studies have found that women need a 20% lower dose to control symptoms [7, 54], others have reported no gender differences [56, 62] or even higher doses in women [39]. Reaction to medication also seems to vary with gender. Differences in the severity of extrapyramidal symptoms and adverse effects have not been consistently studied, but some adverse effects (e.g., weight gain, hyperprolactinemia, and cardiac effects) are reported to be particularly problematic for women [2].

Although relevant prognostic factors in patients with first-episode psychosis (FEP) have been widely analyzed, few studies have acknowledged gender as a key factor in the early course and outcome of these patients [16, 39, 48, 62]. Furthermore, even though published data suggest the existence of gender-associated differences in the clinical presentation of schizophrenia, treatment response, and outcome, results are inconclusive and to some extent contradictory [43]. Our limited knowledge of gender differences in FEP may be the result of methodological inconsistencies across studies—due mainly to the definition of the sample assessed (some studies include patients with both affective and non-affective psychosis, whereas others include only patients with schizophrenia; some studies include substance dependence as a criteria for exclusion, whereas others do not) and of variability in the types of antipsychotics prescribed. The aims of this study were to determine gender differences in phenotypic expression in non-substance-dependent patients (except tobacco) with a first episode of schizophrenia/schizophreniform disorder ($FE_{sz/szform}$) treated with risperidone and to analyze possible gender differences in early course.

Methods

Study setting and recruitment

Data were collected as part of a large-scale 2-year multicenter naturalistic observational open-label trial with risperidone based on a flexible protocol of low doses up to a maximum tolerated dose within the range recommended in the summary of product characteristics. The aims of the original multicentre trail were as follows: (a) to assess the course of FEP and identify the presence of possible prognostic factors; and (b) to determine the efficacy and safety of oral risperidone in treating the disease. From the original sample ($n = 436$), only patients with a diagnosis of $FE_{sz/szform}$ confirmed at 6 months of follow-up according to DSM-IV criteria [5] were included in the present analysis ($n = 231$). The study was conducted from January 1998 to December 2001 at 7 spanish university hospitals with experience in the treatment of FEP. Patients recruited were either inpatients treated at these facilities or outpatients referred from their corresponding local mental health services. Participants did not obtain any payment for their participation. Consistent clinical care was provided—as normally delivered—to those patients who refused to participate in the study.

The study was approved by the Institutional Review Boards of all the participating hospitals. The protocol was designed according to the guidelines of the Spanish Medications Agency.

Participants

Patients were included if they met the following criteria: (i) age between 15 and 65 years; (ii) presence of positive symptoms within FEP; (iii) no previous antipsychotic medication; (iv) suitability for treatment with oral risperidone. The exclusion criteria were as follows: (i) presence of a concomitant Axis I disorder; (ii) presence of a neurological or medically relevant condition; (iii) history of head trauma with loss of consciousness; (iv) current diagnosis of substance dependence (except tobacco); (v) treatment with antipsychotic medication for more than 2 weeks before the initiation of oral risperidone. All participants understood the nature of the study and gave their written informed consent before enrollment.

Data collection

Visits were at baseline and at months 1, 6, 12, and 24. Every interview lasted approximately 45 min, with the exception of the baseline and month 6 visits that lasted 120 min—divided in two separate sessions—mainly due to the diagnostic assessments. Clinical interviews and assessments were performed by experienced psychiatrists. The intraclass correlations (ICC) on clinical scales ranked from 0.87 to 0.96. Socio-demographic, family, and developmental data were collected from the patient's medical records and interviews with patients and their relatives whenever possible. The presence of obstetric complications (OC) was assessed using the Lewis–Murray scale [44]. FEP, defined as the first time the patient came for treatment for a psychotic disorder, was diagnosed at baseline according to DSM-IV criteria using the Structured Clinical Interview-I (SCID I) [20]. This same interview was re-conducted at 6 months to determine and confirm specific psychotic diagnoses. The presence and severity of psychotic symptoms were evaluated using the Spanish version of the Positive and Negative Syndrome Scale (PANSS) [55]. Other clinical scales used were the Hamilton Depression Rating Scale (HDRS) [34], the Young Mania Rating Scale (YMRS) [72], the severity subscale of the Clinical Global Impression Scale (CGI) [25], the Global Assessment of Functioning Scale (GAF) [19], and the Premorbid Adjustment Scale (PAS) [10]. Data related to the presence of prodromal symptoms and date of onset of psychosis were collected by means of a semi-structured interview according to the models of Haffner et al. [31] and Larsen et al. [42] with the patient and a close relative familiar with the patient's early course whenever possible. Prodromal symptoms were defined as follows: attenuated positive, negative, or disorganized with no significant clinical relevance for a psychiatric diagnosis; or sufficiently intense symptoms that were present for a period lower than or equal to 1 week. Duration of untreated psychosis (DUP) was calculated as the number of months between the first psychotic symptom (DSM-IV criteria: delusions, hallucinations, formal thought disorder, and strange behavior with relevant severity and a duration of at least 1 week) and the date of initiation of appropriate antipsychotic treatment, which was implemented immediately after enrollment. Psychosocial stress was assessed using the DSM-III-R psychosocial stress axis. Premorbid IQ was estimated using the Information subtest of the Wechsler Adult Intelligence Scale Revised (WAIS-R) [70]. This subtest was administered by clinical psychologists (ICC range = 0.97–0.99).

Treatment

All patients received oral risperidone after being diagnosed with an FEP. Treatment was based on a flexible protocol of low doses up to a maximum tolerated dose within the range recommended in the summary of product characteristics. Drugs other than risperidone were permitted according to the clinician's judgment (e.g., benzodiazepines, mood stabilizers, and/or antiparkinsonian treatments). Tolerance was assessed using a self-reported questionnaire on adverse reactions to medication and the UKU Side Effect Rating Scale (UKU) [46]. In addition, patients were invited to participate in a variety of non-pharmacological therapies (e.g., cognitive-behavioral therapy, individual psychotherapy, and group therapy or family interventions).

Statistical analyses

Data are summarized using standard descriptive statistics (mean, standard deviation, and frequency). All variables were checked for skewed distributions and outliers. For pre-onset and socio-demographic data, baseline clinical scores, and treatment measures, a one-way analysis of variance (ANOVA) was performed to compare means for continuous variables. The chi-square test was used for the comparison of categorical measurements. Course of illness was assessed using a general linear model for repeated measures with time as the intra-group factor with 5 levels (baseline and months 1, 6, 12, and 24) and gender as the between-groups variable.

Results

Men accounted for two-thirds of the sample: 67.5% ($n = 156$) men versus 32.5% ($n = 75$) women. Participation rates were 77% at 1 year of follow-up and 60% at 2 years of follow-up. At the final visit, 61% ($n = 95$) of men and 60% ($n = 44$) of women were assessed. The men-to-women ratio (3:1) remained stable throughout the study. At year 2, data on

age, gender, and baseline PANSS in the remaining group did not differ significantly from those of the dropout group. The main identified reasons for dropout were as follows: voluntary withdrawn of the trial 48%, restricted collaboration of the patient and/or poor compliance with the treatment 15%, intolerance 6.5%, lack of clinical response 6.5%, hospitalization 9%, and others (change of residence and different combinations of previous reasons) 15%. For this subsample, the psychiatrist's judgement of the clinical state of the patient recorded at the last assessment completed was worse 2%, slightly worse 4.5%, equal 4.5%, slightly better 13%, better 35%, and much better 41%.

Socio-demographic and pre-onset clinical variables

Socio-demographic and pre-onset clinical variables for each group are shown in Table 1. Age of onset according to family history of psychiatric disorders and of OC in men and women is represented graphically in Fig. 1.

Diagnostic distribution

Specific diagnoses confirmed at the 6-month follow-up are shown in Table 2. There were no significant differences in the distribution by gender: χ^2 (6) = 10.039, $P = 0.262$.

Baseline symptoms

Baseline clinical data for the PANSS, CGI severity, and GAF scales are shown in Table 3. Men scored significantly higher than women on the PANSS negative subscale. No between-group differences were detected for depressive symptoms [HDRS men/women (mean ± SD) 15.52 ± 8.64/16.89 ± 9.79; F (1) = 0.969, $P = 0.326$] or mania [YMRS men/women (mean ± SD) 16.88 ± 7.83/15.20 ± 7.01; F (1) = 0.618, $P = 0.435$].

Disease course

Symptoms and functionality improved significantly over time (Table 3). The influence of gender on disease course was detected in relation to the PANSS negative and general subscales, in which the rate of change was significantly higher for men (Fig. 2). No significant differences were detected between groups for the mean score obtained during the study period for any clinical or functional variable assessed. The number of hospitalizations during the 2 years of the study was similar for men and women [men/women (mean ± SD, range) 0.82 ± 1.38, 0–10/0.68 ± 0.95, 0–4; $Z = 0.522$, $P = 0.398$]. No between-group differences were detected at the 2-year follow-up for depressive symptoms [HDRS men/women (mean ± SD) 5.79 ± 4.84/5.19 ± 5.50; F (1) = 0.188, $P = 0.666$] or mania [YMRS men/women (mean ± SD) 3.99 ± 5.66/3.06 ± 5.79; F (1) = 0.652, $P = 0.421$].

Treatment

At inclusion, 54% ($n = 84$) of men and 61% ($n = 46$) of women were enrolled in one of the different non-pharmacological treatments offered, with no significant differences in the distribution (χ^2 (1) = 1.154, $P = 0.322$). Antipsychotic treatment-related variables are presented in Table 4. No differences between groups were found concerning the percentage of patients that presented at least one extrapyramidal symptom during the study: 25% of men ($n = 39$) and 32% of women ($n = 24$), χ^2 (1) = 1.251, $P = 0.273$.

Discussion

The principal finding of this study was that, although there were gender differences in the phenotypic expression of schizophrenia in non-substance-dependent patients, the clinical and functional outcome 2 years after the first contact with the psychiatric service was similar for men and women. Therefore, our results do not support gender as a determinant prognostic factor during the early course of the disease in this population.

Gender differences at the onset of illness

Differences in phenotypic expression were detected in: (a) the incidence of cases among groups, (b) pre-onset clinical variables and socio-demographic characteristics at onset, and (c) initial psychopathological presentation.

Incidence of schizophrenia and gender

In our sample (231 patients with $FE_{sz/szform}$, age 15–65 years), males were over-represented (67.5% vs. 32.5%). This predominance (3:1) is consistent with the ratios reported in previous studies including patients with a similar age of onset [39: Willhite 2008 #6203, 58, 71]. This result might support the hypothesis that incidence is higher in males [11, 35, 37]. However, Hafner et al. [31] suggested that the lifetime risk for schizophrenia is equal for males and females. This proposal is based on the antipsychotic effect of estrogens on dopamine D2 receptors, and therefore, in a proportion of women, the disorder only would become apparent after menopause [61].

Considering that the present study has an artificial age cutoff at 65 years with the result that very late onset (VLO) schizophrenia has not been included and women would be over-represented in a VLO group [38], we cannot conclude a real higher incidence of schizophrenia in males.

Pre-onset clinical variables and socio-demographic characteristics at onset

Women were more frequently married and living with their partner and children than men. This result may be associated—among other socio-cultural factors—with their better premorbid adjustment [57], lower number of prodromal symptoms than men, and later age of onset. Onset of illness occurred approximately 4 years later in women. This result is consistent with one of the most replicated findings in this area, namely, 2- to 5-year earlier age of onset of schizophrenia in males [13, 30, 32, 50]. Both a positive family

Table 1 Baseline socio-demographic and pre-onset clinical data for men and women with a first episode of schizophrenia/schizophreniform disorder

	Men $N = 156$	Women $N = 75$	F/χ^2	*df*	*P*
Age of onset, mean (s.d.)	24.89 (7.01)	29.01 (10.55)	12.394	1	0.001
Range	15–53	15–65			
Years of education completed, mean (s.d.)	9.01 (6.41)	10.24 (7.07)	0.980	1	0.324
Marital status % (*n*)			9.619	2	0.007
Single	139% (89)	73% (55)			
Married	7% (11)	20% (15)	9.093	1	0.003
Divorced/separated	4% (6)	7% (5)			
Household, % (*n*)			22.263	2	<0.001
Parents/family	85% (132)	63% (47)			
Partner/children	7% (10)	30% (22)	22.008	1	<0.001
Others (friends, alone, assisted)	5% (8)	5% (4)			
Work: active (full-time/part-time), % (*n*)	39% (60)	41% (30)	0.037	1	0.848
Positive FH-p, % (*n*)	67% (105)	67% (50)	0.009	1	1.000
Obstetric complications, % (*n*)	35% (55)	24% (18)	3.142	1	0.076
Information subtest-WAIS, mean (s.d.)	11.1 (3.11)	10.82 (2.99)	0.435	1	0.510
Premorbid adjustment, mean (s.d.)					
Childhood	7.47 (4.63)	6.55 (4.28)	2.984	1	0.086
Early adolescence	8.92 (5.01)	7.89 (4.83)	3.734	1	0.055
Late adolescence	13.91 (7.36)	11.20 (6.12)	6.429	1	0.012
Adulthood	9.01 (5.15)	6.66 (4.90)	7.875	1	0.006
General	28.39 (11.68)	24.05 (10.63)	6.669	1	0.011
DUP (months), median (s.d.)	4.00 (15.7)	3.00 (13.76)	0.621	1	0.431
Prodromal symptoms, % (*n*)					
Social isolation	82% (110)	69% (48)	4.811	1	0.035
Deterioration in activities	72% (93)	65% (44)	1.147	1	0.326
Strange behavior	75% (97)	59% (40)	5.223	1	0.024
Deterioration in personal hygiene	44% (53)	24% (16)	7.017	1	0.011
Dulled or inappropriate affect	66% (82)	59% (40)	0.870	1	0.435
Disorganized, vague speech	53% (64)	37% (23)	4.319	1	0.043
Strange ideation or magical thinking	78% (109)	79% (55)	0.001	1	1.000
Unusual perceptual experiences	75% (99)	71% (46)	0.401	1	0.606
Lack of initiative	66% (85)	43% (29)	9.868	1	0.002
Status			1.357	1	0.261
Inpatient	47% (73)	39% (29)			
Outpatient	53% (83)	61% (46)			
Acute onset (<6 months), % (*n*)	55% (86)	65% (49)	1.257	1	0.262
Acute DSM-III-R psychosocial stress, % (*n*)	20.5% (32)	44% (33)	4.835	1	0.041
Concomitant illness, % (*n*)	9% (14)	7% (5)	0.357	1	0.619

FH-p Family history of psychiatric disorders

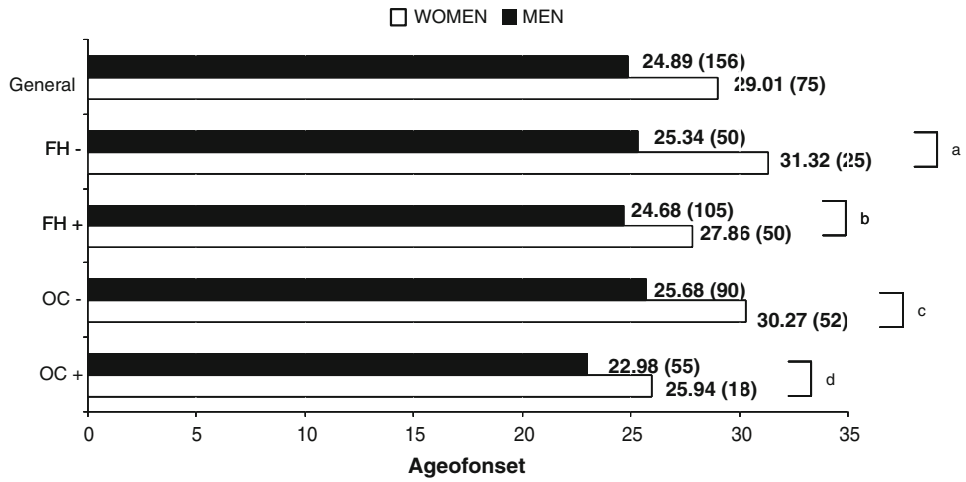

Fig. 1 Age of onset according to family history of psychiatric disorders and obstetric complications in men and women with a first episode of schizophrenia/schizophreniform disorder. Data are described as mean age (number of patients in the group). *FH* Family history of psychiatric disorders, positive (FH+) and negative (FH−); *OC* Obstetric complications, presence (OC+) and absence (OC−). **a** Significant differences F (1) = 6.437, $P = 0.013$; **b** Significant differences F (1) = 5.947, $P = 0.016$; **c** Significant differences F (1) = 8.932, $P = 0.003$; **d** Non-significant differences F (1) = 3.114, $P = 0.082$

history of psychiatric disorders and presence of OC have been related to earlier age of onset [3, 36, 68]. Accordingly, Fig. 1 shows a tendency for younger ages of onset in both males and females when considering these two variables. Differences in age of onset between genders disappeared only when comparing patients with a past history of OC. For females, this was the group with an earlier age of onset, and as suggested by Gureje et al. [24], the presence of OC accompanied with an earlier age of onset probably does of this subgroup of women the one with a poorer course and outcome. However, this result may be interpreted cautiously as the small sample size for women with OC ($n = 18$) could explain the lack of significant gender differences.

Initial psychopathological presentation

Consistent with the results of previous studies, men with $FE_{sz/szform}$ presented higher levels of negative symptoms than women at baseline [16, 38, 39, 63, 71]. This is not surprising if we consider that men more frequently presented prodromal symptoms classified in the negative dimension (social isolation, deterioration in personal hygiene, and lack of initiative) and poorer premorbid adjustment. Indeed, the association between poorer premorbid adjustment and higher levels of negative symptoms has been outlined [26, 52, 57, 63]. In the case of women, previous studies have reported that this group exhibit more affective symptoms than men [4, 16, 22, 23, 39, 49, 62]. Although women more frequently presented acute stress during the previous year than men, no differences were detected at baseline in mania or depressive symptoms. In our opinion, this discrepancy with previous results could be related to differences in the definition of the samples included across studies. Whereas our sample had homogeneous symptoms of schizophrenia, some previous studies have included affective psychosis or schizoaffective disorders that may have led to the differences reported [39, 47, 69]. This effect of heterogeneity in diagnosis was observed in the study by Cotton et al. [16], in which depressive symptoms are more frequent in women with an FEP. However, when only non-affective psychoses (schizophrenia or schizophreniform disorder) in the total sample were taken into consideration, gender differences in depressive symptoms were no longer detected. In our sample, males and females did not differ in disease severity and social functioning at entry. Once again, this finding agrees with the results of Cotton et al., in which differences disappeared when only $FE_{sz/szform}$ patients were compared, despite the fact that gender differences in CGI severity or GAF scores were detected for the total sample of FEP patients.

Table 2 Diagnostic distribution by gender

	Men $N = 156$	Women $N = 75$
Diagnosis, % (*n*)		
Disorganized schizophrenia	6.4% (10)	4% (3)
Catatonic schizophrenia	0.6% (1)	–
Paranoid schizophrenia	60.9% (95)	50.7% (38)
Schizophreniform disorder	8.3% (13)	17.3% (13)
Schizophreniform disorder in remission	12.2% (19)	18.6% (14)
Residual schizophrenia	5.1% (8)	4% (3)
Undifferentiated schizophrenia	6.4% (10)	5.3% (4)

Table 3 Early clinical and functional course for men and women with a first episode of schizophrenia/schizophreniform disorder

	Baseline					2 years		Disease course								
	Men	Women	*F*	*df*	*P*	Men	Women	Differences between assessment points[a]			Interaction gender * time			Differences in mean values between genders		
								F	*df*	*P*	*F*	*df*	*P*	*F*	*df*	*P*
PANSS																
Positive	25.71 (7.20)	26.18 (7.23)	0.211	1	0.647	10.15 (5.36)	9.57 (3.90)	181.8	4,221	<0.001	0.122	1,224	0.727	1.398	1,224	0.238
	$n = 154$	$n = 72$				$n = 95$	$n = 44$									
Negative	25.48 (9.53)	22.32 (9.34)	5.533	1	0.020	12.91 (5.86)	13.14 (7.64)	66.9	4,221	<0.001	5.897	1,224	0.016	1.879	1,224	0.172
	$n = 154$	$n = 72$				$n = 95$	$n = 44$									
General	47.56 (12.86)	45.42 (12.20)	1.417	1	0.235	23.85 (8.91)	23.43 (9.60)	138.9	4,221	<0.001	3.954	1,224	0.048	0.011	1,224	0.915
	$n = 154$	$n = 72$				$n = 95$	$n = 44$									
CGI severity	5.14 (0.80)	5.03 (0.82)	0.930	1	0.336	2.44 (1.28)	2.16 (1.24)	179.4	4,224	<0.001	0.024	1,227	0.877	0.066	1,227	0.797
	$n = 154$	$n = 75$				$n = 95$	$n = 44$									
GAF	37.35 (14.78)	40.11 (17.49)	1.557	1	0.213	77.87 (15.37)	78.14 (16.44)	163.7	4,224	<0.001	1.051	1,227	0.306	0.066	1,227	0.797
	$n = 155$	$n = 74$				$n = 95$	$n = 44$									

Time assessments at baseline and months 1, 6, 12, and 24

[a] For all participants, Pillai's Trace Criterion

Course and outcome of illness

Initiation of appropriate treatment helped both genders after 2 years. As expected, clinical symptoms and social functioning improved significantly in all patients, although there were no significant differences in the mean scores obtained during the study for PANSS subscales, CGI severity, or GAF. Progress was also similar between men and women, with the exception of the PANSS negative and general subscales, for which men displayed a more pronounced improvement during the first year. The more marked improvement in negative symptoms for men, who presented higher scores at baseline, meant that their final score was similar to that of women. Therefore, a higher score on negative symptoms at onset does not necessarily imply a worse outcome in non-substance-dependent male patients. We did not detect gender differences in the number of hospitalizations. Although the literature indicates than men have more hospitalizations and longer stays than women [66], not all studies have replicated this finding [6]. We consider that the clinical profile of the patients assessed as non-substance dependents may result in a lower number of inpatient admissions in men than that in studies including substance-dependent FEP patients [41]. The wider range in the number of hospitalizations observed in men may be probably due to gender-associated differences in social behaviors between men and women, for which men usually present more aggressive behaviors that might require hospitalization [66].

Antipsychotic treatment

No significant gender differences were detected in the dose of antipsychotic prescribed, either at baseline or at the 2-year follow-up visit. Although some authors report that women need a lower dose [7, 54], other authors have found similar doses for men and women [56, 62]. This discrepancy may be related to the differences in body mass index between groups and/or type of antipsychotic prescribed. For example, cigarette smoking is significantly higher in men and has been reported to increase the metabolism of some antipsychotic drugs [12, 18]. In the present study, the relevant factors mediating variability in the doses prescribed are dissipated, as there were no differences in BMI between the groups and all participants were receiving an antipsychotic whose metabolism is not altered by smoking [17].

There were no significant gender differences between the scores obtained for the UKU scale at the different assessment points. This result is consistent with the conclusion of a meta-analysis rebutting gender differences for any of the second-generation antipsychotics with respect to a higher rate of extrapyramidal symptoms, acute dystonia, or other movement disturbance [2]. A later study on gender differences in

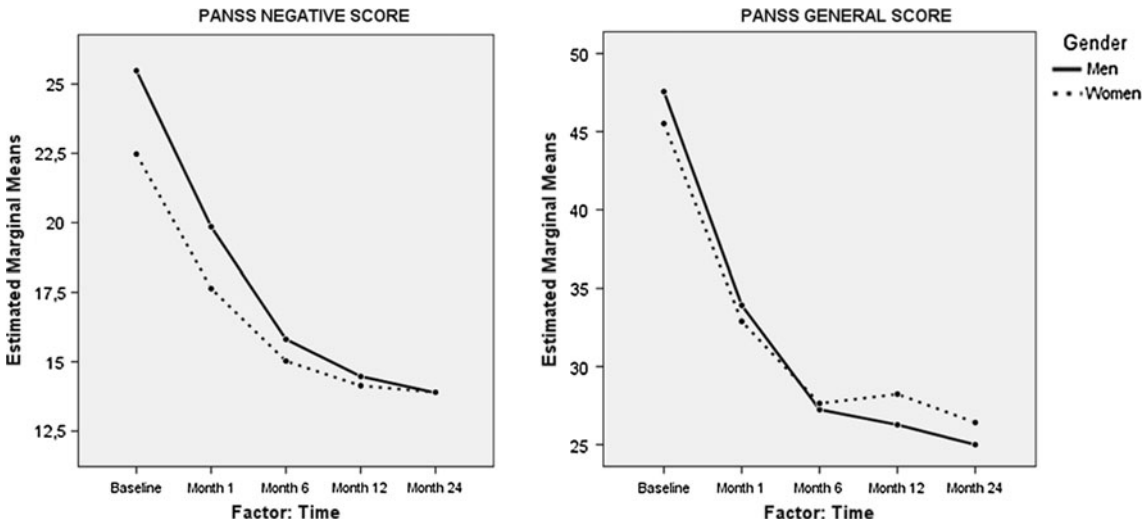

Fig. 2 Significant clinical interactions between gender and time during the early course of first-episode schizophrenia/schizophreniform disorders

Table 4 Antipsychotic treatment-associated variables for men and women with a first episode of schizophrenia/schizophreniform disorder

	Men	Women	t/χ^2	*df*	*P*
Mean dose risperidone, mean (s.d.), *n*					
Baseline	6.26 (2.51), 156	5.61 (2.56), 75	3.338	1	0.069
Month 24	4.66 (3.00), 92	4.17 (3.31), 42	0.740	1	0.391
BMI mean (s.d.), *n*	23.59 (2.71), 151	22.70 (4.35), 72	3.427	1	0.065
UKU, mean (s.d.), *n*					
Month 1	1.88 (2.08), 146	1.83 (2.44), 71	0.165	120	0.869
Month 6	0.89 (1.40), 148	0.61 (1.30), 72	1.433	150	0.153
Month 12	0.59 (1.34), 124	0.65 (1.53), 57	−0.234	96	0.816
Month 24	0.35 (0.86), 94	0.58 (1.31), 44	−1.059	62	0.294
Definitive compliance, % (*n*)*					
Month 1	70% (100)	85% (60)	5.024	1	0.025
Month 6	66% (88)	83% (52)	5.930	1	0.015
Month 12	72% (78)	88% (44)	4.863	1	0.028
Month 24	65% (51)	89% (32)	6.873	1	0.009

BMI Body mass index

* Compliance was summarized on a scale of 2 items; definitive and uncertain

response to antipsychotic treatment confirms no differences in response to risperidone [67]. Adherence to treatment was significantly better in women throughout the study. This is an unexpected finding, as both genders presented similar symptoms and functioning at the follow-up visit. Nevertheless, this finding has been previously reported [16].

Strengths and limitations of the study design

This paper should be interpreted in light of its methodology. The study has significant strengths, including the offer of participation to all consecutively detected FEP cases (both in/outpatients) in a wide and representative geographical catchment area, covering the principal rural, urban, and metropolitan regions of Spain. Additionally, the homogeneity of diagnosis and antipsychotic treatment in the present study is an important methodological strength that avoids confounders arising from the inclusion of different diagnoses (e.g., affective psychoses) and treatments (e.g., differential protective influence of estrogens to specific antipsychotics and clinical response). However, relevant limitations should be also considered. Firstly, we acknowledge that constituting a clinical trial, the principal

aim of the study might interfere in the representativeness of the sample recruited, for example including patients willing to start the antipsychotic treatment. Therefore, it might be impute that it constitutes a selected sample in which an epidemiological variable like gender cannot be thoroughly analyzed. However, the recruitment of patients was carried out in a naturalistic way, and the ratio 3:1 obtained in our sample is similar to the one reported in other epidemiological studies [16, 39, 63]. Secondly, it should be considered the clinical profile of the patients included, non-substance-dependent FEP patients. Persistent substance use, being more prevalent in males with a FEP, results in a reduction in illness insight, increases medication and treatment non-adherence and service disengagements, and results in a greater number of inpatient admissions and poorer longer-term outcome in FEP [16, 39]. Under our judgement, this factor may be probably—among others—at the basis of our results indicating a lack of differences among men and women in the early course and outcome of the illness and indirectly stress the clinical consequences of substance dependence for men. Finally, another limitation is the lack of data on history of substance use, a factor that has been shown to be relevant when considering gender differences [16, 39].

Conclusion

The results of the present study indicate that, although significant gender differences may be observed in the phenotypic expression of schizophrenia at the first episode, clinical differences are attenuated during the early course. This may be a result, among other factors, to the exclusion of substance-dependent patients, more frequently being men with a poorer prognosis than non-dependent patients. Our results indicate that gender alone may not constitute a specific prognostic factor during the early course of schizophrenia and indirectly stress the clinical consequences of substance dependence for men and the relevance of appropriated therapeutic interventions. Further research should consider the possibility of identifying specific prognostic factors associated with men and women independently to detect patients at risk of an unfavorable outcome.

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