Schizophrenia Research and Treatment

Psychosis and Gender

Guest Editors: Susana Ochoa, Judith Usall, Jesús Cobo, Javier Labad, and Jayashri Kulkarni

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Editorial Board

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Editorial

Psychosis and Gender

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Psychosis, mainly schizophrenia, is a heterogeneous disorder with a great variability in its clinical presentation. This heterogeneity may be explained by the role of gender; thus a gender-based approach could help us to better define the disease. Gender differences in social functioning, age of onset, course of the illness, and other domains have been described by several authors, showing better functioning and improved outcome in women with schizophrenia. Moreover, several treatments are gender sensitive, with differences in treatment response depending upon gender. The estrogen hypothesis is one of the most interesting explanations for this gender difference. Estrogens could be useful for understanding the pathophysiology of the illness or tailoring specific gender-related treatments.

The aim of this special issue is to address specific aspects related to gender in people with psychosis. The design of more effective preventive and intervention actions in the future may benefit from a better understanding of how gender issues affect subjects with schizophrenia.

Our special issue in the Schizophrenia Research and Treatment journal brings different perspectives in this new area. This issue includes seven paper: three revisions and four original research articles. Introducing the issue, two of them are focused on assessing gender differences in biological aspects of the illness such as brain activation mediated by progesterone in emotion processing and assessing gender difference in facial, prosodic, and social context emotional recognition. The following papers deal with gender differences in remission, recovery, or course of the illness in people with schizophrenia and schizoaffective disorder or describe gender differences in patterns of care in schizophrenia and other psychosis. One paper presents a panoramic view of the gender differences in psychosis. Another paper, which is related to more specific gender-related areas, addresses the role of estrogens in the treatment of symptoms in schizophrenia. One additional paper provides different insights in specific legal aspects and interventions to prevent child custody loss in mothers with schizophrenia.

One of the studies aims to assess whether there are gender differences in cerebral function and progesterone levels during an emotion processing task in people with schizophrenia and a control group of healthy subjects. Women with schizophrenia showed a different pattern of brain activity during the processing of positive emotions, when compared to women without any mental disorder. In contrast, no differences were found in the processing of positive emotions between men with or without schizophrenia. On the other hand, the relationship between progesterone levels and patterns of brain activation during the emotion processing task between patients and controls differs in men, but not women. The main finding of this study is that progesterone levels affect differently men and women with schizophrenia in the processing of emotions.

One more study explores potential gender differences in facial, prosodic, and social context emotional recognition in a sample of people with schizophrenia and controls. People with schizophrenia showed lower accuracy and longer response times than controls, but no significant sex differences were observed in either facial or prosody recognition. Females showed higher empathy than males in social context

emotions regarding happiness. Women reported higher identification with fear films than men. This paper reported emotional recognition deficits in people with schizophrenia, independent of gender.

One additional paper assesses gender differences in remission and recovery in people with schizophrenia and schizoaffective disorder. No gender differences were found related to the number of hospitalizations. Men showed, when compared to women, longer time since last hospitalization. Regarding gender differences in diagnoses, a greater proportion of women suffered from schizoaffective disorder. Women also showed improved recovery in terms of clinical, functional, and subjective wellbeing. The clinical implications of these results are related to treatment and a better course of the illness in female patients.

One more tests whether there are gender differences in prevalence and service use in people with schizophrenia and other psychoses. Increased prevalences of schizophrenia, schizophreniform disorder, substance-induced psychosis, and psychotic disorder NOS were found in men whereas women had increased prevalences of schizoaffective and delusional disorder. Women with schizophrenia (specially paranoid and residual) and brief psychosis required fewer hospital admissions than men. On the other hand, the number of hospitalized days was greater in men with disorganized, residual, and undifferentiated subtype of schizophrenia and delusional disorder. These results show a different pattern of service use related to gender in schizophrenia and other psychoses.

Another paper is an extensive revision of gender differences in several domains of people with schizophrenia and first-episode psychosis. The topics discussed in the review are prevalence and incidence, age of onset, symptoms, premorbid, social, and cognitive functioning, substance abuse, course of illness, physical health and metabolic complications, and familial risk and obstetric complications. In summary, the revision concludes that women presented lower incidence of the illness, better prognosis and social functioning, and a greater response to treatment. However, several issues remain uncertain, and future research studies are needed to clarify these controversial issues.

In one paper there is a revision about the role of estrogens and other hormones in the pathophysiology and treatment of people with schizophrenia. The paper revises the epidemiological, life cycle, preclinical, and clinical findings regarding the role of estrogens in schizophrenia. The authors describe the estrogen protection hypothesis and the hypothesis of hypoestrogenism related to clinical and epidemiological results of several studies in women and men. Estrogens have been found to be effective as a coadjuvant treatment in people with schizophrenia.

Also one of the papers revises the interventions to prevent child custody loss in mother with schizophrenia. Results of studies related to this topic are presented from an elaborate search. Discussed topics include the prevalence of custody loss in mother with psychosis, the impact of diagnosis in custody loss, the impact of custody loss in mothers, the postpartum vulnerability to custody loss, and several recommendations for mothers and care providers for preventing custody loss. Most mothers with schizophrenia lose custody of their children only for having a schizophrenia diagnosis, especially in the postpartum period. Several interventions addressed to administrative policies, service providers, and mothers are needed in order to ensure the best situation for the children in their own family.

As a conclusion, this special issue approaches gender differences and gender-related aspects in several domains in schizophrenia and other psychoses. The estrogen hypothesis is present in several papers as one of the possible explanations to these differences. However, some domains have yielded inconclusive data. The aim of this issue is to detect the most controversial areas that need to be clarified in further research.

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Review Article

Gender Differences in Schizophrenia and First-Episode Psychosis: A Comprehensive Literature Review

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Recent studies have begun to look at gender differences in schizophrenia and first-episode psychosis in an attempt to explain the heterogeneity of the illness. However, a number of uncertainties remain. This paper tries to summarize the most important findings in gender differences in schizophrenia and first-psychosis episodes. Several studies indicate that the incidence of schizophrenia is higher in men. Most of the studies found the age of onset to be earlier in men than in women. Findings on symptoms are less conclusive, with some authors suggesting that men suffer more negative symptoms while women have more affective symptoms. Premorbid functioning and social functioning seem to be better in females than males. However, cognitive functioning remains an issue, with lack of consensus on differences in neuropsychological profile between women and men. Substance abuse is more common in men than women with schizophrenia and first-episode psychosis. In terms of the disease course, women have better remission and lower relapse rates. Lastly, there is no evidence of specific gender differences in familial risk and obstetric complications. Overall, gender differences have been found in a number of variables, and further study in this area could help provide useful information with a view to improving our care of these patients.

1. Introduction

Schizophrenia and first-episode psychosis are disorders with considerable heterogeneity in several of its basic features. There is great variability in clinical presentation, disease course, and response to both pharmacological and psychosocial treatment. Some aspects of this heterogeneity may be gender related and, given the reliability, stability, and validity of its definition, study of the gender variable may help explain the differences. Gender differences have been studied extensively in recent decades and although there are definite findings, much uncertainty remains about the extent of the differences. This paper will try to summarize the most relevant research done around the world on gender differences in schizophrenia and first-psychosis episodes. The topics discussed in this paper will be prevalence and incidence, age of onset, symptoms, premorbid, social and cognitive functioning, substance abuse, course of illness, physical health and metabolic complications, and familial risk and obstetric complications. The paper will try to assess gender differences studies on each of these topics in people with schizophrenia and in first-episode psychosis. A greater understanding of the gender differences presents in schizophrenia and first-episode psychosis can help us design more effective preventive and intervention actions.

2. Prevalence and Incidence of Schizophrenia

The existence of gender differences in the incidence of schizophrenia has been subject to debate. Traditionally, it was accepted that the incidence and prevalence of schizophrenia was the same in men and women [1]; however, recent studies

suggest gender differences in the incidence of the illness. Lewine et al. [2] were the first to note that by using more restrictive criteria for the diagnosis of schizophrenia, the number of women excluded from the definition is greater than men. Castle et al. [3] applied a different set of diagnostic criteria to an incidence sample of patients with a wide range of nonaffective psychosis presentations and found that the effect of different diagnostic criteria on the gender ratio is profound. For example, the Feighner restrictive criteria found a ratio of female-men 0.41 : 1 and the ICD the ratio female-men is 0.92 : 1. Using standard diagnostic criteria in an incidence population study, a meta-analysis by Aleman et al. [4] confirmed that the men had a higher incidence (ratio 1.42). However, the recent studies of prevalence of schizophrenia in general population did not find gender differences [5, 6]. One possible explanation for the disparity between incidence and prevalence could be related to compliance with treatment and higher rates of suicide completion in men than in women [7]. Another possible explanation could be related to the design of the studies, for example, one centered more in epidemiological resources and the incidence was centered in clinical data.

No gender differences have been found in prevalence of schizophrenia in epidemiological studies; however, it seems that more new cases of schizophrenia have been detected in men.

3. Age of Onset

Differences in age of onset are the most replicated finding in studies into gender differences in schizophrenia. [8–10] Men usually develop the illness at age 18–25, while in women, the mean age of onset is 25–35. Furthermore, the onset distribution curves for males and females are not isomorphic. Women seem to have two peaks in the age of onset of disease: the first after menarche and the second once they are over 40 [3, 11]. However, in 1998, Castle et al. found that early-onset age distribution is similar between men and women [12]. The major prevalence of women once they are over 40 years could be explained by the reduction of estrogens after menopause according the estrogenic hypothesis of schizophrenia [13]. However, a number of studies found no gender difference in the age of onset [14–16].

Some authors have suggested that differences in age of onset appear to depend on the presence or absence of family history, with no differences being found between men and women if they had a family history [17, 18].

Besides, the findings of early age of onset in men have been replicated in first-episode psychosis [19, 20], indicating a consistency with the results found in schizophrenia.

Gender differences have been found in most of the studies done in age of onset in schizophrenia and first-episode psychosis, showing a different profile of onset of illness between women and men.

4. Symptoms

The study of gender differences in symptoms of schizophrenia has been one of the most explored issues. However, the results in this area are inconclusive.

Several studies have found gender differences in negative symptoms, showing that in males, they were more severe [21–23]. Moreover, in a sample of 276 people with schizophrenia, Galderisi et al. [10] found that men scored higher in disorganization and negative symptoms. In a large sample of patients with psychosis, Morgan et al. [24] identified a higher prevalence of depressive symptoms and lower prevalence of negative symptoms in women. Higher prevalence of depressive and anxiety symptoms in women had been found in previous studies [3, 25].

Nevertheless, most of the studies [15, 26, 27] found no significant clinical differences in symptoms, [19, 26, 27] which is in line with our team's findings [28].

Results from the assessment of symptoms in first-episode psychosis are also inconclusive. In a group of patients with schizophrenia admitted for the first time, Szymanski et al. [28] found that women presented more anxiety, illogical thinking, inappropriate affect, and bizarre behavior than men. Cotton et al. [29] found that women presented higher levels of affective symptoms than men. However, no gender differences were found in the study by Barajas et al. [30].

In relation to diagnosis, Andia et al. [31] found a higher percentage of women diagnosed with paranoid schizophrenia.

There is not a clear influence of gender in the symptoms presented in people with schizophrenia and first-episode psychosis. However, the studies that found gender differences describe higher presence of negative and disorganization symptoms in men and higher prevalence of affective symptoms in women.

5. Premorbid Functioning

Better premorbid functioning has been associated with a better prognosis for the illness. Gender differences here could, therefore, have a bearing on how the schizophrenia evolves. In general, most studies have found gender differences in premorbid functioning, this being worse in men than in women [21, 24, 32–34]. McGlashan and Bardenstein [32] found that women had better premorbid social functioning and marital adjustment. However, in a sample of 113 patients, females and those with a diagnosis of schizoaffective disorder had better premorbid adjustment in the academic domain, but not in the social domain [34].

These results have been replicated in a sample of first-episode psychosis [35, 36]. Little is known about gender differences in the psychosis prodromes. In adolescents at ultra-high-risk (UHR) of imminent onset of psychosis, being female was a significant predictor of conversion to affective psychosis two years after ascertainment [36] and young male adults with a diagnosis of schizotypal disorder had a fourfold risk of conversion to schizophrenia one-year after enrolment when compared to females [36].

In a study by Rachel Willhite with sixty-eight ultra-high-risk patients in California (USA), the authors investigated gender differences in symptoms, functioning, and social support. There were no gender differences in demographic variables, symptoms, or functioning at baseline. Males were found to have significantly higher levels of negative symptoms and

marginally lower levels of functioning and females reported higher levels of social support at baseline. Differences in negative symptoms were found to mediate differences in functioning between male and female patients. This study suggests that gender-based differences in symptom presentation and functional outcome may predate conversion to psychosis [37].

Also interesting is the association found between worse premorbid adjustment, insidious onset, and negative symptoms [33, 38]. Thus, one explanation for the worse premorbid functioning in men could be the earlier age of onset.

Most of the literature that assesses premorbid functioning found that women have higher levels of premorbid adjustment and reported higher levels of social support than men.

6. Social Functioning

In general, studies that have examined gender differences in social functioning have found better performance in women. Chaves et al. [38] found that women were better adapted and presented less disability than men. In a three-year follow-up study of 86 patients who had a first episode of schizophrenia, using the DAS scale, Vázquez-Barquero et al. [39] found that men had a worse prognosis. A previous study by our group of 239 patients with schizophrenia living in the community also found that men scored higher in disability (measured with the DAS scale) [40, 41]. Vila-Rodriguez et al. [42] replicated these results, finding that women scored higher in social functioning assessed by LSP. Recently, following a 20-year longitudinal study, Grossman et al. [43] found that women had better global functioning over the course of the illness.

However, after assessing the occupation rate and several psychosocial functioning indices (PSP, PSRS, and UPSA-B) in patients with schizophrenia, Galderisi et al. [10] found no gender differences in social outcome. Additionally, in a long-term study (15 years), Bottlender et al. [44] failed to detect gender differences in social disability in patients with schizophrenia, schizoaffective, and affective disorders through the DAS.

In first-episode psychosis, the results obtained by Cotton et al. [29] show that women had higher levels of functioning (assessed by GAF, unemployment index and living with family).

In relation to stressful life events, several studies have found that females need more exposure to stressful life events than males to trigger a psychotic disorder [45, 46]. It seems that women with schizophrenia presented higher resilience than men to cope with stress situations and women need higher risk factors in order to develop a psychosis than men do.

Regarding the needs of patients with schizophrenia, men presented more basic (accommodation, food, daily activities) and functional needs (education, money, personal care), while women scored higher in the prevalence of service needs (information about the illness, benefits, transport) [47]. This finding indicates that women perform better in basic and functional domains than men, and men should be trained in order to acquire these functional skills.

In relation to fertility, some reports suggest reduced procreation among men with schizophrenia, but the cause is unknown. Male cases were significantly more likely than female cases to be single and childless [48]. In contrast, the Indo-US Project on Schizophrenia Genetics detected that a reproductive deficit observed among US males was not observed among the Indian men. Conjugal status was a significant covariate for reproduction in both samples. The reproductive deficit may be due to difficulties in establishing long-term conjugal relationships among the US men and not in the Indian sample. According to the authors, the differences may also reflect underlying cultural variations related to marital practices [49].

Women with schizophrenia and first-episode psychosis performed better in social functioning according to objective assessments (fertility, being married) and social scales assessment. Moreover, women presented less basic and functional needs and need more exposure to life events in order to develop a psychosis illness.

7. Cognitive Functioning

Gender differences in cognitive domains have been another controversial issue. A number of authors have demonstrated that men score worse in attention, language, and executive function than women [50–53]. Vaskinn et al. [54] suggest better functioning in neuropsychological performance in women than men, except in the category of attention. Bozikas et al. [55] found that women performed better than men in verbal learning and memory.

Bilder et al. [56] found that males performed better in the information subtest of the WAIS, while women performed better in the Digit Symbol subtest. Other studies have shown cognitive functioning to be worse in women with schizophrenia than men [57, 58].

In the study by Karilampi et al. [59], better cognitive function was predicted by higher psychosocial functioning levels in males but by lower symptom levels in females, suggesting a slight difference between women and men in the domains relating to cognitive function, which need to be taken into account.

Other studies, however, found no gender difference in the assessment of cognitive domains [60–62].

Gender differences in cognitive function in people with schizophrenia remained controversial. The studies that found gender differences indicate higher levels of functioning in women especially in the language, executive, and memory domains.

8. Substance Abuse

Substance abuse presented a higher prevalence in people with schizophrenia and first-episode psychosis [63–65]. The rates indicated that men consume more cannabis than women [64, 66]. In the case of first-episode psychosis, men had a higher prevalence of cannabis use than women [29, 64, 66, 67]. Moreover, Rodríguez-Jiménez et al. [68] found that men have higher comorbidity of cocaine and hallucinogen use and

of cannabis use than women. In the case of alcohol abuse, the data show that males present higher levels of consumption than women [10].

In addition, Arendt et al. [69] demonstrate that the risk of developing psychosis is higher in men who consume cannabis than women. The study assessed a total of 535 people with a cannabis-induced psychosis over three years, and the rates for developing schizophrenia were 47.6% in males versus 29.8% in women.

Men presented higher prevalence of substance abuse and higher levels of comorbidity than women. Moreover, it seems that substance abuse could be a risk factor for developing psychosis in males.

9. The Course of the Illness

The disease course for schizophrenia has been reported as following different patterns in males and females. Uggerby et al. [70] studied the prevalence of institutionalized and noninstitutionalized people with schizophrenia in Denmark in a sample of 22,395 people. The results showed that being male was one of the predictors of institutionalization. Gender has also been identified as one of the factors influencing clinical remission, with relapse rates being higher in men and remission rates higher in women [71].

With regard to hospitalizations, Usall et al. [40] found that the number of previous hospitalizations was similar for both men and women. However, women required less time in hospital than men at baseline. After a three-year followup of these patients, the results indicated that women had fewer admissions than men and the length of stay was shorter (men, 40 days versus women, 5.8) [72]. In the SOHO Study, however, Haro et al. [71] found that women presented a higher risk of hospitalization than men.

The efficacy and tolerance of the different antipsychotic treatments may be gender-sensitive. Most studies found that women respond better to typical antipsychotics [28, 73] and olanzapine [74, 75] The results for clozapine are more controversial [75–77]; as for risperidone, the few studies in this direction have not found differences [78]. Premenopausal women had a significantly better treatment response to olanzapine than postmenopausal women, regardless of chronicity and treatment [74].

No significant gender differences were found, either in treatment response or neurological side effects, in patients treated with risperidone [78]. There were, however, some concerns about parkinsonian symptoms with atypical neuroleptics being more frequent in women [79].

The results found regarding course of illness are controversial; however, it seems that women presented higher rates of remission, less days of hospitalization, and better response to typical antipsychotics than men.

10. Physical Health and Metabolic Complications

There have also been concerns about gender differences in relation to physical health and metabolic complications in psychosis.

The metabolic impact of antipsychotic treatments in women (and men) is significant. Atypical and older antipsychotics are very useful drugs, but they can be associated with hyperprolactinemia and related disorders. These endocrine aspects are particularly significant. Women have greater metabolic and endocrine-induced antipsychotic side effects. In fact, every woman exposed to atypical antipsychotics is at risk of developing hyperprolactinemia-related problems, particularly young women [80–82]. Previous studies have consistently reported a higher prevalence of hyperprolactinemia in women receiving antipsychotics, and cross-sectional studies in the USA and UK have estimated hyperprolactinemia prevalence rates of up to 42% in men and 75% in women with schizophrenia who were receiving conventional antipsychotics or risperidone [83, 84]. It is known that hyperprolactinemia is associated with a number of physical health problems in males and females, particularly endocrine and immunological system changes, as well as growth hormone alterations. For example, in one study which included 150 women, 14% were observed to develop galactorrhea within 75 days of initiating treatment with conventional antipsychotics [85]. Hyperprolactinemia affects long-term health in women. Menstrual irregularities have been found in up to 48% of women receiving antipsychotic treatment [80, 82]. Reduced bone mineral density has been demonstrated in 57% of men and 32% of women treated with prolactin-raising antipsychotics for over 10 years [86]. One case-control study investigated whether potential treatment-emergent decreases in bone mineral density could confer an increased risk of hip fractures in patients with a history of schizophrenia [87].

Although sexual dysfunction appears to be inherent to the illness in patients with schizophrenia, it is also frequently reported during antipsychotic treatment, with interesting gender differences. More than 50% of males and 30% of females have been shown to experience sexual dysfunction during conventional antipsychotic treatment. This specific secondary effect may be relevant to adherence in some patients [88, 89].

A Spanish national cross-sectional study in 733 patients diagnosed with schizophrenia on treatment with second generation antipsychotics and admitted to short-stay hospital units detected different cardiovascular risk factors in women than in men. Men were treated for hypertension (OR = 25.34, $P < 0.03$) and women for diabetes (OR = 0.02, $P < 0.03$) [90].

Metabolic syndrome is associated with the development of coronary heart disease and diabetes mellitus. A higher presence of metabolic syndrome has been detected in females. In a Turkish sample, Boke et al. found that 61.4% of females, but only 22.4% of males, had metabolic syndrome [91].

The prevalence of metabolic syndrome in 1460 US patients from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed important gender differences. In females, depending on the criteria used, it was 51.6% (NCEP) or 54.2% (AHA), compared to 36.0% (NCEP; $P = 0.0002$) or 36.6% (AHA; $P = 0.0003$) for males. 73.4% of all females (including nonfasting subjects) met the waist

circumference criterion compared to 36.6% of males. In a logistic regression model with age, race, and ethnicity as covariates, CATIE males were 138% more likely to have metabolic syndrome than a general population-matched sample (NHANES), and CATIE females, 251% more likely than their general-population counterparts. Even when controlling for differences in body mass index, CATIE males were still 85% more likely to have MS than the NHANES male sample and CATIE females, 137% more likely to have MS than females in NHANES [92].

In contrast, in a study devoted to detect coronary heart disease risk and prevalence of metabolic syndrome in 268 patients with schizoaffective disorder receiving antipsychotics, the authors detected no gender differences, but coronary heart disease risk and prevalence of metabolic syndrome were higher among patients with schizoaffective disorder. The prevalence of metabolic syndrome was associated with age and severity of disease, but not with gender [93].

Individuals with nonaffective psychosis appear to have an increased prevalence of abnormal glucose tolerance prior to antipsychotic treatment, but this predisposition also appears not to be gender sensitive [94]. Similarly, a large community study in Ontario (Canada) with 1123 schizophrenic outpatients failed to detect gender differences in dysglycemia [95].

Regarding metabolic and endocrine-induced antipsychotic side effect, women presented higher prevalence of symptoms. Hyperprolactinemia and diabetes are more present in women, while hypertension is more prevalent in men with schizophrenia.

11. Familial Risk and Obstetric Complications

Various studies have found a higher risk of schizophrenia in relatives of women than in relatives of men [96–98].

However, Kendler and Walsh found no gender differences in the familial risk of schizophrenia [99]. These authors studied familial risk in a sample of 354 first-degree relatives of patients with schizophrenia from the Roscommon Family Study who were interviewed personally. It also explored the possible association between age at onset, gender, and familial risk. The results of Pulver and Liang [97] showed that relatives of men with schizophrenia who have an age of onset under 17 have a significantly higher risk of schizophrenia. However, the authors also found an association between age at onset of schizophrenia and familial risk in women. Other studies have found no interaction between age of onset, gender, and familial risk [100].

Results on whether gender differences exist in the incidence of obstetric complications in patients who will develop schizophrenia have been inconsistent. Some studies have found more obstetric complications in men [101, 102]. However, other studies have found no gender differences [103, 104] and others still have found more obstetric complications in women [105]. The influence of gender in the prevalence of obstetric complications, therefore, remains unclear.

Women need higher presence of familial risk than men in order to develop the illness. However, there are not clear results about the influence of gender in the number of obstetric complications.

12. Conclusions

In conclusion, although the extent of gender differences in schizophrenia and first-episode psychosis is a controversial issue, this paper discusses some of the most replicated gender differences in schizophrenia and first-episode psychosis. Several studies indicate that schizophrenia and first-episode psychosis are less incident in women than in men but, in the case of women, it seems that the prognosis of the illness, the social functioning and the response to treatment is better. According to most of the studies revised, one possible explanation of this better adjustment could be that women presented a higher age of onset than men, which allows them to adjust better to the requirements of the community. The estrogen hypothesis tries to explain why women have a later age of the onset. According to this hypothesis some therapeutic treatments associated with estrogens could be useful for improving symptoms and cognition, especially in women. Moreover, the review shows us that women need more risk factors in order to develop schizophrenia than men (more familial risk, more presence of life events). This findings are in agreement with the neurodevelopment hypothesis, where men seem to present a more deteriorated profile than women before the onset of the illness.

One of the limitations of this paper is that, given the breadth of the subject, some issues have not been commented. Social influence of the context and the fact that most of the studies have been done in developed countries is a clear limitation that should be taken into account in the future.

From the reviewed literature, we conclude that women with schizophrenia perform better in several areas than men; however, future research should be addressed to study gender differences to clarify the remaining controversial issues. Novel sex-specific treatments could be developed to better meet the needs of people with schizophrenia and first-episode psychosis.

References

[1] R. J. Wyatt, R. C. Alexander, M. F. Egan, and D. G. Kirch, "Schizophrenia, just the facts. What do we know, how well do we know it?" *Schizophrenia Research*, vol. 1, no. 1, pp. 3–18, 1988.

[2] R. Lewine, D. Burbach, and H. Y. Meltzer, "Effect of diagnostic criteria on the ratio of male to female schizophrenic patients," *American Journal of Psychiatry*, vol. 141, no. 1, pp. 84–87, 1984.

[3] D. J. Castle, S. Wessely, and R. M. Murray, "Sex and schizophrenia: effects of diagnostic stringency, and associations with premorbid variables," *British Journal of Psychiatry*, vol. 162, pp. 658–664, 1993.

[4] A. Aleman, R. S. Kahn, and J. P. Selten, "Sex differences in the risk of schizophrenia: evidence from meta-analysis," *Archives of General Psychiatry*, vol. 60, no. 6, pp. 565–571, 2003.

[5] J. Perälä, J. Suvisaari, S. I. Saarni et al., "Lifetime prevalence of psychotic and bipolar I disorders in a general population," *Archives of General Psychiatry*, vol. 64, no. 1, pp. 19–28, 2007.

[6] J. McGrath, S. Saha, D. Chant, and J. Welham, "Schizophrenia: a concise overview of incidence, prevalence, and mortality," *Epidemiologic Reviews*, vol. 30, no. 1, pp. 67–76, 2008.

[7] M. A. Test, S. Senn Burke, and L. S. Wallisch, "Gender differences of young adults with schizophrenic disorders in community care," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 331–334, 1990.

[8] J. M. Goldstein, M. T. Tsuang, and S. V. Faraone, "Gender and schizophrenia: implications for understanding the heterogeneity of the illness," *Psychiatry Research*, vol. 28, no. 3, pp. 243–253, 1989.

[9] O. Gureje, "Gender and schizophrenia: age at onset and sociodemographic attributes," *Acta Psychiatrica Scandinavica*, vol. 83, no. 5, pp. 402–405, 1991.

[10] S. Galderisi, P. Bucci, A. Uçok, and J. Peuskens, "No gender differences in social outcome in patients suffering from schizophrenia," *European Psychiatry*. In press.

[11] S. Ochoa, J. Usall, V. Villalta-Gil et al., "Influence of age at onset on social functioning in outpatients with schizophrenia," *European Journal of Psychiatry*, vol. 20, no. 3, pp. 157–163, 2006.

[12] D. Castle, P. Sham, and R. Murray, "Differences in distribution of ages of onset in males and females with schizophrenia," *Schizophrenia Research*, vol. 33, no. 3, pp. 179–183, 1998.

[13] A. Riecher-Rossler, H. Hafner, M. Stumbaum, K. Maurer, and R. Schmidt, "Can estradiol modulate schizophrenic symptomatology?" *Schizophrenia Bulletin*, vol. 20, no. 1, pp. 203–214, 1994.

[14] Z. Folnegovic and V. Folnegovic-Smalc, "Schizophrenia in Croatia: age of onset differences between males and females," *Schizophrenia Research*, vol. 14, no. 1, pp. 83–91, 1994.

[15] D. Addington, J. Addington, and S. Patten, "Gender and affect in schizophrenia," *Canadian Journal of Psychiatry*, vol. 41, no. 5, pp. 265–268, 1996.

[16] H. Naqvi, M. M. Kahn, and A. Faizi, "Gender differences in age at onset of schizophrenia," *Journal of the College of Physicians and Surgeons Pakistan*, vol. 15, no. 6, pp. 345–348, 2005.

[17] M. Albus, J. Scherer, S. Hueber et al., "The impact of familial loading on gender differences in age at onset of schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 89, no. 2, pp. 132–134, 1994.

[18] H. Häfner, K. Maurer, W. Löffler et al., "The ABC schizophrenia study: a preliminary overview of the results," *Social Psychiatry and Psychiatric Epidemiology*, vol. 33, no. 8, pp. 380–386, 1998.

[19] T. K. Larsen, T. H. McGlashan, and L. C. Moe, "First-episode schizophrenia—I. Early course parameters," *Schizophrenia Bulletin*, vol. 22, no. 2, pp. 241–256, 1996.

[20] H. Häfner, W. An Der Heiden, S. Behrens et al., "Causes and consequences of the gender difference in age at onset of schizophrenia," *Schizophrenia Bulletin*, vol. 24, no. 1, pp. 99–113, 1998.

[21] D. L. Shtasel, R. E. Gur, F. Gallacher, C. heimberg, and R. C. Gur, "Gender differences in the clinical expression of schizophrenia," *Schizophrenia Research*, vol. 7, no. 3, pp. 225–231, 1992.

[22] P. E. Cowell, D. J. Kostianovsky, R. C. Gur, B. I. Turetsky, and R. E. Gur, "Sex differences in neuroanatomical and clinical correlations in schizophrenia," *American Journal of Psychiatry*, vol. 153, no. 6, pp. 799–805, 1996.

[23] A. Riecher-Rössler and H. Häfner, "Gender aspects in schizophrenia: bridging the border between social and biological psychiatry," *Acta Psychiatrica Scandinavica*, vol. 102, no. 407, pp. 58–62, 2000.

[24] V. A. Morgan, D. J. Castle, and A. V. Jablensky, "Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders," *Australian and New Zealand Journal of Psychiatry*, vol. 42, no. 1, pp. 74–82, 2008.

[25] E. Walker, B. A. Bettes, E. L. Kain, and P. Harvey, "Relationship of gender and marital status with symptomatology in psychotic patients," *Journal of Abnormal Psychology*, vol. 94, no. 1, pp. 42–50, 1985.

[26] E. Lindstrom and L. Von Knorring, "Symptoms in schizophrenic syndromes in relation to age, sex, duration of illness and number of previous hospitalizations," *Acta Psychiatrica Scandinavica*, vol. 89, no. 4, pp. 274–278, 1994.

[27] N. Hayashi, Y. Igarashi, M. Yamashina, and K. Suda, "Is there a gender difference in a factorial structure of the positive and negative syndrome scale? A test by structural equation modeling," *Psychopathology*, vol. 35, no. 1, pp. 28–35, 2002.

[28] S. Szymanski, J. A. Lieberman, J. M. Alvir et al., "Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients," *American Journal of Psychiatry*, vol. 152, no. 5, pp. 698–703, 1995.

[29] S. M. Cotton, M. Lambert, B. G. Schimmelmann et al., "Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis," *Schizophrenia Research*, vol. 114, no. 1–3, pp. 17–24, 2009.

[30] A. Barajas, I. Baños, S. Ochoa et al., "Age of onset of a first psychotic episode: are there any clinical differences between men and women?" *Psiquiatria Biologica*, vol. 14, no. 4, pp. 136–141, 2007.

[31] A. M. Andia, S. Zisook, R. K. Heaton et al., "Gender differences in schizophrenia," *Journal of Nervous and Mental Disease*, vol. 183, no. 8, pp. 522–528, 1995.

[32] T. H. McGlashan and K. K. Bardenstein, "Gender differences in affective, schizoaffective, and schizophrenic disorders," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 319–329, 1990.

[33] S. E. Childers and C. M. Harding, "Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 309–318, 1990.

[34] R. M. G. Norman, A. K. Malla, R. Manchanda, and L. Townsend, "Premorbid adjustment in first episode schizophrenia and schizoaffective disorders: a comparison of social and academic domains," *Acta Psychiatrica Scandinavica*, vol. 112, no. 1, pp. 30–39, 2005.

[35] G. P. Amminger, S. Leicester, A. R. Yung et al., "Early-onset of symptoms predicts conversion to non-affective psychosis in ultra-high risk individuals," *Schizophrenia Research*, vol. 84, no. 1, pp. 67–76, 2006.

[36] M. Nordentoft, A. Thorup, L. Petersen et al., "Transition rates from schizotypal disorder to psychotic disorder for first-contact patients included in the OPUS trial. A randomized clinical trial of integrated treatment and standard treatment," *Schizophrenia Research*, vol. 83, no. 1, pp. 29–40, 2006.

[37] R. K. Willhite, T. A. Niendam, C. E. Bearden, J. Zinberg, M. P. O'Brien, and T. D. Cannon, "Gender differences in symptoms, functioning and social support in patients at ultra-high risk for developing a psychotic disorder," *Schizophrenia Research*, vol. 104, no. 1–3, pp. 237–245, 2008.

[38] A. C. Chaves, M. V. Seeman, J. J. Mari, and A. Maluf, "Schizophrenia: impact of positive symptoms on gender social role," *Schizophrenia Research*, vol. 11, no. 1, pp. 41–45, 1993.

[39] J. L. Vázquez-Barquero, M. J. Cuesta, S. H. Castanedo, I. Lastra, A. Herrán, and G. Dunn, "Cantabria first-episode schizophrenia study: three-year follow-up," *British Journal of Psychiatry*, vol. 174, pp. 141–149, 1999.

[40] J. Usall, S. Araya, S. Ochoa, E. Busquets, A. Gost, and M. Márquez, "Gender differences in a sample of schizophrenic outpatients," *Comprehensive Psychiatry*, vol. 42, no. 4, pp. 301–305, 2001.

[41] J. Usall, J. M. Haro, S. Ochoa, M. Márquez, S. Araya, and NEDES Group (Assessment Research Group in schizophrenia), "Influence of gender on social outcome in schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 106, pp. 337–342, 2002.

[42] F. Vila-Rodriguez, S. Ochoa, J. Autonell, J. Usall, and J. M. Haro, "Complex interaction between symptoms, social factors, and gender in social functioning in a community-dwelling sample of schizophrenia," *Psychiatric Quarterly*, vol. 82, no. 4, pp. 261–274, 2011.

[43] L. S. Grossman, M. Harrow, C. Rosen, R. Faull, and G. P. Strauss, "Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery," *Comprehensive Psychiatry*, vol. 49, no. 6, pp. 523–529, 2008.

[44] R. Bottlender, A. Strauß, and H. J. Möller, "Social disability in schizophrenic, schizoaffective and affective disorders 15 years after first admission," *Schizophrenia Research*, vol. 116, no. 1, pp. 9–15, 2010.

[45] D. M. Almeida and R. C. Kessler, "Everyday stressors and gender differences in daily distress," *Journal of Personality and Social Psychology*, vol. 75, no. 3, pp. 670–680, 1997.

[46] I. Myin-Germeys, L. Krabbendam, P. A. E. G. Delespaul, and J. Van Os, "Sex differences in emotional reactivity to daily life stress in psychosis," *Journal of Clinical Psychiatry*, vol. 65, no. 6, pp. 805–809, 2004.

[47] S. Ochoa, J. Usall, J. M. Haro et al., "Estudio comparativo de las necesidades de las personas con esquizofrenia en función del género," *Actas Españolas de Psiquiatría*, vol. 29, no. 3, pp. 165–171, 2001.

[48] P. Thomas, J. Wood, A. Chandra, V. L. Nimgaonkar, and S. N. Deshpande, "Differences among men and women with schizophrenia: a study of US and Indian samples," *Psychiatry Investigation*, vol. 7, no. 1, pp. 9–16, 2010.

[49] T. Bhatia, M. A. Franzos, J. A. Wood, V. L. Nimgaonkar, and S. N. Deshpande, "Gender and procreation among patients with schizophrenia," *Schizophrenia Research*, vol. 68, no. 2-3, pp. 387–394, 2004.

[50] J. M. Goldstein, L. J. Seidman, S. Santangelo, P. H. Knapp, and M. T. Tsuang, "Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions," *Journal of Psychiatric Research*, vol. 28, no. 6, pp. 483–498, 1994.

[51] L. J. Seidman, J. M. Goldstein, J. M. Goodman et al., "Sex differences in olfactory identification and Wisconsin card sorting performance in schizophrenia: relationship to attention and verbal ability," *Biological Psychiatry*, vol. 42, no. 2, pp. 104–115, 1997.

[52] J. M. Goldstein, L. J. Seidman, J. M. Goodman et al., "Are there sex differences in neuropsychological functions among patients with schizophrenia?" *American Journal of Psychiatry*, vol. 155, no. 10, pp. 1358–1364, 1998.

[53] A. L. Hoff, M. Wieneke, W. O. Faustman et al., "Sex differences in neuropsychological functioning of first-episode and chronically III schizophrenic patients," *American Journal of Psychiatry*, vol. 155, no. 10, pp. 1437–1439, 1998.

[54] A. Vaskinn, K. Sundet, C. Simonsen, T. Hellvin, I. Melle, and O. A. Andreassen, "Sex differences in neuropsychological performance and social functioning in schizophrenia and bipolar disorder," *Neuropsychology*, vol. 25, no. 4, pp. 499–510, 2011.

[55] V. P. Bozikas, M. H. Kosmidis, A. Peltekis et al., "Sex differences in neuropsychological functioning among schizophrenia patients," *Australian and New Zealand Journal of Psychiatry*, vol. 44, no. 4, pp. 333–341, 2010.

[56] R. M. Bilder, L. Lipschutz-Broch, G. Reiter, S. H. Geisler, D. I. Mayerhoff, and J. A. Lieberman, "Intellectual deficits in first-episode schizophrenia: evidence for progressive deterioration," *Schizophrenia Bulletin*, vol. 18, no. 3, pp. 437–448, 1992.

[57] D. Perlick, S. Mattis, P. Stastny, and J. Teresi, "Gender differences in cognition in schizophrenia," *Schizophrenia Research*, vol. 8, no. 1, pp. 69–73, 1992.

[58] R. R. J. Lewine, E. F. Walker, R. Shurett, J. Caudle, and C. Haden, "Sex differences in neuropsychological functioning among schizophrenic patients," *American Journal of Psychiatry*, vol. 153, no. 9, pp. 1178–1184, 1996.

[59] U. Karilampi, L. Helldin, and T. Archer, "Cognition and global assessment of functioning in male and female outpatients with schizophrenia spectrum disorders," *Journal of Nervous and Mental Disease*, vol. 199, no. 7, pp. 445–448, 2011.

[60] T. E. Goldberg, J. M. Gold, E. F. Torrey, and D. R. Weinberger, "Lack of sex differences in the neuropsychological performance of patients with schizophrenia," *American Journal of Psychiatry*, vol. 152, no. 6, pp. 883–888, 1995.

[61] R. K. R. Salokangas, "Prognostic implications of the sex of schizophrenic patients," *British Journal of Psychiatry*, vol. 142, no. 2, pp. 145–151, 1983.

[62] P. J. Moriarty, D. Lieber, A. Bennett et al., "Gender differences in poor outcome patients with lifelong schizophrenia," *Schizophrenia Bulletin*, vol. 27, no. 1, pp. 103–113, 2001.

[63] D. Wade, S. Harrigan, J. Edwards, P. M. Burgess, G. Whelan, and P. D. McGorry, "Substance misuse in first-episode psychosis: 15-month prospective follow-up study," *British Journal of Psychiatry*, vol. 189, pp. 229–234, 2006.

[64] T. R. E. Barnes, S. H. Mutsatsa, S. B. Hutton, H. C. Watt, and E. M. Joyce, "Comorbid substance use and age at onset of schizophrenia," *British Journal of Psychiatry*, vol. 188, pp. 237–242, 2006.

[65] M. T. Compton, M. E. Kelley, C. E. Ramsay et al., "Association of pre-onset cannabis, alcohol, and tobacco use with age at onset of prodrome and age at onset of psychosis in first-episode patients," *American Journal of Psychiatry*, vol. 166, no. 11, pp. 1251–1257, 2009.

[66] D. J. Foti, R. Kotov, L. T. Guey, and E. J. Bromet, "Cannabis use and the course of schizophrenia: 10-year follow-up after first hospitalization," *American Journal of Psychiatry*, vol. 167, no. 8, pp. 987–993, 2010.

[67] M. Hambrecht and H. Häfner, "Cannabis, vulnerability, and the onset of schizophrenia: an epidemiological perspective," *Australian and New Zealand Journal of Psychiatry*, vol. 34, no. 3, pp. 468–475, 2000.

[68] R. Rodríguez-Jiménez, M. Aragüés, M. A. Jiménez-Arriero et al., "Dual diagnosis in psychiatric inpatients: prevalence and general characteristics," *Investigacion Clinica*, vol. 49, no. 2, pp. 195–205, 2008.

[69] M. Arendt, R. Rosenberg, L. Foldager, G. Perto, and P. Munk-Jørgensen, "Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases," *British Journal of Psychiatry*, vol. 187, pp. 510–515, 2005.

[70] P. Uggerby, R. E. Nielsen, C. U. Correll, and J. Nielsen, "Characteristics and predictors of long-term institutionalization in patients with schizophrenia," *Schizophrenia Research*, vol. 131, no. 1–3, pp. 120–126, 2011.

[71] J. M. Haro, A. Ciudad, J. Alonso et al., "Remission and relapse in the ambulatory treatment of patients with schizophrenia. Outcomes at 3 years," *Actas Espanolas de Psiquiatria*, vol. 36, no. 4, pp. 187–196, 2008.

[72] J. Usall, S. Ochoa, S. Araya, and M. Márquez, "Gender differences and outcome in schizophrenia: a 2-year follow-up study in a large community sample," *European Psychiatry*, vol. 18, no. 6, pp. 282–284, 2003.

[73] M. V. Seeman, "Neuroleptic prescriptions for men and women," *Social Pharmacology*, vol. 3, pp. 219–236, 1989.

[74] J. M. Goldstein, L. S. Cohen, N. J. Horton et al., "Sex differences in clinical response to olanzapine compared with haloperidol," *Psychiatry Research*, vol. 110, no. 1, pp. 27–37, 2002.

[75] J. Usall, D. Suarez, and J. M. Haro, "Gender differences in response to antipsychotic treatment in outpatients with schizophrenia," *Psychiatry Research*, vol. 153, no. 3, pp. 225–231, 2007.

[76] P. J. Perry, D. D. Miller, S. V. Arndt, and R. J. Cadoret, "Clozapine and norclozapine plasma concentrations and clinical response of treatment-refractory schizophrenic patients," *American Journal of Psychiatry*, vol. 148, no. 2, pp. 231–235, 1991.

[77] S. Szymanski, J. Lieberman, S. Pollack et al., "Gender differences in neuroleptic nonresponsive clozapine-treated schizophrenics," *Biological Psychiatry*, vol. 39, no. 4, pp. 249–254, 1996.

[78] A. Labelle, M. Light, and F. Dunbar, "Risperidone treatment of outpatients with schizophrenia: no evidence of sex differences in treatment response," *Canadian Journal of Psychiatry*, vol. 46, no. 6, pp. 534–541, 2001.

[79] P. Seeman, "Atypical neuroleptics: role of multiple receptors, endogenous dopamine, and receptor linkage," *Acta Psychiatrica Scandinavica*, vol. 82, no. 358, pp. 14–20, 1990.

[80] S. M. Dursun, H. J. Wildgust, P. Strickland, G. M. Goodwin, L. Citrome, and M. Lean, "The emerging physical health challenges of antipsychotic associated hyperprolactinaemia in patients with serious mental illness," *Journal of Psychopharmacology*, vol. 22, no. 2, supplement, pp. 3–5, 2008.

[81] P. M. Haddad and A. Wieck, "Antipsychotic-induced hyperprolactinaemia: mechanisms, clinical features and management," *Drugs*, vol. 64, no. 20, pp. 2291–2314, 2004.

[82] V. O'Keane, "Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia," *Journal of Psychopharmacology*, vol. 22, no. 2, pp. 70–75, 2008.

[83] B. J. Kinon, J. A. Gilmore, H. Liu, and U. M. Halbreich, "Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone," *Psychoneuroendocrinology*, vol. 28, no. 2, supplement, pp. 55–68, 2003.

[84] S. M. Smith, V. O'Keane, and R. Murray, "Sexual dysfunction in patients taking conventional antipsychotic medication," *British Journal of Psychiatry*, vol. 181, pp. 49–55, 2002.

[85] K. Windgassen, U. Wesselmann, and H. Schulze Mönking, "Galactorrhea and hyperprolactinemia in schizophrenic patients on neuroleptics: frequency and etiology," *Neuropsychobiology*, vol. 33, no. 3, pp. 142–146, 1996.

[86] A. M. Meaney, S. Smith, O. D. Howes, M. O'Brien, R. M. Murray, and V. O'Keane, "Effects of long-term prolactin-raising antipsychotic medication an bone mineral density in patients with schizophrenia," *British Journal of Psychiatry*, vol. 184, pp. 503–508, 2004.

[87] L. Howard, G. Kirkwood, and M. Leese, "Risk of hip fracture in patients with a history of schizophrenia," *British Journal of Psychiatry*, vol. 190, pp. 129–134, 2007.

[88] A. M. Ghadirian, G. Chouinard, and L. Annable, "Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients," *Journal of Nervous and Mental Disease*, vol. 170, no. 8, pp. 463–467, 1982.

[89] A. L. Montejo, "Prolactin awareness: an essential consideration for physical health in schizophrenia," *European Neuropsychopharmacology*, vol. 18, supplement, pp. S108–S114, 2008.

[90] J. Bobes, C. Arango, P. Aranda, R. Carmena, M. Garcia-Garcia, and J. Rejas, "Cardiovascular and metabolic risk in outpatients with schizophrenia treated with antipsychotics: results of the CLAMORS Study," *Schizophrenia Research*, vol. 90, no. 1-3, pp. 162–173, 2007.

[91] O. Boke, S. Aker, G. Sarisoy, E. B. Saricicek, and A. R. Sahin, "Prevalence of metabolic syndrome among inpatients with schizophrenia," *International Journal of Psychiatry in Medicine*, vol. 38, no. 1, pp. 103–112, 2008.

[92] J. P. McEvoy, J. M. Meyer, D. C. Goff et al., "Prevalence of the metabolic syndrome in patients with schizophrenia: baseline results from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) schizophrenia trial and comparison with national estimates from NHANES III," *Schizophrenia Research*, vol. 80, no. 1, pp. 19–32, 2005.

[93] J. Bobes, C. Arango, P. Aranda, R. Carmena, M. Garcia-Garcia, and J. Rejas, "Cardiovascular and metabolic risk in outpatients with schizoaffective disorder treated with antipsychotics: results from the CLAMORS study," *European Psychiatry*. In press.

[94] E. Fernandez-Egea, M. Bernardo, T. Donner et al., "Metabolic profile of antipsychotic-naive individuals with non-affective psychosis," *The British Journal of Psychiatry*, vol. 194, no. 5, pp. 434–438, 2009.

[95] L. P. Voruganti, Z. Punthakee, R. J. Van Lieshout et al., "Dysglycemia in a community sample of people treated for schizophrenia. The Diabetes in Schizophrenia in Central-south Ontario (DiSCO) study," *Schizophrenia Research*, vol. 96, no. 1–3, pp. 215–222, 2007.

[96] J. M. Goldstein, S. V. Faraone, W. J. Chen, G. S. Tolomiczencko, and M. T. Tsuang, "Sex differences in the familial transmission of schizophrenia," *British Journal of Psychiatry*, vol. 156, pp. 819–826, 1990.

[97] A. E. Pulver and K. Y. Liang, "Estimating effects of proband characteristics on familial risk—II. The association between age at onset and familial risk in the Maryland schizophrenia sample," *Genetic Epidemiology*, vol. 8, no. 5, pp. 339–350, 1991.

[98] W. Maier, D. Lichtermann, J. Minges, R. Heun, and J. Hallmayer, "The impact of gender and age at onset on the familial aggregation of schizophrenia," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 242, no. 5, pp. 279–285, 1993.

[99] K. S. Kendler and D. Walsh, "Gender and schizophrenia: results of an epidemiologically-based family study," *British Journal of Psychiatry*, vol. 167, pp. 184–192, 1995.

[100] J. M. Godstein, S. V. Faraone, W. J. Chen, and M. T. Tsuang, "Gender and the familial risk for schizophrenia. Disentangling confounding factors," *Schizophrenia Research*, vol. 7, no. 2, pp. 135–140, 1992.

[101] E. Cantor-Graae, T. F. McNeil, K. Sjostrom, L. G. Nordstrom, and T. Rosenlund, "Obstetric complications and their relationship to other etiological risk factors in schizophrenia: a controlled study," *Journal of Nervous and Mental Disease*, vol. 182, no. 11, pp. 645–650, 1994.

[102] G. Kirov, P. B. Jones, I. Harvey et al., "Do obstetric complications cause the earlier age at onset in male than female schizophrenics?" *Schizophrenia Research*, vol. 20, no. 1-2, pp. 117–124, 1996.

[103] R. Heun and W. Maier, "The role of obstetric complications in schizophrenia," *Journal of Nervous and Mental Disease*, vol. 181, no. 4, pp. 220–226, 1993.

[104] C. M. Hultman, A. Ohman, S. Cnattingius, I. M. Wieselgren, and L. H. Lindstrom, "Prenatal and neonatal risk factors for schizophrenia," *British Journal of Psychiatry*, vol. 170, pp. 128–133, 1997.

[105] H. Verdoux and M. Bourgeois, "A comparative study of obstetric history in schizophrenics, bipolar patients and normal subjects," *Schizophrenia Research*, vol. 9, no. 1, pp. 67–69, 1993.

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Research Article

Gender Differences in Service Use in a Sample of People with Schizophrenia and Other Psychoses

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Objective. The main objective is to analyze the use of mental health services in a sample of people with schizophrenia and other psychoses according to gender. *Method*. The sample of this observational and retrospective study ($n = 7483$) consisted of all the persons who visited any mental health service of the Parc Sanitari Sant Joan de Déu from 2001 to 2007 with a diagnosis of schizophrenia and other psychoses. The main measures analyzed regarding gender were the frequency of patients for each diagnosis, their risk of being admitted into hospital, and the number and length of hospitalizations for the subsample of inpatient people during the study period. *Results*. Men are more frequent in the total sample (58.1%). For diagnosis of schizoaffective or delusional disorder, women have a higher frequency than men. Women with diagnosis of schizophrenia have a lower risk of being admitted to the hospital (RR = 0.84, 95% CI (0.72, 0.97)). We found a higher risk of longer stays for men with schizophrenia of the disorganized type (RR = 0.49, 95% CI (0.30, 0.81)), undifferentiated (RR = 0.41, 95% CI (0.27, 0.61)), or delusional disorder (RR = 0.65, 95% CI (0.49, 0.87)). *Conclusion*. Gender of patients is a relevant variable in mental health service use by patients with schizophrenia and other psychoses.

1. Introduction

Gender differences in schizophrenia have received widespread empirical support with respect to incidence, age at onset, familial transmission, and neurobiological factors [1, 2]. However, gender differences in the use of mental health services have been less studied, and the results are controversial.

The most studied variables are number of hospitalizations and length of hospital stay. Some researchers have found a higher number of hospitalizations and length of stays in men than women [3–5]. However, Lindamer et al. [6] found that women with schizophrenia have a higher risk of being hospitalized than men.

Specifically, gender differences in the use of services with regard to the different subtypes of schizophrenia have been less explored. Beratis et al. [7] found that the frequency of men was more than three times greater than that of women in the residual and the catatonic subtypes. Tang et al. [8], using the ICD-10 classification system, found differences in the overall subtype distribution between male and female patients, with the paranoid subtype being more common in females; however, they did not explore hospitalizations regarding the subtypes of schizophrenia.

On the other hand, Mimica et al. [9] found a different hospitalization pattern between subtypes of schizophrenia; the catatonic subtype are admitted to hospital earlier than the paranoid subtype since the onset of the illness. The authors did not found gender influence between subtypes of schizophrenia and days prior to hospitalization.

Furthermore, it is necessary to explore gender differences with regard to mental health service use in other psychosis diagnoses. According to Høye et al. [10], psychiatrists tend to diagnose schizophrenia more often in men than women, so women might have been diagnosed with other psychoses. Therefore, the diagnosis of other psychoses should be studied in relation to prevalence and service use by gender.

However, gender differences studies in other psychosis disorders are scarce. McGlashan et al. [11] found that the profile of people with a schizoaffective disorder is similar to that of people with schizophrenia; however, the gender pattern of the two diagnoses is different, showing no gender

differences in the schizoaffective disorders. In delusional disorders, course type and use of resources appeared to be similar in both genders as discussed by de Portugal et al. [12]. Substance-induced psychosis seems to be more prevalent in men, and in most cases it evolves into a schizophrenia disorder [13]. Therefore, it seems that there is no specific information about gender differences in the service use and outcome in all these diagnoses.

In first-episode psychosis, gender differences with regard to the number of hospitalizations are controversial. Cotton et al. [14] found lower hospital admission in women; however, when they analyzed affective and nonaffective psychosis separately, the differences were only found in the affective psychosis. Segarra et al. [15] did not find gender differences in the number of admissions to hospital in first-episode-psychosis non-substance-dependent patients. Malla et al. [16] did not find any gender differences in the relapse rates in a first-episode psychosis sample (including 81.7% schizophrenia, 7.9% delusional disorder, brief psychosis, and psychosis not otherwise specified, and 10% affective psychosis). Thus, it seems that patterns of service use in first-episode psychosis are different than in schizophrenia.

In general, most studies found that women with schizophrenia require less hospitalizations and shorter length of stay, but we do not know if there are any differences in relation to subtypes of diagnosis. Moreover, there is no evidence of gender differences in other psychosis diagnoses. Therefore, the aim of our study is to assess gender differences in the number of hospitalizations and length of hospital stays in schizophrenia, the subtypes of schizophrenia, and other psychosis diagnoses.

2. Materials and Methods

2.1. Study Design. Using clinical data stored in the computerized clinical records of the Parc Sanitari Sant Joan de Déu Mental Health Services Network (PSSJD), this 7-year observational and retrospective study aimed to describe and compare the use of the mental health services of the network by all the people on file with a diagnosis of "schizophrenia" or "other psychotic disorder" from 2001 to 2007. The institution has computerized clinical records operating since 2001 which enable to obtain data of the patients who have visited the health services. The Parc Sanitari Sant Joan de Déu Mental Health Services Network (PSSJD) is very wide and includes hospital and outpatient care in Barcelona and the metropolitan area. PSSJD centers are the reference mental health services in this area with a total coverage population of 800,000 people.

2.2. Measures and Outcomes. From all the cases included in the clinical records, only those cases with a diagnosis of "schizophrenia" or "other psychotic disorder" were selected for further analyses. The total sample size was 7483 patients. The diagnosis was that last determined as principal by the reference therapist according to the DSM-IV-R criteria. In this selected population, we analyzed gender, age of patients at the beginning of the followup, the time between the first visit in our institution and the last visit included in our study period, and a series of variables regarding use of services: the frequency of patients in each diagnose, the number of admissions in hospital care departments, and the total number of days of hospitalization in each department during the study period. Frequency of patients in each diagnosis and the risk of having at least an admission during the observed period were studied in the total sample. Number of admissions of more than 24 hours was analyzed for people who were in-patients at least a time during the analyzed period ($N = 3755$), and length of stay was studied in patients who stayed at hospital at least for a day ($N = 2419$). The difference between sample sizes was due to the presence of missing values in the variable that registered the count of number of days in hospital.

2.3. Ethical Aspects. All the patients treated at PSSJD signed a consent form stating that all the data regarding their clinical record is confidential and will be subject to the data protection law currently in force.

The information about patients was not included in the database, following the data protection law in order to ensure the anonymity and confidentiality of the data.

Moreover, the study was approved by the Ethics Committee of Hospital Sant Joan de Déu.

2.4. Statistical Analysis. The statistical analysis of the data aimed to describe gender differences with regard to the count of cases found for schizophrenia disorder, for each subtype (paranoid, disorganized, catatonic, undifferentiated, and residual) and for schizophreniform disorder, schizoaffective disorder, delusional disorder, other nonorganic psychoses, brief psychosis, shared psychotic disorder, psychotic disorder due to a general medical condition, substance-induced psychosis, and psychotic disorder NOS. The Chi-square test was used to analyze gender distribution. In order to study admission variables, two analyses were carried out. First, for the total sample we analyzed the risk of having at least one hospital admission during the study period according to gender and diagnoses by means of a logistic regression model, regardless of the total number of admissions. Second, gender differences were analyzed in the total number of patient admissions for both genders in the sample of patients admitted to any hospital department at least once during this period. Due to the overdispersion of data, the negative binomial regression with log link was used. To analyze the differences regarding the length of hospital stay per patient according to gender and diagnosis, this study took into account the patients admitted at least for a day in any of the hospital departments during the study period. Since the day count was also significantly overdispersed for each diagnosis, data was modeled once again according to the negative binomial regression model. All the models have been adjusted by age and years of treatment to avoid a confounding effect. Confidence intervals were calculated at 95%. Analyses were carried out with R 2.12.0.

3. Results

The sample analyzed in this study consisted of a total of 7483 patients, 3,137 (41.9%) females and 4,346 (58.1%)

Table 1: Frequence of attended diagnosis by gender.

	Female	Male	Total	P value†
Schizophrenia *(whole sample)*	1140 (31.76)	2449 (68.24)	3589	<0.001
Subtypes				
Paranoid	695 (32.1)	1469 (67.9)	2164	<0.001
Disorganized	51 (30.2)	118 (69.8)	169	<0.001
Catatonic	8 (53.3)	7 (46.7)	15	0.9
Undifferentiated	108 (35.9)	193 (64.1)	301	<0.001
Residual	278 (29.6)	662 (70.4)	940	<0.001
Schizophreniform disorder	86 (37.1)	146 (62.9)	232	<0.001
Schizoaffective disorder	438 (59.7)	296 (40.3)	734	<0.001
Delusional disorder	619 (59.1)	428 (40.9)	1047	<0.001
Other psychoses nonorganic	53 (48.6)	56 (51.4)	109	0.848
Brief psychosis	115 (51.8)	107 (48.2)	222	0.6385
Shared psychotic disorder	10 (76.9)	3 (23.1)	13	0.0961
Psychotic disorder medical cond.	15 (48.4)	16 (51.6)	31	0.9
Substance-induced psychosis	2 (4.2)	45 (95.8)	47	<0.001
Psychotic disorder NOS	659 (45.2)	800 (54.8)	1459	<0.001
Total $n = 7483$	3137 (41.9)	4346 (58.1)	7483	<0.001

n (%) †χ^2 Chi-square test.

Table 2: Adjusted odds ratio of being admitted at least a time to the hospital by gender.

	OR†	CI 95%
Schizophrenia *(whole sample)*	0.84	(0.72, 0.97)**
Subtypes		
Paranoid	0.83	(0.68, 1.01)*
Disorganized	1.07	(0.53, 2.17)
Catatonic	1.34	(0.01, 171.72)
Undifferentiated	0.96	(0.59, 1.57)
Residual	0.75	(0.55, 1.02)*
Schizophreniform disorder	1.11	(0.64, 1.92)
Schizoaffective disorder	0.91	(0.67, 1.22)
Delusional disorder	1.08	(0.83, 1.41)
Other psychoses nonorganic	0.77	(0.36, 1.65)
Brief psychosis	0.64	(0.44, 0.94)**
Shared psychotic disorder	9.28	(0.12, 744.57)
Psychotic disorder medical cond.	5.78	(0.42, 78.83)
Substance-induced psychosis	0.85	(0.05, 14.95)
Psychotic disorder NOS	1.19	(0.96, 1.48)
Total $n = 7483$	0.90	(0.82, 0.99)**

† Odds ratio of being admitted to the hospital at least once by gender, adjusted by age and years of treatment. Men are the reference category.
* P value < 0.1.
** P value < 0.05.

males with a diagnosis of "schizophrenia" with the subtype reported or with a diagnosis of "other psychotic disorder." The mean age of men in this sample was 45.30 (SD 17.09) and 47.67 (SD 15.55) for women. The average number of years of treatment for men was 11 (SD 12.16) and for women 7.25 (SD 5.05). Both age and years of treatment values showed statistical differences between genders (P value < 0.001). As shown in Table 1, for the whole sample, diagnoses of "schizophrenia" or "other psychotic disorder", men had a higher frequency (58.1%) than women (P value < 0.001). When analyzing by type, only the catatonic subtype of schizophrenia, other nonorganic psychosis, brief psychosis, shared psychotic disorder, and those diagnosed with a psychotic disorder due to a general medical condition had equal gender distribution (see Table 1). For all of the others, men had a higher frequency with the exception of schizoaffective and delusional disorder, showing statistically significant higher frequency for women. Regardless of the type of diagnosis, a total of 3719 (49.70%) patients were admitted to the hospital. The risk of being admitted for the first time was less in women for the whole sample (OR = 0.90, 95% CI (0.82, 0.99)) and for those women diagnosed with schizophrenia (OR = 0.84, 95% CI (0.72, 0.97)) (Table 2). Women diagnosed with brief psychosis also showed a lower risk of being admitted than men (OR = 0.64 95% CI (0.44, 0.94)). Table 3 shows the number of admissions to hospital in patients who were admitted at least once during the study period by gender ($n = 2419$). In this sample, regardless subtypes of diagnosis, there was no statistical difference between women and men. Women diagnosed with catatonic schizophrenia in a sample of 10 patients showed a higher risk of a new admission than men (RR = 4.40, 95% CI (1.67, 11.62)). Table 4 shows the number of days in hospital for patients who were admitted at least once by gender. The median of length of stay in hospital was 32.5 days with a range of 1–2586 for women and 47 days with a range of 1–2586 for men. There was a statistically lower risk for adding an additional day for women (RR = 0.78, 95% CI (0.72, 0.85)). Differentiating by diagnosis, men had a statistically significant higher risk of being admitted to hospital more days than women if they had schizophrenia of the disorganized type (RR = 0.49, 95% CI (0.30, 0.81)), undifferentiated (RR = 0.41, 95% CI (0.27, 0.61)), and delusional disorder (RR = 0.65, 95% CI (0.49, 0.87)).

4. Discussion

The first result of our study regards health care use prevalence, which is higher in men than in women for the total

Table 3: Number of admissions in hospital in patients who have been admitted at least one time by gender.

	$n^{\dagger}$		Nadmission‡			
	Female	Male	Female	Male	RR[1]	CI 95%
Schizophrenia *(whole sample)*	588	1508	2 (1–43)	2 (1–49)	1.08	(0.96, 1.21)
Subtypes						
Paranoid	368	888	1.5 (1–23)	2 (1–25)	0.98	(0.85, 1.14)
Disorganized	33	80	2 (1–25)	2 (1–20)	1.27	(0.79, 2.03)
Catatonic	5	5	5 (1–8)	2 (1–4)	4.40	(1.67, 11.62)**
Undifferentiated	54	100	2.5 (1–37)	2 (1–27)	1.40	(0.96, 2.04)*
Residual	128	435	2 (1–43)	1 (1–49)	1.08	(0.86, 1.36)
Schizophreniform disorder	41	67	1 (1–5)	1 (1–14)	1.39	(0.93, 2.08)
Schizoaffective disorder	233	170	2 (1–37)	2 (1–26)	1.11	(0.88, 1.39)
Delusional disorder	220	138	1 (1–15)	1 (1–20)	1.03	(0.79, 1.34)
Other psychoses nonorganic	23	26	1 (1–5)	1 (1–5)	1.58	(0.96, 2.58)
Brief psychosis	45	54	1 (1–3)	1 (1–7)	1.24	(0.84, 1.84)
Shared psychotic disorder	4	0	*na*	*na*	*na*	*na*
Psychotic Disorder medical cond.	3	3	*na*	1 (1–20)	*na*	*na*
Substance-induced psychosis	1	22	*na*	1 (1–4)	1.00	(0.06, 15.99)
Psychotic disorder NOS	283	326	1 (1–16)	1 (1–24)	0.99	(0.80, 1.22)
Total $n = 3755$	1441	2314	1 (1–43)	1 (1–49)	1.02	(1.01, 1.03)*

†Number of persons who have been admitted at least one time in hospital.
‡Median and range of admissions during the study period.
[1]RR of adding a new admission for patients who have been admitted at least once, regarding gender, adjusted by age and years of treatment.
Men are the reference category.
* P value < 0.1.
** P value < 0.05.

Table 4: Number of days in hospital in patients who have been admitted at least one time by gender.

	$n^{\dagger}$		n days‡			
	Female	Male	Female	Male	RR[1]	CI 95%
Schizophrenia *(whole sample)*	351	949	64 (1–2586)	92 (1–2586)	0.92	(0.81, 1.05)
Subtypes						
Paranoid	217	579	51 (1–2586)	56 (1–2586)	0.99	(0.84, 1.16)
Disorganized	24	62	134 (24–1142)	253 (1–2586)	0.49	(0.30, 0.81)**
Catatonic	4	3	1887 (664–2586)	2586 (1960–2586)	1.04	(0.00, 486.6)
Undifferentiated	40	67	37 (6–2586)	105 (1–2586)	0.41	(0.27, 0.61)***
Residual	66	238	70.5 (6–2586)	1165 (1–2586)	0.76	(0.57, 1.02)*
Schizophreniform disorder	27	37	22 (1–103)	27 (4–141)	1.04	(0.60, 1.79)
Schizoaffective disorder	153	106	49 (1–2586)	58.5 (1–2586)	1.23	(0.95, 1.59)
Delusional disorder	139	78	30 (1–2293)	39.5 (12586)	0.65	(0.49, 0.87)**
Other psychoses nonorganic	4	6	32 (9–2586)	14 (6–21)	1.17	(0.17, 8.20)
Brief psychosis	39	48	10 (1–84)	12 (1–106)	1.05	(0.68, 1.62)
Shared psychotic disorder	3	0	19 (7–22)	*na*	*na*	*na*
Psychotic Disorder medical cond.	1	1	*na*	*na*	*na*	*na*
Substance-induced psychosis	0	8	*na*	57 (2–1615)	1.02	(0.93, 1.11)
Psychotic disorder NOS	207	262	18 (1–2586)	17 (1–2586)	0.85	(0.70, 1.04)
Total $n = 2419$	924	1495	32.5 (1–2586)	47 (1–2586)	0.78	(0.72, 0.85)***

†Number of persons who have been admitted at least one day in hospital.
‡Median and range of days during the study period.
[1]RR of adding a new day of hospitalisation for patients who have been admitted at least once, regarding gender, adjusted by age and years of treatment.
Men are the reference category.
* P value < 0.1.
** P value < 0.05,
*** P value < 0.001.

sample and for schizophrenia cases. These results concur with the findings from other studies [3] and are in line with results showing that men have a higher risk of developing schizophrenia [17]. The finding that women have a higher prevalence of service use for schizoaffective disorders concurs with the majority of studies which have found that affective disorders are more common in women [18]. Our results on delusional disorders also coincide with another finding [12], which finds the female-to-male ration to be 1.6 : 1.

Our results on the risk of hospitalization show that women are admitted to the hospital less than men for the general sample, the schizophrenia patient sample, and the paranoid subtype, which is the most common. These results concur with the findings of our team in a previous study. In a follow-up study at 2 years for a sample of 200 patients with schizophrenia, we found that men had a higher number of hospitalizations [19]. This also coincides with Uggerby et al. [4], who studied the prevalence of institutionalized and noninstitutionalized patients with schizophrenia in Denmark in a sample of 22,395 people. The results showed that being male was one of the predictors of institutionalization. Similarly, in a revision of 388 hospital records, Agbir et al. [5] found that men were more frequently admitted than women. However, Lindamer et al. [6] found that women with schizophrenia have a higher risk of being hospitalized than men.

As regards other diagnoses, no differences have been found with regard to risk of hospitalization, except in brief psychoses in which women also have a lower risk of hospitalization than men. These data do not coincide with previous studies in first psychotic episodes which found no difference in the pattern of service use with regard to gender [14, 15]. However, it is important to note that brief psychoses comprise a small percentage of people with first psychotic episode.

We also specifically studied the influence of gender in the subgroup of patients who have been hospitalized at least once, and we found differences in the total sample but not in schizophrenia patients. This result concurs with the findings made by our team in a study which has been mentioned above [19] and could explain why our hospitalized female patients may be more severe than males.

In reference to the results on length of hospital stay, the results for the general sample show that men have a longer stay. In our study in 2003 [19], we also found this difference. However, the previously mentioned study by [5] found that length of stay was similar in men and women.

In conclusion, our data indicate that gender affects service use in patients with psychotic disorders and that, in general, women have a better disease course than men with regard to number of hospitalizations and days of hospitalization; however, gender does not have the same impact on all schizophrenia subtypes or different psychotic disorders.

Some strengths of our study are that the data were collected from clinical records in a computerized registry and we have analyzed the total treated population over 7 years in a large section of the Barcelona metropolitan area which represents 800,000 people. The results from this study give us an overview of the type of care received by men and women with psychotic disorders who are treated in mental health.

4.1. Limitations. Our data only account for public mental health services, and it referred to the information registered by our institution. We do not have previous clinical information for patients included in this study, although it should be emphasized that the public national health system is the most frequently used health service in Spain, especially for people who suffer from severe mental disorders. Furthermore, most of the centers of reference of our area are depressed areas that use more public services.

Admission rates do not directly represent clinical need or morbidity differences, but rather only the use of existing mental health services.

Given that our data have been extracted solely from clinical records, many of the diagnoses are not made by means of a structured clinical interview. For people with more than one diagnosis, we have included the principal diagnosis determined by the reference therapist in the last visit included in the study, according to DSM-IV-R criteria.

In some of the diagnoses, the samples are small and might prevent differences from being found, or the differences found are not clinically significant.

4.2. Practical Implications. The main result of the study is the relevance of the gender variable in the use of mental health services by patients with schizophrenia and other psychoses. Perhaps this variable must be taken into account in future studies as needs assessments and use of mental health resources in these patients populations [20].

References

[1] A. Leung and P. Chue, "Sex differences in schizophrenia, a review of the literature," *Acta Psychiatrica Scandinavica, Supplement*, vol. 101, no. 401, pp. 3–38, 2000.

[2] K. M. Abel, R. Drake, and J. M. Goldstein, "Sex differences in schizophrenia," *International Review of Psychiatry*, vol. 22, no. 5, pp. 417–428, 2010.

[3] J. Usall, S. Araya, S. Ochoa, E. Busquets, A. Gost, and M. Márquez, "Gender differences in a sample of schizophrenic outpatients," *Comprehensive Psychiatry*, vol. 42, no. 4, pp. 301–305, 2001.

[4] P. Uggerby, R. E. Nielsen, C. U. Correll, and J. Nielsen, "Characteristics and predictors of long-term institutionalization in patients with schizophrenia," *Schizophrenia Research*, vol. 131, no. 1–3, pp. 120–126, 2011.

[5] T. M. Agbir, M. Oyigeya, M. Audu, D. D. Dapap, and S. G. Goar, "Gender and psychiatric diagnosis: a 5-year retrospective study in a Nigerian Federal Medical Centre," *Nigerian Journal of Medicine*, vol. 19, no. 4, pp. 455–458, 2010.

[6] L. A. Lindamer, A. Bailey, W. Hawthorne et al., "Gender differences in characteristics and service use of public mental health patients with schizophrenia," *Psychiatric Services*, vol. 54, no. 10, pp. 1407–1409, 2003.

[7] S. Beratis, J. Gabriel, and S. Hoidas, "Gender differences in the frequency of schizophrenic subtypes in unselected hospitalized patients," *Schizophrenia Research*, vol. 23, no. 3, pp. 239–244, 1997.

[8] Y. L. Tang, C. F. Gillespie, M. P. Epstein et al., "Gender differences in 542 Chinese inpatients with schizophrenia," *Schizophrenia Research*, vol. 97, no. 1–3, pp. 88–96, 2007.

[9] N. Mimica, N. Henigsberg, S. Uzun, T. Ljubin, Z. Folnegović, and V. Folnegović-Šmalc, "Catatonic schizophrenia has a shorter pre-hospitalisation interval than other types of schizophrenia," *Journal of Neural Transmission*, vol. 109, no. 2, pp. 203–212, 2002.

[10] A. Høye, G. Rezvy, V. Hansen, and R. Olstad, "The effect of gender in diagnosing early schizophrenia: an experimental case simulation study," *Social Psychiatry and Psychiatric Epidemiology*, vol. 41, no. 7, pp. 549–555, 2006.

[11] T. H. McGlashan and K. K. Bardenstein, "Gender differences in affective, schizoaffective, and schizophrenic disorders," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 319–329, 1990.

[12] E. de Portugal, N. González, V. Miriam, J. M. Haro, J. Usall, and J. A. Cervilla, "Gender differences in delusional disorder: evidence from an outpatient sample," *Psychiatry Research*, vol. 177, no. 1-2, pp. 235–239, 2010.

[13] M. Arendt, R. Rosenberg, L. Foldager, G. Perto, and P. Munk-Jørgensen, "Cannabis-induced psychosis and subsequent schizophrenia-spectrum disorders: follow-up study of 535 incident cases," *British Journal of Psychiatry*, vol. 187, pp. 510–515, 2005.

[14] S. M. Cotton, M. Lambert, B. G. Schimmelmann et al., "Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis," *Schizophrenia Research*, vol. 114, no. 1–3, pp. 17–24, 2009.

[15] R. Segarra, N. Ojeda, A. Zabala et al., "Similarities in early course among men and women with a first episode of schizophrenia and schizophreniform disorder," *European Archives of Psychiatry and Clinical Neuroscience*, vol. 262, no. 2, pp. 95–105, 2012.

[16] A. Malla, R. Norman, L. Bechard-Evans, N. Schmitz, R. Manchanda, and C. Cassidy, "Factors influencing relapse during a 2-year follow-up of first-episode psychosis in a specialized early intervention service," *Psychological Medicine*, vol. 38, no. 11, pp. 1585–1593, 2008.

[17] A. Aleman, R. S. Kahn, and J. P. Selten, "Sex differences in the risk of schizophrenia: evidence from meta-analysis," *Archives of General Psychiatry*, vol. 60, no. 6, pp. 565–571, 2003.

[18] L. Miquel, J. Usall, C. Reed et al., "Gender differences in outcomes of acute mania: a 12-month follow-up study," *Archives of Women's Mental Health*, vol. 14, no. 2, pp. 107–113, 2011.

[19] J. Usall, S. Ochoa, S. Araya, and M. Márquez, "Gender differences and outcome in schizophrenia: a 2-year follow-up study in a large community sample," *European Psychiatry*, vol. 18, no. 6, pp. 282–284, 2003.

[20] P. McGorry, "Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders," *Australian and New Zealand Journal of Psychiatry*, vol. 39, no. 1-2, pp. 1–30, 2005.

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Clinical Study

Sex Differences in Facial, Prosodic, and Social Context Emotional Recognition in Early-Onset Schizophrenia

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The purpose of the present study was to determine sex differences in facial, prosodic, and social context emotional recognition in schizophrenia (SCH). Thirty-eight patients (SCH, 20 females) and 38 healthy controls (CON, 20 females) participated in the study. Clinical scales (BPRS and PANSS) and an Affective States Scale were applied, as well as tasks to evaluate facial, prosodic, and within a social context emotional recognition. SCH showed lower accuracy and longer response times than CON, but no significant sex differences were observed in either facial or prosody recognition. In social context emotions, however, females showed higher empathy than males with respect to happiness in both groups. SCH reported being more identified with sad films than CON and females more with fear than males. The results of this study confirm the deficits of emotional recognition in male and female patients with schizophrenia compared to healthy subjects. Sex differences were detected in relation to social context emotions and facial and prosodic recognition depending on age.

1. Introduction

Sex differences in schizophrenia regarding to clinical, neuroanatomical, cognitive, emotional and social domains have been reported (i.e.,[1–6]). With respect to psychopathological characteristics, male patients suffer more acute symptoms than females, with higher prevalence of paranoid symptoms, aggression, and antisocial behavior [7]. The latter, on the other hand, show more affective disorders, such as anxiety and depression [8], as well as sudden changes in appetite, weight, and sexual activity [9]. Schizophrenic females also show a less deteriorative course during the illness [10], a better premorbid adjustment in the social, sexual, and marital domains, and improved outcomes with a higher index of spontaneous remissions and better treatment response than males, probably due to the protector effects of sexual hormones [11–13]. Other authors have pointed out that females are more capable of living independently, while male patients are more used to living in sheltered houses [13]. Furthermore, males present a higher number of hospitalizations and greater deterioration; thus, their outcomes and social reintegration tend to be unfavourable [7].

Some studies have reported sex differences in cognitive functions in schizophrenia [3, 14–16]. Results of these studies suggest that females perform better than males in executive functions, visual working memory, verbal memory, and learning. In this regard, schizophrenic females may be less vulnerable to cognitive deficits than their males counterparts although the former still show lower performance than healthy controls on different tasks [6, 17–20]. However, studies regarding sex differences in affect recognition in cases of schizophrenia are scarce. One showed that schizophrenic females outperform males when asked to label negative facial emotions, a skill that may contribute to improving their

abilities in social life [21]. Weiss et al. [22] found that males with schizophrenia tend to interpret neutral faces as anger, while females interpret them as sadness. In addition, females outperform schizophrenic males in emotional prosodic and semantic processing [23]. In another study, an effect of sex was found in both facial and prosodic emotional recognition performance, where schizophrenic females were observed to be more accurate than men though they still presented difficulties in these processes when compared to control subjects [24].

Regarding sex differences in affect recognition abilities in healthy subjects, several studies have revealed that females generally outperform males, especially for negative facial emotional expressions [25–31]. Sex differences in emotional prosody have also been reported, showing that females can integrate both semantic content and emotional intonation information more quickly than males [32].

Results from various studies that included males exclusively or males and females together have demonstrated that schizophrenics show impairments in recognizing, expressing and regulating emotions [33–39]. Impairments in facial emotional recognition in schizophrenic patients are present from early stages of the illness and are greater for negative emotional stimuli, especially for fear and disgust [34, 40–42]. Difficulties in prosodic recognition have also been described in schizophrenia mainly for sadness and fear [23, 34, 36, 38, 43]. However, few studies have explored emotional recognition deficits in schizophrenic patients within social contexts. Studying impairments in emotional recognition in all modalities is relevant since this element contributes to abnormal social functioning, mainly in patients with a predominancy of negative symptoms [44, 45].

The question here is whether schizophrenic patients present similar sex differences for emotional recognition to those found in healthy subjects, based on an assessment of three modalities: facial, prosodic, and within a social context. Studying these three different modalities in the same subjects will make it possible to ascertain whether recognition disorders are similar in visual and prosodic recognition, as a general effect on emotion, and if they are present in a more ecological and complex modality, that is, a social context in which people express similar or different emotions in a dynamic behavioural pattern. It is possible than it in social contexts, the disorders observed in specific visual or auditory modalities could be compensated to recognize an expressed emotion, based on the conjunction of different sensory information. Furthermore, this approach will be able to evaluate other socioemotional aspects, such as the empathy level experienced by an observer while watching a film. Given the foregoing, one would expect that schizophrenic patients would show a poorer performance than healthy controls in emotional recognition tasks and, moreover, that females would show a greater preservation of emotional recognition than men.

Based on the findings reviewed above, the aim of the present study was to determine the existence of sex differences in facial, prosodic, and social context emotional recognition in patients with schizophrenia when compared to healthy controls.

2. Methods

2.1. Participants. Schizophrenic patients were recruited from the Guadalajara Mental Health Center of the Mexican Social Security Institute (IMSS). Thirty-eight paranoid schizophrenic patients (SCH 20 females and 18 males) with recent onset illness (from 6 months to 4 years) and 38 healthy control subjects (CON, 20 females and 18 males) matched with the patients for age (18–45 years) and years of formal education (minimum 9 years) met the inclusion criteria. Patients who had been submitted to electroconvulsive therapy within the previous 6 months, or had presented severe psychiatric comorbidity, were not included in the sample. All subjects were right-handed, according to Annette's test [46] but showed no neurological or chronic-degenerative disorders, addictions, carcinoma, diabetes, or infections.

In addition, the female menstrual cycle was considered when programming the evaluations, such that they were distributed similarly across the different menstrual phases. This was done in order to avoid hormonal effects on emotional recognition, since some authors [47] have found that females perform more accurately in recognizing emotional expressions of fear during the preovulatory phase compared to the menstrual phase. Also, better recognition of emotions was found in the follicular phase, in association with stronger amygdala and orbitofrontal activation in females [48, 49].

Patients were clinically assessed in two moments by an experienced psychiatrist, taking into account their clinical medical history and the international DSM-IV criteria [50]. Symptoms were rated by means of the Brief Psychiatric Rating Scale (BPRS, [51]) and the Positive and Negative Symptom Scale (PANSS, [52]).

The study was approved by the Ethic Committees of the IMSS and the Neuroscience Institute of the University of Guadalajara and was conducted according to Code of Ethics of the World Medical Association (Declaration of Helsinki). All subjects gave their informed consent before participating in the study.

2.2. Procedure. Patients arrived at the hospital in acute stage. In that moment, the first psychopathological assessment was conducted. The second psychopathological assesment was carried out during a remission stage under neuroleptic treatment. In this second session, the Affective States Scale was applied. This scale was also applied to control subjects. Subsequently, facial, prosodic, and social context emotional tasks were counterbalanced administered to the participants.

2.2.1. Clinical Assessment. The first psychopathological assessment was conducted when patients arrived to the psychiatric hospital in acute condition without medication for their first admission due to diagnoses of schizophrenia. Thereafter, patients remained at the hospital for at least 15 days. The second assesment was conducted after approximately 15 days of hospitalization (females $X = 14.25 \pm 4.12$, males $X = 15.33 \pm 5.58$), once positive symptom were remitted under pharmacological treatment with typical (haloperidol: 15 mg/day) or atypical (olanzapine: 10 mg/day) neuroleptics.

With the two completed assessments, it was possible to test whether there were clinical sex differences in both the acute phase and/or after a similar neuroleptic treatment with an equal dosage for all patients. A structured clinical interview was also applied to all subjects, as well as the laterality test [46] to confirm right handedness. These procedures were performed by one of the researchers, who is an experienced psychiatrist (VMH). Only the BPRS and PANSS were applied in both sessions.

2.2.2. Affective States Scale. The Affective States Scale was applied to controls and patients, in order to determine their basal emotional state, as this could influence their performance on the emotional recognition tasks. At the beginning of the evaluation session, participants were asked to judge their personal emotional state on a continuous linear scale ranking from 0 to 10 cm in two subscales: (1) pleasant: animated, inspired, enchanted, comfortable, happy, pleased, cheerful, and calm and; (2) unpleasant: uncomfortable, angry, sad, afflicted, frightened, tense, annoyed, and worried [53].

2.2.3. Facial Emotional Recognition Task. This test has been used previously in other studies, both in schizophrenic patients and epileptic patients [36, 54]. Facial emotional expressions of 8 models (4 males and 4 females) from Ekman and Friesen [55] were presented on a computer screen (15 in). Each model portrayed six basic emotions (happiness, sadness, anger, fear, surprise, and disgust) and one emotionally neutral expression. Participants were seated at a distance of 60 cm from the computer screen. They were instructed to press a key and, at the same time, to label the emotion that each stimulus represented, performing it as precisely and quickly as possible. Presentation of each one of the 56 stimuli lasted until the subject responded with a maximum of 2000 ms. A list with the possible emotional expressions represented in the photographs was shown to them previously, and it was confirmed that they had understood the instructions completely. Also rehearsal essays were performed before the task. Response times were recorded on a computer at the moment the subjects pressed the key. The answers were written down by hand by the experimenter.

A facial identity recognition task was presented. The goal of this task was to control for possible difficulties in face configuration processing in schizophrenics that may affect emotional recognition. Participants were asked to press a key when a previously indicated person appeared (28%) on the computer screen, with no regard for the emotional expression. Presentation of each of the 56 stimuli lasted until the subject responded with a maximum of 2000 ms. number of correct responses and response times were recorded in the computer.

2.2.4. Prosodic Emotional Recognition Task. This test consisted of 32 sentences in Spanish presented on a computer. The semantic content of the sentences was emotionally neutral but were spoken with different affective prosody—happy, sad, angry, and fear—by two professional radio announcers, one male and one female (e.g., "The table is square"; "The moon is a satellite"). The stimuli with different emotional intonation were presented randomly. Participants were asked to label the emotional tone expressed in the sentences, given a list with the four possible emotions. Answers were recorded by the experimenter to determine the number of correct responses. This task has been used in other experiments, and tested previously in a normal sample [36, 54].

2.2.5. Social Context Emotional Recognition Task. Four films with an approximate duration of 2 min were presented. All in Spanish, without music; they included several characters, and the dialogues represented situations for each one of the four aforementioned emotions (happiness, sadness, anger and fear). The films had been used in a previous study [36] and were presented randomly on a computer screen (15 in). Each participant was seated at a distance of 60 cm while watching the stimuli. At the end of each film, participants were asked to respond to a questionnaire to determine their ability to describe the scene, identify the emotions expressed by the principal and secondary characters, and indicate their perception of the intensity with which the characters experienced that emotion. In addition, participants were asked to indicate their emotional reaction when watching each film and the intensity they experienced (empathy). To evaluate the emotional intensity of the characters and that experienced by participants, an emotional scale, similar to the Emotional States Scale mentioned above, was applied to the participants. It consisted of a continuous line 10 cm long, on which they had to make a mark; the lowest intensity corresponded to the extreme left (0 cm) and the greatest intensity to the extreme right (10 cm).

2.2.6. Statistical Analysis. In order to measure sex differences in clinical symptomatology, one-way Analysis of Variance (ANOVA) test was applied for BPRS and PANSS. Two-way ANOVAs for independent groups were used in order to compare the data obtained from SCH and CON groups (Factor A) as a function of sex (Factor B) for: (a) sociodemographic data (b) Affective States Scale scores: for pleasant and unpleasant (c) identity and (d) social context emotional recognition: attribution of intensity to emotional expression of the principal character and empathy level experienced by the participant. A three-way ANOVA—A: groups; B: sexes; C: emotions—for mixed designs was applied to analyze the facial emotional recognition task: number of correct responses and response times and prosodic recognition task: number of correct responses. In order to assess the effect of age on facial and prosodic recognition, an Analysis of Covariance (ANCOVA) was applied, since females were older than males. Significant levels were adjusted using the Greenhouse-Geisser epsilon correction for factors, and corrected P values are reported. The percentage of congruent responses with that represented in the scene, identification with the principal character, and association of the scenes with their personal life were evaluated by means of a chi square test.

Table 1: Sociodemographic characteristics from healthy controls (CON) and schizophrenic patients (SCH).

	CON				SCH			
	Females ($n = 20$)		Males ($n = 18$)		Females ($n = 20$)		Males ($n = 18$)	
	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD	$\overline{X}$	SD
Age (years)	34.20	±9.46	26.06	±7.16	36.15	±7.01	27.06	±7.22
Formal education (years)	13.87	±2.62	13.88	±2.83	13.87	±2.87	12.36	±2.58
	% Subjects							
Single	30%		55%		35%		61%	
Married or stable partner	60%		33%		40%		33%	
Widow	0%		0%		5%		0%	
Divorced/separated	10%		11%		20%		6%	
Occupation	% Subjects							
Student	25%		33%		0%		22%	
Employee	5%		50%		45%		50%	
Professional	10%		17%		15%		6%	
House worker	55%		0%		30%		0%	
None	0%		0%		5%		22%	
Others (commerce)	5%		0%		5%		0%	

Table 2: Clinical characteristics of the schizophrenic patients; BPRS and PANSS were applied twice, first in the acute phase (1) and later in the remission phase (2).

	Females ($n = 20$)		Males ($n = 18$)	
	$\overline{X}$	DS	$\overline{X}$	DS
Number of Hospitalizations	1.65	±1.18	1.44	±.61
Duration of illness (months)	22.50	±16.87	24.44	±13.57
Days of Hospitalization at the time of evaluation	14.25	±4.12	15.33	±5.58
BPRS (1)	44.89	±16.46	45.94	±7.32
PANSS positive (1)	24.00	±7.10	25.66	±5.96
PANSS negative (1)	21.52	±7.16	23.33	±7.06
PANSS general (1)	36.16	±9.48	37.16	±6.4
PANSS global (1)	81.75	±19.40	86.16	±10.6
BPRS (2)	24.52	±7.61	25.29	±8.04
PANSS positive (2)	8.36	±4.25	9.56	±2.92
PANSS negative (2)*	11.47	±5.18	14.93	±3.67
PANSS general (2)	20.42	±8.96	22.00	±2.36
PANSS global (2)	44.73	±9.56	47.35	±7.94

* $P < .03$.

3. Results

3.1. Sociodemographic Data. Age was significantly different between sexes ($F(1, 72) = 23.10$, $P < .001$). Schizophrenic females (SCHf) were about 8 years older than males (SCHm) and, as a result, the matched control females (CONf) compared to males (CONm). No differences were found in years of formal education (Table 1).

3.2. Clinical Characteristics. With regard to the initial psychopathological assessment, no differences either in BPRS or PANSS were found in the patient group. In the second assessment, SCHm showed higher scores than SCHf only on the Negative Symptoms Subscale ($F(1, 34) = 2.23$, $P < .03$). (see Table 2).

There were no differences between SCHf and SCHm in the number of previous hospitalizations, duration of illness,

number of days between the initial and second evaluations, or in the type of medication. Two SCHf and two SCHm were medicated with 15 mg/day of haloperidol (250 chlorpromazine equivalent) while 18 SCHf and 16 SCHm were taking 10 mg/day of olanzapine (200 chlorpromazine equivalent).

3.3. Affective States Scale. There were no significant differences between SCH and CON, or between males and females, on the pleasant affective states subscale ($F(1,72) = 0.06$, $P < .79$); however, the SCH group reported higher unpleasant affectivity than CON ($F(1,72) = 16.53$, $P < .001$), both in the case of males and females at the beginning of the assessment session. No sex differences were observed. (Figure 1).

3.4. Emotional Recognition

3.4.1. Facial Recognition. There were no significant differences on the identity control task between CON and SCH, or between sexes in terms of the number of correct responses and response times.

Figure 2 shows that SCH achieved a lower number of correct responses for all emotions with the exception of happiness ($F(1,72) = 13.74$, $P < .001$) compared to CON as a main factor. With regard to sex, the statistical analysis did not reach significant values. Females in both groups CON and SCH, showed a tendency to have a higher number of correct responses in sadness recognition than males. The factor of emotions showed significant differences ($F(6,432) = 36.92$, $P < .001$) in the number of correct responses. As expected, happiness had the highest values and fear the lowest (Figure 2).

With respect to response times, SCH were slower to recognize all the emotions than CON ($F(1,72) = 7.36$, $P < .008$). There was no significant effect of sex. Response times were also significant between emotions ($F(6,432) = 24.27$, $P < .001$), with happiness showing the fastest response times (Figure 2). There were no significant interactions for either the number of correct responses or response times.

When age was considered as a covariate, the number of correct responses was still significant for emotions ($F(6,432) = 3.1$, $P < .01$) and for groups ($F(1,72) = 12.81$, $P < .001$). Although gender did not reach the level of significant differences, when age is considered as a covariate, it showed a trend ($F(1,72) = 3.58$, $P < .06$). There were no significant interactions between factors.

3.4.2. Prosodic Recognition. There were significant differences between emotions on the prosodic recognition task ($F(3,1892) = 31.21$, $P < .001$). SCH showed a significantly lower number of correct responses in prosodic emotional recognition than CON ($F(1,72) = 16.53$, $P < .001$) as a main factor. In addition, an interaction of emotion by group was found ($F(3,1892) = 4.24$, $P < .01$). No sex differences were observed. As can be seen in Figure 3, the easiest emotion to recognize was happiness, whereas the most difficult one was fear. SCH showed a lower number of correct responses than CON with respect to all emotions. In addition, results demonstrate that only for SCH was recognizing sadness as difficult as identifying fear.

The ANCOVA with age, included as a covariate, revealed a significant effect ($F(1,71) = 9.05$, $P < .004$). The significant differences between emotions in prosodic recognition disappeared ($F(1,71) = 2.21$, $P < .10$). The main effect for group remained, with SCH showing a significantly lower number of correct responses in prosodic emotional recognition than CON ($F(1,72) = 15.79$, $P < .001$). Although no sex differences were observed, an interaction of group by gender was found ($F(1,71) = 4.06$, $P < .04$). A Pearson correlation analysis between the global number of correct responses and age revealed a significant negative correlation only for SCHm ($r = -0.52$, $P < .005$).

3.4.3. Social Context Emotional Recognition. All the participants in CON and SCH groups were able to recognize all the emotions expressed by the characters in the 4 films.

With respect to the intensity of the emotions expressed by the principal character, there were no differences between CON and SCH or between the sexes, but a significant interaction of group by sex ($F(1,72) = 4.18$, $P < .04$) revealed that SCHm attributed less intensity to the expression of happiness by the principal character than CONm. Both CON and SCH females attributed a higher intensity to the expression of happiness by the secondary character ($F(1,72) = 9.35$, $P < .003$) and reported greater empathy with the characters in the films when they expressed happiness, compared to males in both groups ($F(1,72) = 11.94$, $P < .001$) (see Figure 4).

A higher percentage of females compared to males in both groups reported identifying with the principal character in the case of fear ($P < .001$); and a higher percentage of SCH females and males identified more closely with sadness ($P < .05$, $P < .001$, resp.), compared to CON. Similar results were found in fear and sadness in terms of the percentage of subjects when they relate the films scenes to their personal lives ($P < .001$ in all cases) (Figure 5).

4. Discussion

The purpose of the present study was to determine sex differences in schizophrenic patients with regards to emotional recognition, considering three modalities: facial, prosodic and in a socioemotional context, as well as to confirm impairments in those modalities in early onset schizophrenic patients.

4.1. Sociodemographic and Clinical Characteristics. As has been reported by Kraepelin in 1919, and other authors have replicated [2, 3, 56], both illness onset and first hospital admission occurred later in schizophrenic females than in males by approximately 8 years. More males than females were single or had no stable partner; half of the patients, both females and males had jobs; some males were students, while some females were homemakers. In general, patients showed adequate social functioning, perhaps due to the recent onset of the illness.

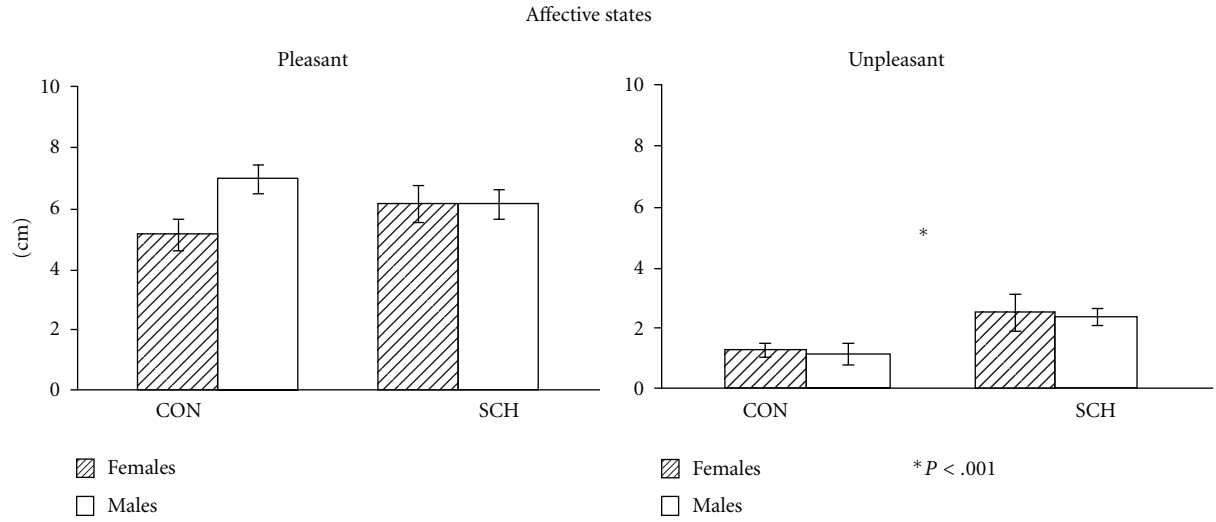

Figure 1: Means and standard errors on the pleasant and unpleasant Affective States Scale in controls (CON) and schizophrenic patients (SCH). SCH group reported higher unpleasant affectivity than CON.

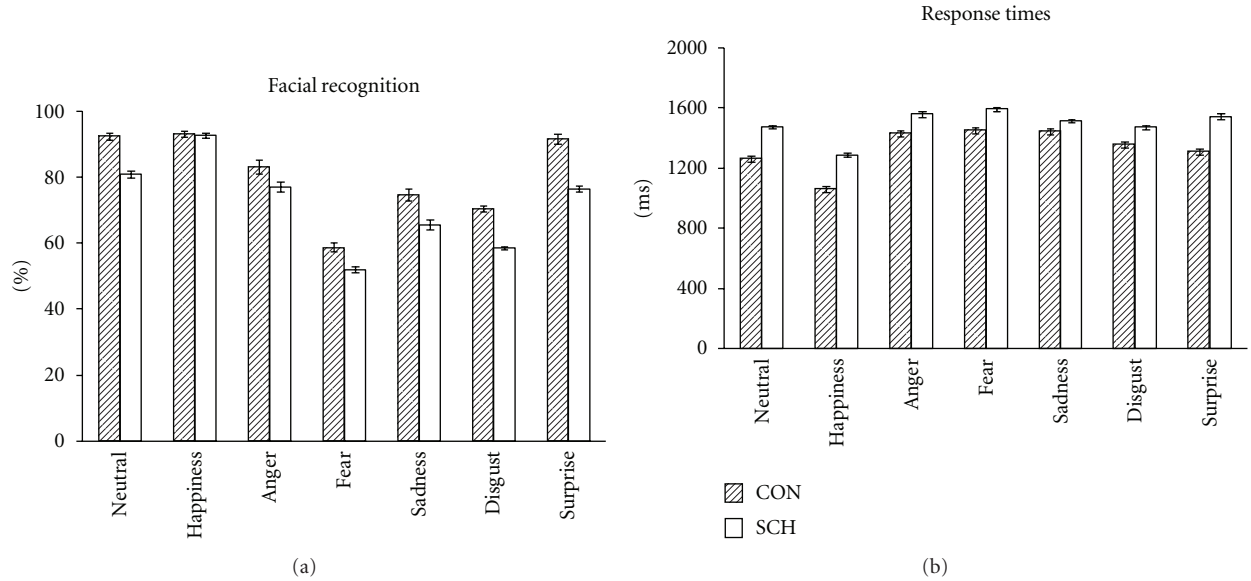

Figure 2: Means and standard errors of the percentage of correct responses and response times in the facial emotional recognition tasks for the control (CON) and schizophrenic groups (SCH).

Regarding psychiatric symptoms, no differences were observed between the sexes when the patients arrived at the hospital in the acute phase of the illness. Although other studies have affirmed that males present more acute symptomatology, and a higher prevalence of paranoid symptoms, aggression and antisocial behaviour [7] compared to females, we did not find similar results.

However, in the second psychopathological assessment, during the remission stage, males showed higher scores of negative symptoms than females. The better outcomes for the latter have been associated with better responses to treatment, a higher number of spontaneous remissions and the later onset of the illness, compared to males [7, 13, 15]. Rao and Kölsch [57] have attributed the higher severity in negative symptoms in males to lower concentrations of estradiol.

Turning to emotional states, we observed no differences by sex in the Affective States Scale scores. While both groups showed higher scores on the pleasant scale in comparison to the unpleasant scale, schizophrenics reported a higher level of unpleasant states. This finding is significant, since a negative emotional state could work as a marker for

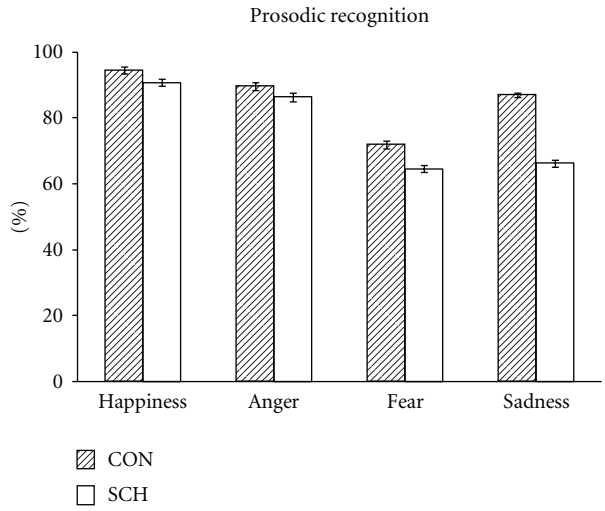

Figure 3: Means and standard errors for the percentage of correct responses in the prosodic emotional recognition task for males and females from the control (CON) and schizophrenic groups (SCH).

overlooked negative emotions on neutral faces. For instance, studies in depressive patients have described that they tend to attribute sadness to faces showing neutral expressions [58].

In conclusion, sex differences in schizophrenic patients were observed only in negative symptoms in the remission stage after medication, with a higher level in males than females.

4.2. Facial Emotional Recognition. Schizophrenic patients showed lower accuracy than controls in the recognition of all emotions, with the exception of expressions of happiness. The main effect for group remained when age was introduced as a covariate, indicating an independence of emotional recognition abilities in relation to age. In addition, the schizophrenic patients presented longer response times. These findings agree with those reported by several other studies in which deficits in facial emotional recognition in schizophrenic were found [38, 39]. It has been documented that people with schizophrenia commit more errors in recognizing fear, disgust and sadness, though they have no problem in recognizing happiness, an emotion that is more easily recognized than others [26, 59]. The fact that there were no difficulties in identity recognition suggests that this is not a problem in facial configuration processing.

Another issue has to do with response time. It is commonly accepted that schizophrenic patients generally show a slower processing on most type of tasks, including facial emotional recognition. In previous studies, we have found slower reaction times in male schizophrenics than healthy controls in odd-ball tasks using letters and emotional faces as stimuli [60], as well as on identity and emotional tasks [61]. In addition, longer reaction times (RT) were correlated with higher level of symptomatology and lower number of correct responses on both tasks [60].

On the question of differences between the sexes in emotional recognition, the variation found did not reach significant values. However, when age was introduced as a covariate, a trend was observed in the sense of a better performance in females than males. Other studies have reported better facial emotional recognition in females than males (i.e., [26, 62, 63]). In particular, it has been reported that healthy females outperform males in recognizing sad faces, while males perform better when it comes to identifying fear [31].

4.3. Emotional Prosody. In this research, schizophrenics showed lower accuracy in prosodic emotional recognition than controls as a whole. These results are congruent with those of other studies [34] that also found significant deficits in sadness and fear prosodic recognition in schizophrenics.

In a previous study, we have also found difficulties in prosodic recognition of happiness and sadness in chronic resistant schizophrenics without treatment [36]. However, a significant improvement was observed in the patients after they took olanzapine, as was a reduction in depression, though only for happiness prosodic expressions [36]. The effect of medication is relevant, since almost all the schizophrenics in the present study had taken olanzapine for at least 15 days when they were evaluated; therefore, accuracy in identifying happiness may have improved.

Regarding sex differences in prosodic recognition, no differences were found as long as age was not considered as a covariate; however, when it was, a significant group by gender interaction was found. In addition, a negative correlation between accuracy and age was observed only for schizophrenic males. These results suggest that prosodic recognition depends on age, mainly in schizophrenic males, as their performance worsens as age increases.

The prosodic stimuli used in this work had the particularity that the sentences were semantically neutral, such that the participants only had to pay attention to the emotional prosody. It is relevant because Schirmer et al. [32, 64] proposed that sex differences in emotional prosody depend on whether the subjects are asked to pay attention only to prosody and not to semantic information in the sentence. When the subjects pay attention to semantic content and emotional intonation simultaneously, females can integrate the two types of information more quickly than males, but when they only have to attend to emotional prosody, there are not sex differences. In daily life, speech contains both types of information that must be processed simultaneously, so it would be useful to evaluate emotional prosody processing when semantic information is also present, or even when there is incongruence between them.

Disorders in prosodic emotional recognition are related to difficulties in maintaining social interaction, which leads to social withdrawal even in healthy young adults [65]. In this sense, these disorders would result in lower social adaptive behavior in schizophrenic males than females as age increases.

4.4. Emotional Recognition in a Social Context. Understanding information on socioemotional contexts requires several abilities, including, as a first step, recognizing facial and body

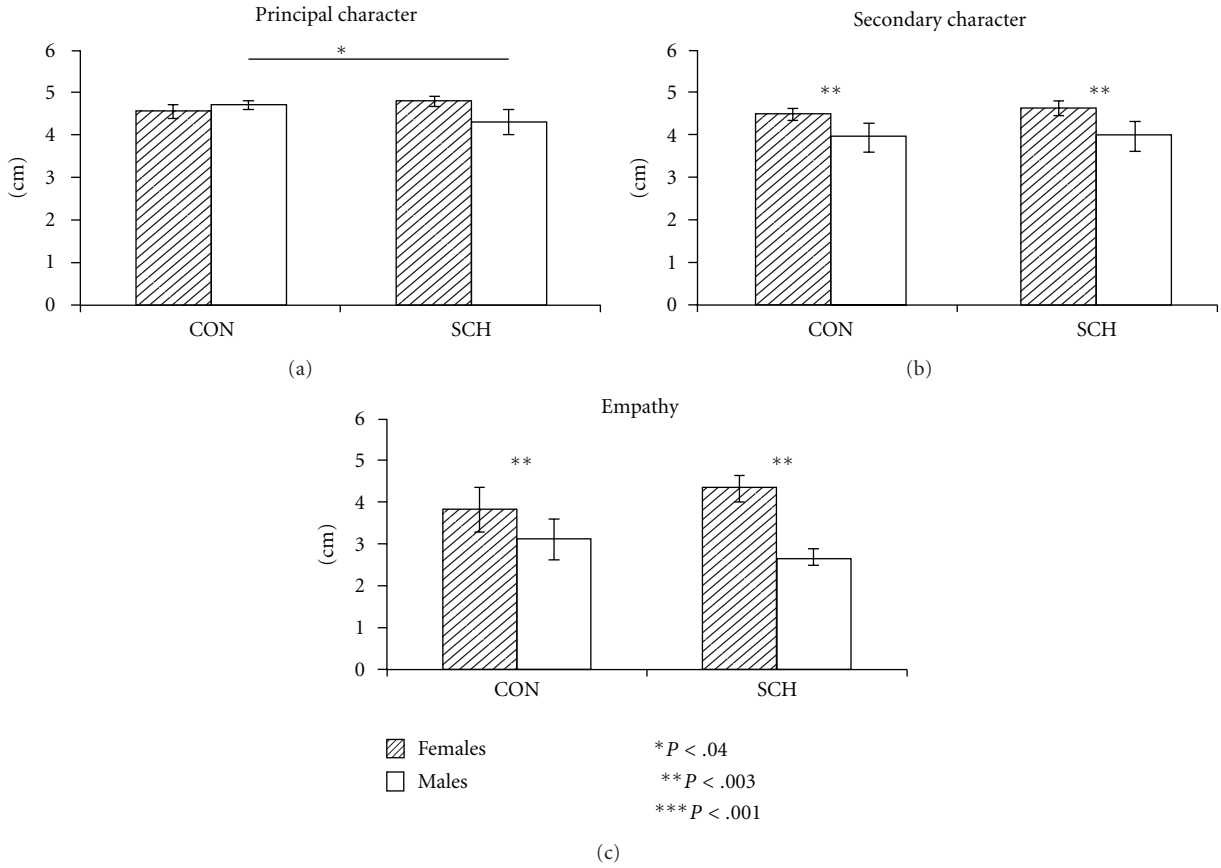

Figure 4: Means and standard errors for intensity level attributed to happiness expression from the principal and second characters and the empathy level experienced during the happiness film for females and males of the control (CON) and schizophrenic groups (SCH).

expressions and emotional prosody, and second, integrating those different types of emotional information. In addition, it requires interpreting all the emotional information within a context that includes, on the one hand, physical and spatial features, but more importantly, the ability to infer mental states and intentions from other individuals, in order to predict their behaviour and interpret the significance of personal relationships, as well as the effect of one's own behavioral responses on others. The final step refers to the empathetic abilities needed to understand the feelings of others (for reviews [66, 67]).

With regard to the recognition of the emotion represented in the films, all participants were capable of reporting their content congruently. These may be due to the fact that there are several simultaneous sensory inputs that allow the patients to compensate possible difficulties in any particular input channel. However, schizophrenic males attributed less intensity to the expression of happiness by the principal character than control males. In addition, both CON and SCH females attributed higher intensity to the expression of happiness by the secondary character. A higher percentage of females compared to males in both groups reported identifying with the principal character in the case of fear, while schizophrenic females and males identified more strongly with sadness than did controls. Similar results were found in the percentage of subjects when they were asked to relate the films scenes with their personal lives. Furthermore, both control and schizophrenic females reported a greater intensity of empathetic feelings during the happiness film. These results are consistent with those of a previous study carried out by Grossman and Wood [68] in which females reported experiencing emotions with greater intensity than males in findings that correlated with higher electromyograph activity.

Both female and male patients showed higher identification with the principal character in sadness films and reported that this scene related more closely to their personal lives than did controls. This may be related to the more unpleasant emotional state reported by the patients on the Affective Scale.

In a previous study conducted with similar facial, prosodic, and social context stimuli, we found that schizophrenic people showed difficulties in making social judgments as to what was happening in the scene, and in attributing intentions to the characters portrayed [36].

The role of emotions in formation and maintenance of interpersonal relationships is crucial. Not surprisingly, then, disturbances in an individual's emotions have important social consequences [69]. Understanding facial expressions in others makes it possible to form a representation of

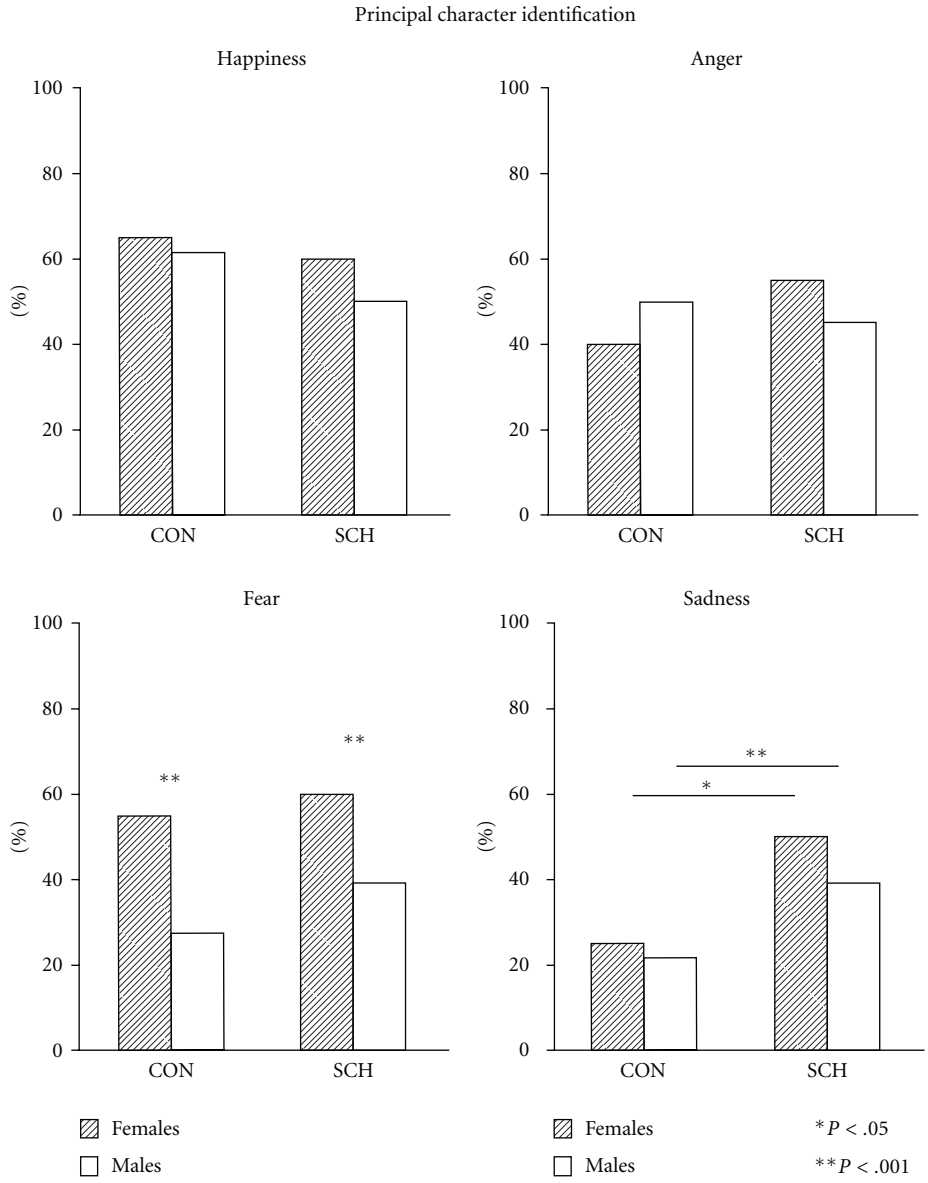

Figure 5: Percentage of controls (CON) and schizophrenic patients (SCH) that reported being identified with the principal character.

their intentions and emotional states and then respond accordingly in an adaptive way. Although there exists an important relationship between emotional recognition and adequate social development [69], it is also suggested that other cognitive abilities, such as executive functions, are fundamental to interpreting emotions in a scene where the role of lateral prefrontal cortex is predominant [70, 71].

It is important to conduct studies with complex emotions such as proud, shame, guilt, frustration, and so forth, because, in daily life, patients are continuously exposed to not only basic emotions, but also complex ones. It is possible that when exposed to such complex emotional expressions schizophrenics would show greater impairment and more pronounced differences between sexes.

This study took into account the fact that there are many variables that can influence emotional recognition performance; however, controlling for all such variables made it difficult to recruit a larger sample. For this reason, there is some question as to what degree these findings could be generalized to a larger population.

In summary, in the results of the present study, both females and males schizophrenic patients showed poorer performance than controls in terms of visual and prosodic modalities with respect to almost all emotions, except for happiness. However, when placed in the social context portrayed in the films, patients with schizophrenia were able to recognize all the emotions, suggesting that simultaneous sensory inputs may allow them to compensate for the difficulties that can appear when information is processed by independent input channels. Schizophrenic patients reported that they identified more with sad films than did controls, a finding that may be related to a more unpleasant

emotional state. Schizophrenic females and males presented similar impairments with regards to facial and prosodic emotional recognition compared to CON, though upon considering age as a covariate, schizophrenic males showed poorer performance as age increased. However, in the social context of emotions, females showed higher empathy in relation to happiness than males in both groups and attributed a greater intensity of happiness to the secondary characters. As well, control and schizophrenic females identified more with fear than males.

Knowledge of emotional impairments in schizophrenia may be useful in designing therapeutic strategies, by taking into account the emotions that present greater difficulties in a particular sensory modality. It would be important to attend not only to emotional recognition of faces and prosody impairments, but to the way the patients interpret those emotions in order to improve formation and maintenance of interpersonal relationships. Together with other findings, the data from this study suggest that both in clinical management and research most take into account sexual differences in schizophrenic patients.

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References

[1] M. C. Angermeyer, L. Kuhn, and J. M. Goldstein, "Gender and the course of schizophrenia: differences in treated outcomes," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 293–307, 1990.

[2] A. Leung and P. Chue, "Sex differences in schizophrenia, a review of the literature," *Acta Psychiatrica Scandinavica*, vol. 101, no. 401, supplement, pp. 3–38, 2000.

[3] H. Häfner, "Gender differences in schizophrenia," *Psychoneuroendocrinology*, vol. 28, no. 2, pp. 17–54, 2003.

[4] J. Edwards, P. E. Pattison, H. J. Jackson, and R. J. Wales, "Facial affect and affective prosody recognition in first-episode schizophrenia," *Schizophrenia Research*, vol. 48, no. 2-3, pp. 235–253, 2001.

[5] R. E. Gur, B. I. Turetsky, P. E. Cowell et al., "Temporolimbic volume reductions in schizophrenia," *Archives of General Psychiatry*, vol. 57, no. 8, pp. 769–775, 2000.

[6] M. Torniainen, J. Suvisaari, T. Partonen et al., "Sex differences in cognition among persons with schizophrenia and healthy first-degree relatives," *Psychiatry Research*, vol. 188, no. 1, pp. 7–12, 2011.

[7] Z. Z. Cernovsky, J. A. Landmark, and R. L. O'Reilly, "Symptom patterns in schizophrenia for men and women," *Psychological Reports*, vol. 80, no. 3, pp. 1267–1271, 1997.

[8] J. M. Goldstein, "Sex, hormones and affective arousal circuitry dysfunction in schizophrenia," *Hormones and Behavior*, vol. 50, no. 4, pp. 612–622, 2006.

[9] T. H. McGlashan and K. K. Bardenstein, "Gender differences in affective, schizoaffective, and schizophrenic disorders," *Schizophrenia Bulletin*, vol. 16, no. 2, pp. 319–329, 1990.

[10] K. K. Bardenstein and T. H. McGlashan, "Gender differences in affective, schizoaffective, and schizophrenic disorders. A review," *Schizophrenia Research*, vol. 3, no. 3, pp. 159–172, 1990.

[11] H. Y. Meltzer, J. Rabinowitz, M. A. Lee et al., "Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance," *American Journal of Psychiatry*, vol. 154, no. 4, pp. 475–482, 1997.

[12] R. Halari, V. Kumari, R. Mehrotra, M. Wheeler, M. Hines, and T. Sharma, "The relationship of sex hormones and cortisol with cognitive Functioning in schizophrenia," *Journal of Psychopharmacology*, vol. 18, no. 3, pp. 366–374, 2004.

[13] L. A. Lindamer, A. Bailey, W. Hawthorne et al., "Gender differences in characteristics and service use of public mental health patients with schizophrenia," *Psychiatric Services*, vol. 54, no. 10, pp. 1407–1409, 2003.

[14] L. J. Seidman, J. M. Goldstein, J. M. Goodman et al., "Sex differences in olfactory identification and Wisconsin card sorting performance in schizophrenia: relationship to attention and verbal ability," *Biological Psychiatry*, vol. 42, no. 2, pp. 104–115, 1997.

[15] J. M. Goldstein and B. G. Link, "Gender and the expression of schizophrenia," *Journal of Psychiatric Research*, vol. 22, no. 2, pp. 141–155, 1988.

[16] J. H. Gruzelier, "Syndromes of schizophrenia and schizotypy, hemispheric imbalance and sex differences: implications for developmental psychopathology," *International Journal of Psychophysiology*, vol. 18, no. 3, pp. 167–178, 1994.

[17] K. L. Narr, P. M. Thompson, T. Sharma, J. Moussai, A. F. Cannestra, and A. W. Toga, "Three-dimensional mapping of temporal-limbic regions and the lateral ventricles in schizophrenia: gender effects," *Society of Biological Psychiatry*, vol. 50, pp. 87–97, 2001.

[18] P. R. Szeszko, R. D. Strous, R. S. Goldman et al., "Neuropsychological correlates of hippocampal volumes in patients experiencing a first episode of schizophrenia," *American Journal of Psychiatry*, vol. 159, no. 2, pp. 217–226, 2002.

[19] J. M. Goldstein, L. J. Seidman, J. M. Goodman et al., "Are there sex differences in neuropsychological functions among patients with schizophrenia?" *American Journal of Psychiatry*, vol. 155, no. 10, pp. 1358–1364, 1998.

[20] M. Albus, W. Hubmann, F. Mohr et al., "Are there gender differences in neuropsychological performance in patients with first-episode schizophrenia?" *Schizophrenia Research*, vol. 28, no. 1, pp. 39–50, 1997.

[21] M. R. M. Scholten, A. Aleman, B. Montagne, and R. S. Kahn, "Schizophrenia and processing of facial emotions: sex matters," *Schizophrenia Research*, vol. 78, no. 1, pp. 61–67, 2005.

[22] E. M. Weiss, C. G. Kohler, C. M. Brensinger et al., "Gender differences in facial emotion recognition in persons with chronic schizophrenia," *European Psychiatry*, vol. 22, no. 2, pp. 116–122, 2007.

[23] M. R. M. Scholten, A. Aleman, and R. S. Kahn, "The processing of emotional prosody and semantics in schizophrenia: relationship to gender and IQ," *Psychological Medicine*, vol. 38, no. 6, pp. 887–898, 2008.

[24] K. Kucharska-Pietura, A. S. David, M. Masiak, and M. L. Phillips, "Perception of facial and vocal affect by people with schizophrenia in early and late stages of illness," *British Journal of Psychiatry*, vol. 187, pp. 523–528, 2005.

[25] R. Campbell, K. Elgar, J. Kuntsi et al., "The classification of 'fear' from faces is associated with face recognition skill in women," *Neuropsychologia*, vol. 40, no. 6, pp. 575–584, 2002.

[26] G. Kirouac and F. Y. Doré, "Accuracy and latency of judgment of facial expressions of emotions," *Perceptual and Motor Skills*, vol. 57, no. 3, pp. 683–686, 1983.

[27] J. A. Hall, "Gender effects in decoding nonverbal cues," *Psychological Bulletin*, vol. 85, no. 4, pp. 845–857, 1978.

[28] E. Hampson, S. M. van Anders, and L. I. Mullin, "A female advantage in the recognition of emotional facial expressions: test of an evolutionary hypothesis," *Evolution and Human Behavior*, vol. 27, no. 6, pp. 401–416, 2006.

[29] Q. Rahman, G. D. Wilson, and S. Abrahams, "Sex, sexual orientation, and identification of positive and negative facial affect," *Brain and Cognition*, vol. 54, no. 3, pp. 179–185, 2004.

[30] J. F. Thayer and B. H. Johnsen, "Sex differences in judgement of facial affect: a multivariate analysis of recognition errors," *Scandinavian Journal of Psychology*, vol. 41, no. 3, pp. 243–246, 2000.

[31] M. K. Mandal and S. Palchoudhury, "Perceptual skill in decoding facial affect," *Perceptual and Motor Skills*, vol. 60, no. 1, pp. 96–98, 1985.

[32] A. Schirmer, S. A. Kotz, and A. D. Friederici, "Sex differentiates the role of emotional prosody during word processing," *Cognitive Brain Research*, vol. 14, no. 2, pp. 228–233, 2002.

[33] F. Schneider, R. C. Gur, R. E. Gur, and D. L. Shtasel, "Emotional processing in schizophrenia: neurobehavioral probes in relation to psychopathology," *Schizophrenia Research*, vol. 17, no. 1, pp. 67–75, 1995.

[34] J. Edwards, P. E. Pattison, H. J. Jackson, and R. J. Wales, "Facial affect and affective prosody recognition in first-episode schizophrenia," *Schizophrenia Research*, vol. 48, no. 2-3, pp. 235–253, 2001.

[35] P. J. Johnston, M. Katsikitis, and V. J. Carr, "A generalised deficit can account for problems in facial emotion recognition in schizophrenia," *Biological Psychology*, vol. 58, no. 3, pp. 203–227, 2001.

[36] G. Y. Ibarraran-Pernas, L. E. Cerdan, M. A. Guevara, and J. Ramos Loyo, "Olanzapine effects on emotional recognition in treatment refractory schizophrenics," *Actas Espanolas de Psiquiatria*, vol. 31, no. 5, pp. 256–262, 2003.

[37] A. M. Kring, S. L. Kerr, and K. S. Earnst, "Schizophrenic patients show facial reactions to emotional facial expressions," *Psychophysiology*, vol. 36, no. 2, pp. 186–192, 1999.

[38] J. Edwards, H. J. Jackson, and P. E. Pattison, "Emotion recognition via facial expression and affective prosody in schizophrenia: a methodological review," *Clinical Psychology Review*, vol. 22, no. 6, pp. 789–832, 2002.

[39] C. G. Kohler, J. B. Walker, E. A. Martin, K. M. Healey, and P. J. Moberg, "Facial emotion perception in schizophrenia: a meta-analytic review," *Schizophrenia Bulletin*, vol. 36, no. 5, pp. 1009–1019, 2010.

[40] C. G. Kohler and E. A. Martin, "Emotional processing in schizophrenia," *Cognitive Neuropsychiatry*, vol. 11, no. 3, pp. 250–271, 2006.

[41] B. Bediou, P. Krolak-Salmon, M. Saoud et al., "Facial expression and sex recognition in schizophrenia and depression," *Canadian Journal of Psychiatry*, vol. 50, no. 9, pp. 525–533, 2005.

[42] R. E. Gur, C. G. Kohler, J. D. Ragland et al., "Flat affect in schizophrenia: relation to emotion processing and neurocognitive measures," *Schizophrenia Bulletin*, vol. 32, no. 2, pp. 279–287, 2006.

[43] D. R. Bach, K. Buxtorf, D. Grandjean, and W. K. Strik, "The influence of emotion clarity on emotional prosody identification in paranoid schizophrenia," *Psychological Medicine*, vol. 39, no. 6, pp. 927–938, 2009.

[44] A. S. Bellack, R. L. Morrison, J. T. Wixted, and K. T. Mueser, "An analysis of social competence in schizophrenia," *British Journal of Psychiatry*, vol. 156, pp. 809–818, 1990.

[45] J. H. Poole, F. C. Tobias, and S. Vinogradov, "The functional relevance of affect recognition errors in schizophrenia," *Journal of the International Neuropsychological Society*, vol. 6, no. 6, pp. 649–658, 2000.

[46] M. Annette, *Left, Right, Hand and Brain: The Right Shift Theory*, Hillsdale, Editors, New York, NY, USA, 1985.

[47] R. Pearson and M. B. Lewis, "Fear recognition across the menstrual cycle," *Hormones and Behavior*, vol. 47, no. 3, pp. 267–271, 2005.

[48] B. Derntl, C. Windischberger, S. Robinson et al., "Facial emotion recognition and amygdala activation are associated with menstrual cycle phase," *Psychoneuroendocrinology*, vol. 33, no. 8, pp. 1031–1040, 2008.

[49] X. Protopopescu, H. Pan, M. Altemus et al., "Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 44, pp. 16060–16065, 2005.

[50] APA, American Psychiatric Association, *Manual Diagnóstico y Estadístico de los Trastornos Mentales. DSM-IV*, Masson, Barcelona, Spain, 1994.

[51] J. E. Overall and D. R. Gorham, "The brief psychiatric rating scale," *Psychological Reports*, vol. 10, pp. 799–812, 1962.

[52] S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophrenia Bulletin*, vol. 13, no. 2, pp. 261–276, 1987.

[53] J. Ramos, M. A. Guevara, A. Martínez et al., "Evaluation of the affective states evoked by music," *Revista Mexicana de Psicologia*, vol. 13, no. 2, pp. 131–145, 1996.

[54] A. Sanz-Martín, M. A. Guevara, M. Corsi-Cabrera, R. Ondarza-Rovira, and J. Ramos-Loyo, "Differential effect of left and right temporal lobectomy on emotional recognition and experience in patients with epilepsy," *Revista de Neurologia*, vol. 42, no. 7, pp. 391–398, 2006.

[55] P. Ekman and W. V. Friesen, *Pictures of Facial Affect*, Consulting Psychologists Press, Palo Alto, Calif, USA, 1986.

[56] R. R. J. Lewine, E. F. Walker, R. Shurett, J. Caudle, and C. Haden, "Sex differences in neuropsychological functioning among schizophrenic patients," *American Journal of Psychiatry*, vol. 153, no. 9, pp. 1178–1184, 1996.

[57] M. L. Rao and H. Kölsch, "Effects of estrogen on brain development and neuroprotection—Implications for negative symptoms in schizophrenia," *Psychoneuroendocrinology*, vol. 28, no. 2, pp. 83–96, 2003.

[58] P. Luck and C. F. Dowrick, "Don't look at me in that tone of voice: disturbances in the perception of emotion in facial expression and vocal intonation by depressed patients," *Primary Care Mental Health*, vol. 2, pp. 99–106, 2004.

[59] P. J. Johnston, H. Devir, and F. Karayanidis, "Facial emotion processing in schizophrenia: no evidence for a deficit specific to negative emotions in a differential deficit design," *Psychiatry Research*, vol. 143, no. 1, pp. 51–61, 2006.

[60] J. Ramos-Loyo, L. F. Cerdán, and M. A. Guevara, "Evaluation of olanzapine effects on attention and emotional recognition processes through event related potentials in treatment refractory schizophrenics," in *Focus on Nonverbal Communication Research*, R. L. Finley, Ed., pp. 215–236, Nova Science Publisher, New York, NY, USA, 2007.

[61] J. Ramos-Loyo, A. A. González-Garrido, L. M. Sánchez-Loyo, V. Medina, and C. Basar-Eroglu, "Event-related potentials

and event-related oscillations during identity and facial emotional processing in schizophrenia," *International Journal of Psychophysiology*, vol. 71, no. 1, pp. 84–90, 2009.

[62] L. F. Barrett, L. Robin, P. R. Pietromonaco, and K. M. Eyssell, "Are women the "More Emotional" sex? Evidence from emotional experiences in social context," *Cognition and Emotion*, vol. 12, no. 4, pp. 555–578, 1998.

[63] R. E. Gur, C. McGrath, R. M. Chan et al., "An fMRI study of facial emotion processing in patients with schizophrenia," *American Journal of Psychiatry*, vol. 159, no. 12, pp. 1992–1999, 2002.

[64] A. Schirmer, S. A. Kotz, and A. D. Friederici, "On the role of attention for the processing of emotions in speech: sex differences revisited," *Cognitive Brain Research*, vol. 24, no. 3, pp. 442–452, 2005.

[65] J. S. Carton, E. A. Kessler, and C. L. Pape, "Nonverbal decoding skills and relationship well-being in adults," *Journal of Nonverbal Behavior*, vol. 23, no. 1, pp. 91–100, 1999.

[66] M. J. Green, P. J. Uhlhaas, and M. Coltheart, "Context processing and social cognition in schizophrenia," *Current Psychiatry Reviews*, vol. 1, pp. 11–21, 2005.

[67] S. M. Couture, D. L. Penn, and D. L. Roberts, "The functional significance of social cognition in schizophrenia: a review," *Schizophrenia Bulletin*, vol. 32, pp. S44–S63, 2006.

[68] M. Grossman and W. Wood, "Sex differences in intensity of emotional experience: a social role interpretation," *Journal of Personality and Social Psychology*, vol. 65, no. 5, pp. 1010–1022, 1993.

[69] C. Hooker and S. Park, "Emotion processing and its relationship to social functioning in schizophrenia patients," *Psychiatry Research*, vol. 112, no. 1, pp. 41–50, 2002.

[70] V. P. Bozikas, M. H. Kosmidis, D. Anezoulaki, M. Giannakou, and A. Karavatos, "Relationship of affect recognition with psychopathology and cognitive performance in schizophrenia," *Journal of the International Neuropsychological Society*, vol. 10, no. 4, pp. 549–558, 2004.

[71] J. R. Gray, T. S. Braver, and M. E. Raichle, "Integration of emotion and cognition in the lateral prefrontal cortex," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 99, no. 6, pp. 4115–4120, 2002.

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Review Article

The Role of Oestrogen and Other Hormones in the Pathophysiology and Treatment of Schizophrenia

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The theory that many serious mental illnesses, in particular psychoses such as schizophrenia, may have a significant hormonal aetiological component is fast gaining popularity and the support of scientific evidence. Oestrogen in particular has been substantially investigated as a potential mediator of brain function in schizophrenia. Epidemiological and life-cycle data point to significant differences in the incidence and course of schizophrenia between men and women suggests a protective role of oestrogen. *In vitro* and *in vivo* preclinical research confirms oestradiol's interactions with central neurotransmitter systems implicated in the pathogenesis of schizophrenia, while results from randomised controlled trials investigating the antipsychotic potential of oestrogen have been positive. Research into other neuroactive hormones with possible effects on mental state is a rapidly evolving field that may hold new promise. Given that schizophrenia and related psychoses are pervasive and debilitating conditions for which currently available treatments are often only partially effective and entail a high risk of serious side-effects, novel therapeutic strategies are needed. The literature reviewed in this paper suggests that hormones such as oestrogen could be a viable option, and it is hoped that with further research and larger trials, the oestrogen hypothesis can be translated into effective clinical practice.

1. Introduction

Over a century ago, the father of modern psychiatry Emil Kraepelin first implicated an imbalance of sexual hormones in the aetiology of "dementia praecox" [1], and reports of gonadal dysfunction in psychotic patients have also been well documented since this time [2]. However it is only with recent scientific advances that the considerable effects of reproductive hormones on central nervous system functioning and mental health have come to light. Such evidence has led multiple researchers [3–6] to investigate the role of oestrogen in the pathogenesis of psychosis and propose the "oestrogen protection hypothesis" and the "hypothesis of hypoestrogenism" as possible explanations for gender differences in schizophrenia.

This paper provides a summary of the current literature with the intention of highlighting the likely role and clinical importance of oestrogen and other reproductive hormones in psychotic illness, in particular in the field of women's mental health.

2. Case Study

Miss R was a 52-year-old woman with a history of schizophrenia which began after the birth of a child she gave up for adoption in her late twenties. She had been treated with olanzapine 15 mg oral per day for the past 10 years and had been very well, with no hospitalisations. Miss R worked as a sales assistant and lived in her own apartment. However from the age of 50, her mental state deteriorated significantly and she experienced auditory hallucinations and paranoid delusions. She believed that the CIA had implanted a microchip into her brain and that she was under constant surveillance. She described hearing several spies talking about her. Miss R's quality of life suffered greatly. She lost her job, was unable to live independently, and financially existed on welfare payments. Miss R lived in a derelict boarding house and had repeated hospitalisations with no real improvement. Miss R did not respond to a succession of treatment trials with a variety of second generation antipsychotic medications. She was treated with adjunctive estradiol

(100 mcg transdermal estradiol) and had a progesterone secreting intrauterine device (IUD) inserted. The hormone treatment was added to her antipsychotic treatment—which had been risperidone 6 mg oral per day for the past two months. Within one week of adding hormone treatment, she made a dramatic improvement in her mental state and had no auditory hallucinations. The paranoid delusions also resolved within two weeks of adding hormone treatment to her antipsychotic medication. Over a period of months, Miss R was able to find herself better accommodation and some part-time employment. She has remained well—both mentally and physically after 4 years, still taking risperidone plus 50 mcg transdermal estradiol plus the IUD.

3. Epidemiological Findings

While the nature of schizophrenia was previously perceived to be similar between men and women [7], it is now widely accepted that schizophrenia is a sexually dimorphic disease.

To begin with, the incidence of schizophrenia in men is consistently observed to be approximately 1.5 times higher than the incidence rate for women [8]. There are also significant differences in age distribution of the illness between males and females: men reliably present on average four years earlier than their female counterparts [6, 9], while women display a second spike in incidence between the ages of 45 and 54 [2, 6]. Thus there is a male predominance in incidence in the early twenties, but a female predominance in older middle age [10]. Two recent large-scale studies [11, 12] of individuals with psychotic illness have also found that premenopausal women tend to experience a more benign course of illness than men, displaying less severe levels of psychopathology and disability, and higher levels of insight, functioning, and response to antipsychotic medication. This holds true until the age of 45, when the resurgence in incidence in women is associated with unusually severe symptomatology and a need for higher doses of antipsychotic medications [13]. It is widely believed that this unique course of illness in older women is related to falling levels of oestrogen during the menopause, the hormone having been protective against psychosis up until this time, that is, the *oestrogen protection hypothesis*.

4. Life-Cycle Findings

The oestrogen protection theory is further supported by evidence from life-cycle studies in females. For example, women have a 20-fold increased risk of suffering a first episode or relapse of psychosis during the postpartum period when oestrogen levels plummet dramatically [14], whereas chronic psychoses tend to improve during pregnancy when oestrogen is extremely high [13].

Similarly, in women with schizophrenia, psychotic symptoms appear to fluctuate throughout the menstrual cycle, a trend first noted by Krafft-Ebing in the late 1800s: the so-called "menstrual psychosis" [15]. Modern-day research shows that during the menstrual cycles of female schizophrenia patients, the high-oestrogen luteal phase is associated with significant improvements in psychopathology and functioning compared to the low-oestrogen follicular phase [16–19].

In short, these epidemiological and life cycle observations offer compelling evidence to suggest that oestrogen protects women against severe psychosis during their childbearing years, and that oestrogen withdrawal of any kind may be able to induce psychosis in vulnerable women [20].

5. Preclinical Findings

Oestrogen is well known to have significant actions in the central nervous system (CNS) beyond its primary endocrine and reproductive functions, so much so that it has been referred to as "nature's psychoprotectant" [21]. Indeed, oestrogen receptors can be found in abundance in multiple extra-hypothalamic regions throughout the brain, in particular the limbic system, basal ganglia, cerebellum, and many areas of the cerebral cortex [22, 23]. Through classical genomic and rapid nongenomic interactions with these receptors, oestrogen functions as a "neuroactive steroid", influencing signalling pathways and neurodegenerative processes within the CNS [24]. Recent biochemical and animal research has helped enhance our understanding of the neuromodulatory and neuroprotective properties of oestrogenic compounds.

5.1. Neurotransmitter Modulation. While the historical dopaminergic hyperactivity hypothesis of schizophrenia endures, it is now widely accepted that other major neurotransmitter systems such as serotonin and glutamate are also involved in the pathophysiology of the disorder [25, 26]. The majority of antipsychotic drugs share the property of dopamine D_2 receptor antagonism, while second generation antipsychotics also interact with serotonin 5-HT_{2A} and 5-HT_{1A} receptors [27]. Oestradiol has been found to significantly influence the dopaminergic, serotonergic, and glutamatergic systems, meaning that it may have properties similar to those of atypical antipsychotics [22, 28].

The effects of oestrogen on the dopaminergic system are thought to be highly complex and not well understood, with different studies reporting extensive variations in the direction, extent, and specificity of oestrogen-dopamine interactions [26, 29]. A number of studies involving ovariectomised (OVX) rats, however, have found an oestrogen treatment-associated increase in D_2 receptor density in the striatum [26]. It has been hypothesised that this could be a compensatory response to an oestrogen-induced reduction in DA levels [22], possibly through enhanced action of the DA transporter (DAT). A recent study by Chavez et al. [29] found that OVX rats had considerably reduced DAT in the nucleus accumbens compared to intact rats, the density of which then increased significantly following chronic oestradiol treatment.

Oestrogen has similarly been found to have considerable effects on the serotonergic system at multiple levels. Lokuge and colleagues [30] recently reviewed extensive rodent and primate data on the CNS effects of oestrogen to conclude

that oestradiol decreases the activity of monoamine oxidase, increases the activity of tryptophan hydroxylase, manipulates expression of the serotonin transporter, downregulates 5-HT_{1A} receptors, and upregulates 5-HT_{2A} receptors.

Hypoglutamatergic neurotransmission has also been implicated in the pathophysiology of schizophrenia given the observation that glutamate NMDA receptor antagonists such as phencyclidine induce a psychomimetic state in animals and humans [31]. Oestradiol is known to upregulate NMDA receptors, change their subunit configuration, and increase NMDA agonist binding in the rat brain [32], which could presumably help reverse hypoactive glutamatergic functioning in schizophrenia.

A number of recently published studies using animal models of schizophrenia have confirmed oestrogen's involvement with central neurotransmitter mechanisms and resultant antipsychotic-like activity. Gogos and colleagues mimicked a psychotic state in OVX rats by administering a D_2 receptor agonist, a 5-HT_{1A} agonist, and a NMDA receptor antagonist, respectively [33, 34]. Chronic oestradiol treatment was able to reverse the psychotic endophenotype in all three instances, strongly suggesting that oestrogen's antipsychotic properties stem from its interactions with dopamine, serotonin, and glutamate. Work by Arad and Weiner [35, 36] supplements these findings and further exhibits oestradiol's antipsychotic potential. They found that oestradiol can ameliorate an amphetamine-induced psychotic state in both OVX and intact female rats as effectively as clozapine or haloperidol; however OVX rats required significantly higher doses of each compound to achieve this [35]. This lends credence to the oestrogen protection hypothesis and its consequences for the menopause as discussed earlier. Also, ineffective low doses of clozapine and haloperidol regained antipsychotic efficacy when combined with a low dose of oestradiol [35], which could have important implications for augmentation of antipsychotic drugs in schizophrenic women. A follow-up study by the same authors importantly demonstrates that oestradiol has efficacy reversing psychotic behaviours in both female and male rats [36], raising the possibility of clinical use of oestrogen in both sexes.

5.2. Neuroprotection. Schizophrenia is considered by many to be at least in part a progressive neurodegenerative disorder [37, 38]. Numerous anatomical abnormalities have been reported in the brains of schizophrenia patients including reduced grey and white matter volume in multiple brain regions, ventricular enlargement, and abnormalities of the medial temporal lobe, prefrontal cortex, and cerebellum [38–40]. Abnormal cytoarchitecture is also common with neuronal soma and neuropil volume reductions, irregular synaptic organisation, ectopic neurons, and decreased expression of neurotrophic factors [37, 41].

Oestrogen is known to have diverse neuroprotective properties that could be of particular relevance to its ability to mediate the onset and course of neuropathology in schizophrenia. Recent *in vitro* and *in vivo* research has confirmed that oestrogenic compounds can protect brain cells against injury from excitotoxicity, oxidative stress, inflammation, ischaemia, and apoptosis [42–46]. They can also enhance neurogenesis, angiogenesis, synaptic density, plasticity and connectivity, axonal sprouting and remyelination, and expression of neurotrophic factors [2, 47–50]. Recent research suggests that the psychoprotective properties of oestrogens might arise from their preservation and enhancement of neuronal mitochondrial function, as mitochondria are responsible for regulating the viability and death of neurons [51] and may be defective in the brains of individuals with schizophrenia [52].

6. Clinical Findings

6.1. The Hypothesis of Hypoestrogenism. In her recent review of the literature, Markham speculates that, given the apparent psychoprotective actions of oestrogen in women, "those women who do end up developing schizophrenia are at greater risk in part because for some reason their oestradiol levels are abnormally low" [9]. This hypothesis was first introduced at the beginning of the 20th century when early researchers such as Kretschmer [53] observed signs of "insufficient functioning of the sexual glands" and "chronic hypoestrogenism" in female schizophrenia patients.

More recent work has confirmed this early theory of gonadal dysfunction in women with schizophrenia, with menstrual irregularities, anovulation, infertility, signs of hyperandrogenism, and reduced circulating levels of oestradiol, progesterone, follicle stimulating hormone, and luteinizing hormone frequently observed (see Riecher-Rossler and Kulkarni, 2011 [2], and Riecher-Rossler, 2002 [13], for reviews). Most interestingly, this historical finding has recently also been extended to men, with separate research groups observing not only significantly reduced circulating oestradiol concentrations in acutely psychotic men compared to controls, but also an inverse correlation between oestrogen levels and negative symptoms [54, 55].

However, it is still not entirely clear whether this gonadal dysfunction precedes or follows the onset of psychosis—that is, whether it is a causative or a resulting factor.

The potential for both the chronic emotional stress associated with a psychiatric disorder such as schizophrenia and antipsychotic medication-induced hyperprolactinaemia to disrupt the hypothalamic-pituitary-gonadal (HPG) axis [56, 57] is a possible way in which hypoestrogenism could be a consequence of schizophrenia. However, several lines of evidence contest this. To begin with, schizophrenia-associated gonadal hypofunction in women was observed by the likes of Kraeplin and Kretschmer long before the introduction of neuroleptic drugs, and other psychiatric diagnoses that also entail a high level of stress appear not to be associated with as great a degree of HPG axis perturbation as schizophrenia [58, 59]. Furthermore, Riecher-Rossler et al. found that a history and signs of "severely disturbed" gonadal function were significantly more common in women admitted for *first episode* psychosis than controls [60], while Maric and colleagues report that bone mass density—an indicator of chronic oestrogen deficiency—is significantly

lower in women with first onset schizophrenia than matched controls [61]. Finally, multiple researchers have noted hypoestrogenism in women with schizophrenia irrespective of prolactin level [58, 62, 63]—that is, not just in those women with hyperprolactinaemia.

These findings would seem to indicate the presence of hypoestrogenism prior to the onset of psychosis and independent of neuroleptic-induced endocrine disturbances or emotional stress. More research is needed to further explore the possibility that underlying oestrogen deficiency could be involved in the initial pathogenesis of psychosis.

6.2. Oestradiol as Treatment: Intervention Studies. Given the evidence in support of both the oestrogen protection hypothesis and the hypothesis of hypoestrogenism, it is not surprising that oestradiol has been targeted as a potential therapeutic agent for schizophrenia. And although two recent reviews in 2005 and 2007 concluded that adjunctive oestrogen does not seem to be any more advantageous than placebo in the treatment of schizophrenia [64, 65], more recent work has yielded some promising results.

In a randomised sample of 102 women diagnosed with a psychotic illness, our research group found that adjunctive treatment with 100 μg per day of transdermal oestradiol for 28 days led to significant improvements in total Positive and Negative Syndrome Scale (PANSS) scores ($P = 0.002$), positive symptoms ($P = 0.005$), general psychopathology ($P = 0.01$), and cognition ($P = 0.01$) when compared with antipsychotic medication alone [66]. These findings are consistent with the results of an earlier, smaller randomised controlled trial by Ahkondzadeh and associates who also reported significant reductions in total, positive symptom and general psychopathology PANSS scores for schizophrenic women treated with haloperidol plus ethinyl oestradiol compared to women treated with haloperidol plus placebo [67].

Most recently, our research group has piloted the use of adjunctive oestrogen therapy in men with schizophrenia [68], as well as adjuvant use of the selective oestrogen receptor modulator (SERM), raloxifene, for postmenopausal psychosis [69]. In a two-week randomised controlled trial we treated 53 men with either 2 mg oral oestradiol valerate or placebo. The oestradiol group displayed a significantly faster improvement in general psychopathology than the placebo group ($P < 0.05$) with no increase in adverse side-effects, providing the first clinical indication that oestrogen could be a viable treatment adjunct in men as well as women. In a preliminary dose-finding study, we also trialled 120 mg augmentation per day of oral raloxifene for 12 weeks in postmenopausal women with schizophrenia. SERM therapy resulted in significantly greater recovery in total ($P < 0.0005$) and general psychopathology ($P < 0.0005$) PANSS scores than was observed with placebo. Importantly, these results have been replicated in a similar study conducted by Usall et al. [70], who observed significant improvements in all PANSS subscales in postmenopausal women treated with adjunctive raloxifene compared to placebo ($P < 0.05$). These findings are also consistent with a small, earlier study by Good et al. [71] who found that hormone replacement therapy in postmenopausal women with a psychotic disorder led to a significant improvement in negative symptoms over six months. Furthermore, other researchers have also reported significant improvements in elements of neuropsychological and cognitive performance for women with schizophrenia treated with oestradiol as compared to placebo [72, 73].

While some other studies [74, 75] have failed to detect a benefit of adjunctive oestrogen over placebo in the management of schizophrenia, these results should be interpreted with caution. For example, Louzã et al. [74] administered conjugated oestrogens to their participants, as opposed to 17-b-oestradiol, while Bergemann et al. [75] administered oestradiol in conjunction with a synthetic progestin. Conjugated oestrogens do not share the same potency as 17-b-oestradiol in the brain, while administration of a progestin in combination with oestradiol is often believed to attenuate any positive effects of oestradiol on mental state [2, 9], which could explain the negative findings in these studies.

7. Other Hormones

Subsequent to the ever-expanding knowledge base on the CNS effects of oestrogen, interest in other neuroactive steroids with neuromodulatory properties and therapeutic potential has intensified [76].

The relationship between androgens and mental state seems particularly complicated. Animal evidence suggests that testosterone may be propsychotic, given that administration of testosterone significantly enhanced an NMDA antagonist-induced psychotic state in OVX rats [34]; however most of the research to date into androgens and mental state has focused on the testosterone precursors dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEA-S). DHEA(S) is neuroprotective in the rodent brain [77], and differences in DHEA(S) blood levels between psychotic patients and healthy controls are widely reported; however the direction of these differences is far from consistent [78]. Results from clinical studies trialling DHEA(S) as an augmentation strategy have been similarly contradictory, with some studies finding a modest treatment effect and others reporting no superiority over placebo [78]. Further research is needed.

Pregnenolone and its metabolites pregnenolone sulfate and allopregnanolone seem more promising. In addition to also possessing neuromodulatory and neuroprotective properties, these neurosteroids exert positive effects in rodent models of cognition and psychosis [79]. Serum levels of pregnenolone have been found to be lower in patients with schizophrenia than in healthy controls, and antipsychotic medications significantly increase pregnenolone levels in the brain [78]. A review of three small pilot studies investigating pregnenolone as an adjunctive intervention for patients with schizophrenia reports that pregnenolone was able to improve psychotic and cognitive symptoms [79], demonstrating the exciting potential of this compound. Similarly, progesterone itself has come under scrutiny in the topic of psychotic illness given that, like oestradiol, levels fluctuate throughout the

menstrual cycle and drop dramatically after partum. Some researchers have found lower plasma progesterone levels in schizophrenia patients compared to healthy controls [80], while many others report antipsychotic-like properties of progesterone in behavioural paradigms of psychosis [81], in both animals [82] and humans [83].

Most recently, oxytocin has also emerged as possibly influencing mental state after one study found that higher peripheral oxytocin levels were associated with decreased symptom severity in women with chronic schizophrenia [17], and another study demonstrated efficacy of intranasal oxytocin as an adjunctive therapy in a randomised, crossover sample of fifteen schizophrenia patients [84].

8. Discussion

The oestrogen protection hypothesis and hypothesis of hypoestrogenism may have important implications for clinical practice, especially in the area of women's mental health.

To begin with, the clinician must be aware of the possibility of an exacerbation or new onset of psychotic illness during the perimenopause, especially in women with a history of deteriorations in mental state during the menstrual cycle or puerperium, as such women seem to be particularly vulnerable to fluctuations in the hormonal milieu. It is these women who might benefit most from oestrogen augmentation therapy, especially considering the additional benefits of oestrogen replacement during the menopause. This clinical scenario is illustrated poignantly in the case of Miss R, detailed earlier.

While oestrogen has proven neuroprotective and antipsychotic effects, its long-term safety for use as an adjunctive treatment in schizophrenia is unclear given its stimulating effects on peripheral tissues such as the breast and endometrium [85]. Hence recent research into SERMs is particularly important. SERMs have been found to share the neuroprotective and neuromodulatory actions of oestradiol in the CNS [42, 86] but have tissue-specific effects on peripheral oestrogen receptors [87]. Raloxifene, for example, has agonist actions in the brain but antagonist actions in the breast and endometrium [85], and the first clinical evidence of raloxifene's potential as a safe and effective augmentation therapy in women with schizophrenia is beginning to emerge [69, 70].

Finding safe and effective treatments to augment antipsychotic medication and thus minimise their dosage is particularly important in women being treated for schizophrenia. Women are more susceptible to antipsychotic-induced hyperprolactinaemia, which can result in serious sequelae such as early menopause, osteoporosis, and perhaps even breast cancer [9, 88]. Raloxifene could thus be an ideal option for augmentation considering that it actually preserves bone density and has anticancer properties in breast tissue.

Finally, that oestrogen has been shown in multiple studies to significantly improve general psychopathologic symptoms such as depression, anxiety, insight, and cognition is of particular importance to the treatment of schizophrenia and not to be underestimated. Improvement in these domains independent of changes in psychotic symptomatology can dramatically improve a patient's quality of life, engagement in services, compliance with treatment, response to stressors, and overall psychosocial functioning [89].

9. Conclusion

The case of Miss R highlights the real clinical relevance and therapeutic potential of oestrogen in schizophrenia, lending credence to the theories discussed in this paper. Study of the complex relationship between hormones—in particular oestrogen—and neuropsychological functioning is a rapidly progressing field, and recent research has significantly enhanced our knowledge about the nature of the connection between oestrogen and schizophrenia. Oestrogen may be effective not only in treating the symptoms of schizophrenia but also in mediating the underlying neurochemical and neuropathological abnormalities; however more work needs to be done to determine the ideal delivery, dose, and duration of treatment to achieve this. Thus research into both the biological underpinnings of neuroactive steroids' mechanisms of action in the brain and the therapeutic potential of different hormonal compounds must persist, so clinical practice in the diagnosis and management of psychotic conditions can continue to evolve.

References

[1] E. Kraepelin, *Dementia Praecox and Paraphrenia. Psychiatrie: Ein Lehrbuch fur Studierende und Artze*, J. A. Barth, Leipzig, Germany, 4th edition, 1893.

[2] A. Riecher-Rossler and J. Kulkarni, "Estrogens and gonadal function in schizophrenia and related psychoses," *Current Topics in Behavioral Neurosciences*, vol. 8, pp. 155–171, 2011.

[3] A. Riecher-Rossler and H. Hafner, "Schizophrenia and oestrogens—is there an association?" *European Archives of Psychiatry and Clinical Neuroscience*, vol. 242, no. 6, pp. 323–328, 1993.

[4] J. Kulkarni, "Women and schizophrenia: a review," *Australian and New Zealand Journal of Psychiatry*, vol. 31, no. 1, pp. 46–56, 1997.

[5] M. V. Seeman, "Psychopathology in women and men: focus on female hormones," *American Journal of Psychiatry*, vol. 154, no. 12, pp. 1641–1647, 1997.

[6] H. Hafner, "Gender differences in schizophrenia," *Psychoneuroendocrinology*, vol. 28, supplement 2, pp. 17–54, 2003.

[7] H. Hafner, K. Maurer, W. Loffler et al., "The epidemiology of early schizophrenia. Influence of age and gender on onset and early course," *British Journal of Psychiatry*, vol. 164, no. 23, pp. 29–38, 1994.

[8] J. McGrath, S. Saha, D. Chant, and J. Welham, "Schizophrenia: a concise overview of incidence, prevalence, and mortality," *Epidemiologic Reviews*, vol. 30, no. 1, pp. 67–76, 2008.

[9] J. A. Markham, "Sex steroids and schizophrenia," *Reviews in Endocrine & Metabolic Disorders*. In press.

[10] K. M. Abel, R. Drake, and J. M. Goldstein, "Sex differences in schizophrenia," *International Review of Psychiatry*, vol. 22, no. 5, pp. 417–428, 2010.

[11] V. A. Morgan, D. J. Castle, and A. V. Jablensky, "Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian national study of

low prevalence (Psychotic) disorders," *Australian and New Zealand Journal of Psychiatry*, vol. 42, no. 1, pp. 74–82, 2008.

[12] S. M. Cotton, M. Lambert, B. G. Schimmelmann et al., "Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis," *Schizophrenia Research*, vol. 114, no. 1–3, pp. 17–24, 2009.

[13] A. Riecher-Rossler, "Oestrogen effects in schizophrenia and their potential therapeutic implications—review," *Archives of Women's Mental Health*, vol. 5, no. 3, pp. 111–118, 2002.

[14] P. Boyce and E. Barriball, "Puerperal psychosis," *Archives of Women's Mental Health*, vol. 13, no. 1, pp. 45–47, 2010.

[15] G. Krafft-Ebing, "Untersuchungen über Irresein zur Zeit der Menstruation: ein klinischer Beitrag zur Lehre vom periodischen Irresein," *Archiv für Psychiatrie und Nervenkrankheiten*, vol. 8, no. 1, pp. 65–107, 1896.

[16] N. Bergemann, P. Parzer, B. Runnebaum, F. Resch, and C. Mundt, "Estrogen, menstrual cycle phases, and psychopathology in women suffering from schizophrenia," *Psychological Medicine*, vol. 37, no. 10, pp. 1427–1436, 2007.

[17] L. H. Rubin, C. S. Carter, L. Drogos, H. Pournajafi-Nazarloo, J. A. Sweeney, and P. M. Maki, "Peripheral oxytocin is associated with reduced symptom severity in schizophrenia," *Schizophrenia Research*, vol. 124, no. 1–3, pp. 13–21, 2010.

[18] Y. H. Ko, S. H. Joe, W. Cho et al., "Estrogen, cognitive function and negative symptoms in female schizophrenia," *Neuropsychobiology*, vol. 53, no. 4, pp. 169–175, 2006.

[19] S. H. Choi, S. B. Kang, and S. H. Joe, "Changes in premenstrual symptoms in women with schizophrenia: a prospective study," *Psychosomatic Medicine*, vol. 63, no. 5, pp. 822–829, 2001.

[20] V. Mahe and A. Dumaine, "Oestrogen withdrawal associated psychoses," *Acta Psychiatrica Scandinavica*, vol. 104, no. 5, pp. 323–331, 2001.

[21] G. Fink, B. E. Sumner, R. Rosie, O. Grace, and J. P. Quinn, "Estrogen control of central neurotransmission: effect on mood, mental state, and memory," *Cellular and Molecular Neurobiology*, vol. 16, no. 3, pp. 325–344, 1996.

[22] Z. A. Hughes, F. Liu, K. Marquis et al., "Estrogen receptor neurobiology and its potential for translation into broad spectrum therapeutics for CNS disorders," *Current Molecular Pharmacology*, vol. 2, no. 3, pp. 215–236, 2009.

[23] G. J. ter Horst, "Estrogen in the limbic system," *Vitamins and hormones*, vol. 82, pp. 319–338, 2010.

[24] R. Cosimo Melcangi and L. M. Garcia-Segura, "Sex-specific therapeutic strategies based on neuroactive steroids: in search for innovative tools for neuroprotection," *Hormones and Behavior*, vol. 57, no. 1, pp. 2–11, 2010.

[25] J. Gonzalez-Maeso, R. L. Ang, T. Yuen et al., "Identification of a serotonin/glutamate receptor complex implicated in psychosis," *Nature*, vol. 452, no. 7183, pp. 93–97, 2008.

[26] M. G. Sanchez, M. Bourque, M. Morissette, and T. Di Paolo, "Steroids-dopamine interactions in the pathophysiology and treatment of cns disorders," *CNS Neuroscience and Therapeutics*, vol. 16, no. 3, pp. e43–e71, 2010.

[27] J. Horacek, V. Bubenikova-Valesova, M. Kopecek et al., "Mechanism of action of atypical antipsychotic drugs and the neurobiology of schizophrenia," *CNS Drugs*, vol. 20, no. 5, pp. 389–409, 2006.

[28] G. T. Taylor, S. Maloney, J. Dearborn, and J. Weiss, "Hormones in the mentally disturbed brain: steroids and peptides in the development and treatment of psychopathology," *Central Nervous System Agents in Medicinal Chemistry*, vol. 9, no. 4, pp. 331–360, 2009.

[29] C. Chavez, M. Hollaus, E. Scarr, G. Pavey, A. Gogos, and M. van den Buuse, "The effect of estrogen on dopamine and serotonin receptor and transporter levels in the brain: an autoradiography study," *Brain Research*, vol. 1321, pp. 51–59, 2010.

[30] S. Lokuge, B. N. Frey, J. A. Foster, C. N. Soares, and M. Steiner, "The rapid effects of estrogen: a mini-review," *Behavioural Pharmacology*, vol. 21, no. 5-6, pp. 465–472, 2010.

[31] V. Bubenikova-Valesova, J. Horacek, M. Vrajova, and C. Hoschl, "Models of schizophrenia in humans and animals based on inhibition of nmda receptors," *Neuroscience & Biobehavioral Reviews*, vol. 32, no. 5, pp. 1014–1023, 2008.

[32] M. M. Adams, S. E. Fink, W. G. Janssen, R. A. Shah, and J. H. Morrison, "Estrogen modulates synaptic N-methyl-D-aspartate receptor subunit distribution in the aged hippocampus," *Journal of Comparative Neurology*, vol. 474, no. 3, pp. 419–426, 2004.

[33] A. Gogos, P. Kwek, C. Chavez, and M. van den Buuse, "Estrogen treatment blocks 8-hydroxy-2-dipropylaminotetralinand apomorphine-induced disruptions of prepulse inhibition: involvement of dopamine D_1 or D_2 or serotonin 5-HT_{1A}, 5-HT_{2A}, or 5-HT_7 receptors," *Journal of Pharmacology and Experimental Therapeutics*, vol. 333, no. 1, pp. 218–227, 2010.

[34] A. Gogos, P. Kwek, and M. van den Buuse, "The role of estrogen and testosterone in female rats in behavioral models of relevance to schizophrenia," *Psychopharmacology*, vol. 219, no. 1, pp. 213–224, 2012.

[35] M. Arad and I. Weiner, "Contrasting effects of increased and decreased dopamine transmission on latent inhibition in ovariectomized rats and their modulation by 17β-estradiol: an animal model of menopausal psychosis?" *Neuropsychopharmacology*, vol. 35, pp. 1570–1582, 2010.

[36] M. Arad and I. Weiner, "Sex-dependent antipsychotic capacity of 17β-estradiol in the latent inhibition model: a typical antipsychotic drug in both sexes, atypical antipsychotic drug in males," *Neuropsychopharmacology*, vol. 35, no. 11, pp. 2179–2192, 2010.

[37] S. Iritani, "Neuropathology of schizophrenia: a mini review," *Neuropathology*, vol. 27, no. 6, pp. 604–608, 2007.

[38] M. E. Shenton, C. C. Dickey, M. Frumin, and R. W. McCarley, "A review of MRI findings in schizophrenia," *Schizophrenia Research*, vol. 49, no. 1-2, pp. 1–52, 2001.

[39] A. Fornito, M. Yucel, and C. Pantelis, "Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder," *Current Opinion in Psychiatry*, vol. 22, no. 3, pp. 312–319, 2009.

[40] N. C. Andreasen and R. Pierson, "The role of the cerebellum in schizophrenia," *Biological Psychiatry*, vol. 64, no. 2, pp. 81–88, 2008.

[41] L. A. Flashman and M. F. Green, "Review of cognition and brain structure in schizophrenia: profiles, longitudinal course, and effects of treatment," *Psychiatric Clinics of North America*, vol. 27, no. 1, pp. 1–18, 2004.

[42] M. A. Arevalo, M. Santos-Galindo, N. Lagunas, I. Azcoitia, and L. M. Garcia-Segura, "Selective estrogen receptor modulators as brain therapeutic agents," *Journal of Molecular Endocrinology*, vol. 46, no. 1, pp. R1–R9, 2011.

[43] M. A. Arevalo, M. Santos-Galindo, M. J. Bellini, I. Azcoitia, and L. M. Garcia-Segura, "Actions of estrogens on glial cells: implications for neuroprotection," *Biochimica et Biophysica Acta*, vol. 1800, no. 10, pp. 1106–1112, 2010.

[44] D. N. Bryant and D. M. Dorsa, "Roles of estrogen receptors alpha and beta in sexually dimorphic neuroprotection against

glutamate toxicity," *Neuroscience*, vol. 170, no. 4, pp. 1261–1269, 2010.

[45] C. Behl, "Estrogen can protect neurons: modes of action," *Journal of Steroid Biochemistry and Molecular Biology*, vol. 83, no. 1–5, pp. 195–197, 2002.

[46] M. L. Rao and H. Kolsch, "Effects of estrogen on brain development and neuroprotection—implications for negative symptoms in schizophrenia," *Psychoneuroendocrinology*, vol. 28, supplement 2, pp. 83–96, 2003.

[47] L. C. Yang, Q. G. Zhang, C. F. Zhou et al., "Extranuclear estrogen receptors mediate the neuroprotective effects of estrogen in the rat hippocampus," *Plos One*, vol. 5, no. 5, Article ID e9851, 2010.

[48] J. Li, M. Siegel, M. Yuan et al., "Estrogen enhances neurogenesis and behavioral recovery after stroke," *Journal of Cerebral Blood Flow and Metabolism*, vol. 31, no. 2, pp. 413–425, 2011.

[49] M. Liu, M. H. Kelley, P. S. Herson, and P. D. Hurn, "Neuroprotection of sex steroids," *Minerva Endocrinologica*, vol. 35, no. 2, pp. 127–143, 2010.

[50] L. M. Garcia-Segura, I. Azcoitia, and L. L. DonCarlos, "Neuroprotection by estradiol," *Progress in Neurobiology*, vol. 63, no. 1, pp. 29–60, 2001.

[51] J. W. Simpkins, K. D. Yi, S. H. Yang, and J. A. Dykens, "Mitochondrial mechanisms of estrogen neuroprotection," *Biochimica et Biophysica Acta*, vol. 1800, no. 10, pp. 1113–1120, 2010.

[52] G. T. Rezin, G. Amboni, A. I. Zugno, J. Quevedo, and E. L. Streck, "Mitochondrial dysfunction and psychiatric disorders," *Neurochemical Research*, vol. 34, no. 6, pp. 1021–1029, 2009.

[53] E. Kretschmer, *Körperbau und Charakter. Untersuchungen zum Konstitutionsproblem und zur Lehre von den Temperamenten*, Berlin, Germany, 1921.

[54] Y. Kaneda and T. Ohmori, "Relation between estradiol and negative symptoms in men with schizophrenia," *Journal of Neuropsychiatry and Clinical Neurosciences*, vol. 17, no. 2, pp. 239–242, 2005.

[55] T. J. Huber, C. Tettenborn, E. Leifke, and H. M. Emrich, "Sex hormones in psychotic men," *Psychoneuroendocrinology*, vol. 30, no. 1, pp. 111–114, 2005.

[56] G. A. Maguire, "Prolactin elevation with antipsychotic medications: mechanisms of action and clinical consequences," *Journal of Clinical Psychiatry*, vol. 63, supplement 4, pp. 56–62, 2002.

[57] C. Rivier and S. Rivest, "Effect of stress on the activity of the hypothalamic-pituitary-gonadal axis: peripheral and central mechanisms," *Biology of Reproduction*, vol. 45, no. 4, pp. 523–532, 1991.

[58] T. J. Huber, J. Rollnik, J. Wilhelms, A. Von Zur Mühlen, H. M. Emrich, and U. Schneider, "Estradiol levels in psychotic disorders," *Psychoneuroendocrinology*, vol. 26, no. 1, pp. 27–35, 2001.

[59] A. Riecher-Rossler, H. Hafner, A. Dutsch-Strobel, and M. Stumbaum, "Gonadal function and its influence on psychopathology," *Archives of Women's Mental Health*, vol. 1, no. 1, pp. 15–26, 1998.

[60] A. Riecher-Rossler, H. Hafner, M. Stumbaum, K. Maurer, and R. Schmidt, "Can estradiol modulate schizophrenic symptomatology?" *Schizophrenia Bulletin*, vol. 20, no. 1, pp. 203–214, 1994.

[61] N. Maric, V. Popovic, M. Jasovic-Gasic, N. Pilipovic, and J. Van Os, "Cumulative exposure to estrogen and psychosis: a peak bone mass, case-control study in first-episode psychosis," *Schizophrenia Research*, vol. 73, no. 2-3, pp. 351–355, 2005.

[62] N. Bergemann, C. Mundt, P. Parzer et al., "Plasma concentrations of estradiol in women suffering from schizophrenia treated with conventional versus atypical antipsychotics," *Schizophrenia Research*, vol. 73, no. 2-3, pp. 357–366, 2005.

[63] C. M. Canuso, J. M. Goldstein, J. Wojcik et al., "Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder," *Psychiatry Research*, vol. 111, no. 1, pp. 11–20, 2002.

[64] W. L. Chua, S. A. de Izquierdo, J. Kulkarni, and A. Mortimer, "Estrogen for schizophrenia," *Cochrane Database of Systematic Reviews*, no. 4, Article ID CD004719, 2005.

[65] A. M. Mortimer, "Relationship between estrogen and schizophrenia," *Expert Review of Neurotherapeutics*, vol. 7, no. 1, pp. 45–55, 2007.

[66] J. Kulkarni, A. de Castella, P. B. Fitzgerald et al., "Estrogen in severe mental illness: a potential new treatment approach," *Archives of General Psychiatry*, vol. 65, no. 8, pp. 955–960, 2008.

[67] S. Akhondzadeh, A. A. Nejatisafa, H. Amini et al., "Adjunctive estrogen treatment in women with chronic schizophrenia: a double-blind, randomized, and placebo-controlled trial," *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, vol. 27, no. 6, pp. 1007–1012, 2003.

[68] J. Kulkarni, A. de Castella, B. Headey et al., "Estrogens and men with schizophrenia: is there a case for adjunctive therapy?" *Schizophrenia Research*, vol. 125, no. 2-3, pp. 278–283, 2011.

[69] J. Kulkarni, C. Gurvich, S. J. Lee et al., "Piloting the effective therapeutic dose of adjunctive selective estrogen receptor modulator treatment in postmenopausal women with schizophrenia," *Psychoneuroendocrinology*, vol. 35, no. 8, pp. 1142–1147, 2010.

[70] J. Usall, E. Huerta-Ramos, R. Iniesta et al., "Raloxifene as an adjunctive treatment for postmenopausal women with schizophrenia: a double-blind, randomized, placebo-controlled trial," *Journal of Clinical Psychiatry*, vol. 72, no. 11, pp. 1552–1557, 2011.

[71] K. P. Good, L. C. Kopala, J. S. Martzke et al., "Hormone replacement therapy in postmenopausal women with schizophrenia: preliminary findings," *Schizophrenia Research*, vol. 12, no. 3, p. 131, 1999.

[72] N. Bergemann, P. Parzer, S. Jaggy, B. Auler, C. Mundt, and S. Maier-Braunleder, "Estrogen and comprehension of metaphoric speech in women suffering from schizophrenia: results of a double-blind, placebo-controlled trial," *Schizophrenia Bulletin*, vol. 34, no. 6, pp. 1172–1181, 2008.

[73] Y. H. Ko, S. H. Joe, W. Cho et al., "Effect of hormone replacement therapy on cognitive function in women with chronic schizophrenia," *International Journal of Psychiatry in Clinical Practice*, vol. 10, no. 2, pp. 97–104, 2006.

[74] M. R. Louzã, A. P. Marques, H. Elkis, D. Bassitt, M. Diegoli, and W. F. Gattaz, "Conjugated estrogens as adjuvant therapy in the treatment of acute schizophrenia: a double-blind study," *Schizophrenia Research*, vol. 66, no. 2-3, pp. 97–100, 2004.

[75] N. Bergemann, C. Mundt, P. Parzer et al., "Estrogen as an adjuvant therapy to antipsychotics does not prevent relapse in women suffering from schizophrenia: results of a placebo-controlled double-blind study," *Schizophrenia Research*, vol. 74, no. 2-3, pp. 125–134, 2005.

[76] R. C. Melcangi, G. Panzica, and L. M. Garcia-Segura, "Neuroactive steroids: focus on human brain," *Neuroscience*, vol. 191, pp. 1–5, 2011.

[77] N. Maninger, O. M. Wolkowitz, V. I. Reus, E. S. Epel, and S. H. Mellon, "Neurobiological and neuropsychiatric effects

of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS)," *Frontiers in Neuroendocrinology*, vol. 30, no. 1, pp. 65–91, 2009.

[78] M. S. Ritsner, "The clinical and therapeutic potentials of dehydroepiandrosterone and pregnenolone in schizophrenia," *Neuroscience*, vol. 191, no. 1, pp. 91–100, 2011.

[79] C. E. Marx, D. W. Bradford, R. M. Hamer et al., "Pregnenolone as a novel therapeutic candidate in schizophrenia: emerging preclinical and clinical evidence," *Neuroscience*, vol. 191, pp. 78–90, 2011.

[80] M. Taherianfard and M. Shariaty, "Evaluation of serum steroid hormones in schizophrenic patients," *Indian Journal of Medical Sciences*, vol. 58, no. 1, pp. 3–9, 2004.

[81] E. M. MacKenzie, J. Odontiadis, J. M. Le Mellédo, T. I. Prior, and G. B. Baker, "The relevance of neuroactive steroids in schizophrenia, depression, and anxiety disorders," *Cellular and Molecular Neurobiology*, vol. 27, no. 5, pp. 541–574, 2007.

[82] R. Rupprecht, M. Koch, A. Montkowski et al., "Assessment of neuroleptic-like properties of progesterone," *Psychopharmacology*, vol. 143, no. 1, pp. 29–38, 1999.

[83] V. Kumari, J. Konstantinou, A. Papadopoulos et al., "Evidence for a role of progesterone in menstrual cycle-related variability in prepulse inhibition in healthy young women," *Neuropsychopharmacology*, vol. 35, no. 4, pp. 929–937, 2010.

[84] D. Feifel, K. MacDonald, A. Nguyen et al., "Adjunctive intranasal oxytocin reduces symptoms in schizophrenia patients," *Biological Psychiatry*, vol. 68, no. 7, pp. 678–680, 2010.

[85] H. U. Bryant, "Selective estrogen receptor modulators," *Reviews in Endocrine and Metabolic Disorders*, vol. 3, no. 3, pp. 231–241, 2002.

[86] M. T. Littleton-Kearney, N. L. Ostrowski, D. A. Cox, M. I. Rossberg, and P. D. Hurn, "Selective estrogen receptor modulators: tissue actions and potential for CNS protection," *CNS Drug Reviews*, vol. 8, no. 3, pp. 309–330, 2002.

[87] L. L. DonCarlos, I. Azcoitia, and L. M. Garcia-Segura, "Neuroprotective actions of selective estrogen receptor modulators," *Psychoneuroendocrinology*, vol. 34, supplement 1, pp. S113–S122, 2009.

[88] J. Kulkarni, "Special issues in managing long-term mental illness in women," *International Review of Psychiatry*, vol. 22, no. 2, pp. 183–190, 2010.

[89] A. Hofer, G. Kemmler, U. Eder, M. Edlinger, M. Hummer, and W. W. Fleischhacker, "Quality of life in schizophrenia: the impact of psychopathology, attitude toward medication, and side effects," *Journal of Clinical Psychiatry*, vol. 65, no. 7, pp. 932–939, 2004.

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Clinical Study

Progesterone and Cerebral Function during Emotion Processing in Men and Women with Schizophrenia

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Schizophrenia has been associated with disturbed levels of sex-steroid hormones, including estrogen and testosterone. In the present study we have examined the implication of a less studied hormone progesterone. Forty-three patients with schizophrenia (21 women) and 43 control participants (21 women) underwent functional MRI while viewing emotionally positive, negative, and neutral images. Blood samples were taken prior to the scanning session to evaluate progesterone levels. Simple regression analyses between levels of progesterone and brain activations associated with emotion processing were performed using SPM5. A positive correlation was found between progesterone levels and brain activations during processing of emotionally charged images in both healthy and schizophrenia men, but no significant relationship was revealed in women. These preliminary results indicate that progesterone is significantly associated with brain activations during processing of positive and negative affect in healthy and schizophrenia men, but not in women. Further investigation is warranted.

1. Introduction

There is some evidence of a relationship between sex-steroid hormones (i.e., estrogen, testosterone, and less commonly progesterone) and emotion processing in the general population [1–3]. Fluctuations in estrogen and progesterone have been linked with increased vulnerability to mood disorders in women, while elevated levels of testosterone have been primarily associated with antisocial behaviours, behaviours of dominance, and aggressiveness in both men and women [4]. In schizophrenia, some studies have found abnormal levels of estrogens and testosterone in patients, but the results have been equivocal and sometimes attributed to the antipsychotic-induced hyperprolactinemia, which may alter levels of gonadal hormones [5]. Despite numerous studies and clinical observations of lower relapse of clinical symptoms during pregnancy, high relapse postpartum, and the fluctuation of symptoms across the menstrual cycle (attributed typically to the changing levels of estrogens), a link between progesterone and affect in schizophrenia has yet to be examined [6].

The little emphasis that has been placed on the relationship between progesterone and emotional functioning has been explored primarily in healthy women because this hormone is a female reproductive hormone. Nonetheless, it is produced in both men and women, and recent evidence suggests that it is implicated in brain function of both sexes. Thus, progesterone has been shown to play an important role in mood regulation [7], cognition [8], inflammation, mitochondrial function, neurogenesis and regeneration, myelination, and recovery from traumatic brain injury in both men and women [9].

The goal of the present study was to explore progesterone's implication in neural correlates of emotion processing in both healthy and schizophrenia men and women.

2. Methods

2.1. Subjects. Forty-three schizophrenia patients (22 men, 21 women) meeting the DSM-IV criteria for schizophrenia [10], in a stable phase of their illness and 43 healthy controls

(22 men, 21 women) participated in the study. The groups were matched for age, handedness (Edinburgh Inventory) [11], and parental socioeconomic status (National Occupational Classification; NOC) [12] (Table 1).

All patients were reevaluated by experienced psychiatrists before being assigned to the research group (DSM-IV, criteria A-E); affective, schizoaffective and schizophreniform psychoses were excluded. Control participants were screened with the nonpatients edition of the Clinical Interview for DSM-IV (SCID) [13].

Symptom severity was rated according to the positive and negative syndrome scale (PANSS) [14]. Illness onset was defined as the date of the first psychiatric consultation. All the patients received at least one atypical antipsychotic (28 patients received one and 15 received two; clozapine: $n = 20$, mean dosage = 413,16 mgs ± 107,77 mgs; olanzapine: $n = 12$, mean dosage = 14.58 mgs ± 5.41 mgs; risperidone: $n = 15$, mean dosage = 3.14 ± 1.67 mgs; quetiapine: $n = 9$, mean dosage = 486,11 mgs ± 274.75 mgs; ziprasidone: $n = 2$, mean dosage = 166,65 mgs ± 47,14 mgs). All antipsychotic doses were calculated according to chlorpromazine equivalence [15].

General exclusion criteria included age below 18 or above 45 years, past or present neurological or Axis-I psychiatric disorder, alcoholism or drug abuse, noncompliance with testing procedures, abnormal uncorrected vision or any contraindication for MRI such as a cardiac pacemaker, an aneurysm clip, a metal prostheses, or cardiac valve replacement, the presence of metal in an eye or any part of the body, certain dental work, or claustrophobia.

In agreement with the Declaration of Helsinki, written informed consent was obtained prior to participation in the experiment. The ability of schizophrenia patients to give informed consent was established using the guidelines of the Canadian Psychiatric Association. The study was approved by the ethics committees of the Fernand-Seguin Research Center of the Louis-H Lafontaine Hospital and the Regroupement Neuroimagerie Québec.

2.2. Experimental Procedure. All participants underwent a functional magnetic resonance imaging (*fMRI*) scan during passively viewing blocks of emotionally positive, negative, and neutral pictures. The stimuli were selected from the International Affective Picture System (IAPS) [16] based on normative valence and arousal ratings, and images from each valence category (negative, positive, and neutral) were matched for content (e.g., people, animals, and landscapes). This task consisted of 48.5-second blocks of emotionally positive, negative, or neutral pictures and 16-second periods of rest separating the blocks from one another. Each block contained 10 images and was repeated 4 times. Each picture appeared for 3000 ms followed by a blank screen with a fixation point for an average of 1.75 s (ranging from 1 to 2.5 s and giving an average interstimulus interval (ISI) of 4.75 s). To assess the participants subjective emotional responses to the presented images, immediately at the end of the *fMRI* session, participants were represented with the images of each block and were asked to rate the block of images as whole on a scale ranging from 0 (absence of any emotional reaction) to 8 (strongest emotion ever felt in one's lifetime).

A blood sample of 10 mL was taken approximately 30 minutes prior to each scanning session to evaluate the levels of progesterone in all participants. The sample was immediately centrifuged and the serum separated. The samples were stored (−40 C) and later transported and analyzed at the laboratory of Maisonneuve-Rosemont Hospital. Serum levels of estradiol and progesterone were determined using the automated chemiluminescence assay system (SYNCHRON LXi 725, Beckman Coulter, USA). The analytical sensitivity was 0.08 ng/mL and dynamic range: 0.08–40.0 ng/mL.

2.3. fMRI Data Acquisition and Analysis. Blood-oxygenated dependent level (BOLD) signals were recorded using a single-shot, gradient-recalled echoplanar imaging sequence [repetition time (TR) = 3000 ms, echo time (TE) = 30 ms, flip angle = 90 degrees, matrix 64 × 64 voxels] on a MRI Siemens TRIO system at 3.0 Tesla, which is operational at the Functional Neuroimaging Unit at the University of Montreal Geriatric Institute.

The *fMRI* data were analyzed using statistical parametric mapping software (SPM5; Wellcome Department of Cognitive Neurology, London, UK) according to methods outlined by Friston and colleagues [17]. Functional images were realigned to the mean volume of each session to correct for artifacts due to subject motion, were spatially normalized into the standardized brain template (voxel size: 3.5 mm × 3.5 mm × 3.5 mm), and were spatially smoothed with a three-dimensional isotropic Gaussian kernel (12 mm FWHM) to improve the signaltonoise ratio.

Statistical analyses were carried out using a standard peak-detection approach and the general linear model implemented in SPM5 to identify the dynamic cerebral changes associated with emotional processing task. First, *fMRI* data of each participant was analyzed using a fixed-effects model to investigate individual brain activation maps and to contrast the brain activity associated with different contrasts. The fixed-effects analysis produced individual contrast images that were then used as raw data for the implementation of a random-effects model to investigate the pattern of activations during the different emotional contrasts (positive minus neutral and negative minus neutral) in each group (i.e., healthy men, healthy women, schizophrenia men, and schizophrenia women). We further examined potential differences between groups (healthy controls minus schizophrenia patients) as well as between groups within the same sex (e.g., activations in healthy women minus activations in schizophrenia women, etc.) using a two-sample t-test. Due to the strict character of the second-level analysis based on a random-effects model, the statistical maps were threshold at a level of $P = 0.005$ uncorrected for multiple comparisons.

To assess correlations between progesterone and brain function, second-level regression analyses were performed in SPM5. Progesterone levels were entered as covariates of interest. These were correlated with brain function during the processing of negative and positive images separately. The

Table 1: Sociodemographic and clinical characteristics.

	Subjects with schizophrenia		Normal control subjects	
	Women ($N = 21$)	Men ($N = 22$)	Women ($N = 21$)	Men ($N = 22$)
Age (years) (mean and SD)	32.86 (6.56)	31.36 (7.36)	29.28 (9.27)	30.55 (7.81)
Parental SES (mean and SD)	2.54 (1.05)	2.79 (0.75)	2.08 (1.10)	2.43 (1.11)
Handedness, no. right (%) (mean and SD)	21 (86.15)	18 (60.47)	21 (65.39)	18 (54.36)
Age at onset (mean and SD)	24.29 (6.14)	20.38 (3.90)**		
Duration of Illness years (mean and SD)	8.14 (5.66)	10.95 (7.64)		
Chlorpromazine equivalents, mg (mean and SD)	467.06 (292.26)	693.18 (378.41)**		
PANSS positive (mean and SD)	19.32 (7.82)	18.18 (5.51)		
PANSS negative (mean and SD)	20.14 (8.69)	20.09 (5.45)		
PANSS general (mean and SD)	42.27 (12.72)	39.32 (6.02)		
Subjective rating positive (mean and SD)	4.75 (1.20)	4.95 (1.35)	5.06 (0.95)	4.38 (1.15)
Subjective rating negative (mean and SD)	5.14 (1.24)	5.36 (1.17)	5.75 (0.58)	5.04 (1.06)

** Significant $P < 0.05$.

threshold level for statistical significance was set at a $P = 0.001$ corrected for multiple comparisons using the small volume correction (SVC) with the sphere volume function in SPM5 (radius = 12 mm). These correlations were done for healthy and schizophrenia men and women separately at the whole-brain level.

The demographic and clinical data were analyzed with the statistical package for the social sciences (SPSS), version 15.0. To examine ratings of emotional stimuli and recognition accuracy we conducted a repeated measures ANOVA with image type (i.e., NEG and POS) as a within-subject factor and diagnostic group and sex as between-subject factors. Where group or stimulus effects were detected the source of these effects was further investigated using post hoc t-tests.

3. Results

3.1. Stimulus Rating. ANOVA revealed no main effect or group or sex and no significant interaction between the two variables (Table 1).

3.2. fMRI—Between-Group Comparisons. Individuals with schizophrenia showed decreased activations in the left lingual gyrus ($z = 3.28$, $k = 63$, $P = 0.001$) relative to healthy subjects during the processing of positive emotions. No significant group differences were observed during negative emotion processing.

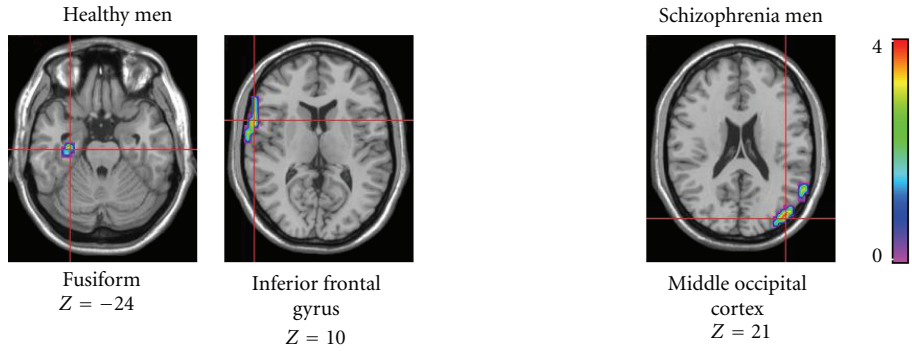
With regards to sex differences, schizophrenia women showed decreased brain activity in bilateral cuneus ($z = 3.23$, $k = 493$, BA = 18, $P = 0.001$), left lingual gyrus ($z = 3.14$, $k = 493$, BA = 19, $P = 0.001$), and right cerebellum ($z = 3.04$, $k = 12$, $P = 0.001$) relative to healthy women during the processing of positive emotion processing. No significant differences between healthy and schizophrenia women were observed during negative emotion processing. No significant differences were observed between healthy and schizophrenia men during the processing of positive or negative emotion.

3.3. fMRI—Correlations between Positive Emotion and Progesterone. Analysis in healthy men revealed a positive correlation between progesterone levels and brain activations in the left fusiform gyrus ($z = 3.07$, $k = 8$, BA = 36, $P = 0.044$) and a trend in the inferior fontal gyrus ($z = 3.00$, $k = 58$, BA = 44, $P = 0.05$) (Figure 1). In schizophrenia men, a positive correlation was observed in the middle occipital cortex ($z = 3.16$, $k = 76$, BA = 19, $P = 0.01$). No significant relationship was observed in either healthy or schizophrenia women.

3.4. fMRI—Correlations between Negative Emotion and Progesterone. In healthy men, there was a positive correlation between progesterone levels and brain activations in the middle orbitofrontal cortex ($z = 3.25$, $k = 40$, BA = 10, $P = 0.034$), superior orbitofrontal cortex ($z = 3.12$, $k = 40$, BA = 11, $P = 0.041$), and a trend was observed in the precentral gyrus ($z = 2.99$, $k = 15$, BA = 6, $P = 0.064$) (Figure 2). No significant relationship between brain function and progesterone levels was seen in healthy women, schizophrenia women, or schizophrenia men.

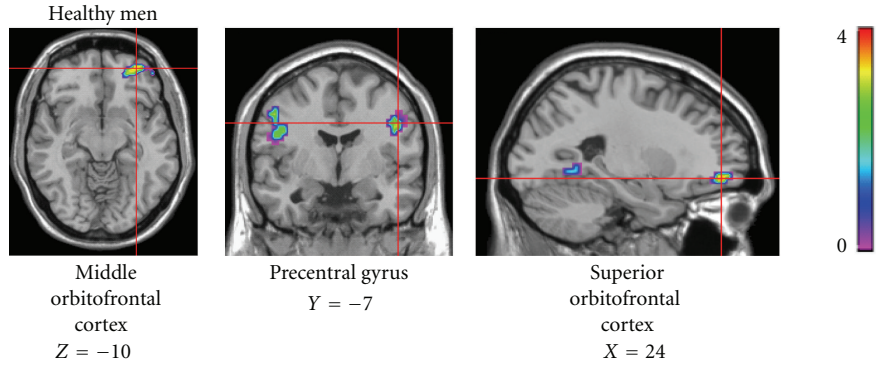
4. Conclusion

To our knowledge, this is the first investigation of progesterone's implication in neural circuitry underlying emotional processing in men and women with schizophrenia. First, however, we had to establish if there were any between-group differences in cerebral activations during viewing of emotional stimuli. The direct comparison between schizophrenia patients and healthy controls revealed only limited differences: relatively less activation in the left lingual gyrus in the patient group during positive condition and no group differences in the negative condition. When we separated the groups by sex, we found that it was women with schizophrenia who demonstrated decreased activity during the positive condition in the posterior cortex, bilateral cuneus, left lingual gyrus, and right cerebellum. Although



The coordinate refers to the MNI space, and the coordinate included underneath the image refers to slice of the brain presented (x for sagittal, y for coronal, and z for axial). The color scale represents the z-scores values.

Figure 1: Correlation between progesterone levels and brain activations during processing of positive images.



The coordinate refers to the MNI space, and the coordinate included underneath the image refers to slice of the brain presented (x for sagittal, y for coronal, and z for axial). The color scale represents the z-scores values.

Figure 2: Correlation between progesterone levels and brain activations during processing of negative images.

these differentially activated regions are not considered to be the core centers of emotion processing, the occipital cortex has been frequently activated during visual emotional tasks [18], while activations in the cerebellum have been reported during the induction of feelings of sadness, anxiety [19, 20], happiness [21], in evoking romantic love [22], and in the "feeling" experience associated with sexual arousal [23].

The main finding of the present study, however, was that progesterone (studied in the past mostly in the context of the female reproductive function) appeared to be associated with the cerebral activations during emotion processing in men but not in women. Thus, during negative emotion processing, the activations in the middle and superior orbitofrontal cortex were significantly correlated with progesterone levels in healthy men only. Numerous neuroimaging studies have shown that the orbitofrontal cortex is implicated in the processing of negative stimuli [24–26], but the role of progesterone has not been addressed. In comparison, during the processing of positive emotion, progesterone levels were correlated with activations in the fusiform gyrus in healthy men and with the middle occipital cortex in male patients. As mentioned above, occipital cortex has been frequently activated during emotional task using visual stimuli. Also, it has been well established that emotional face processing is directly linked with fusiform gyrus activation [27]. Thus, if we assume an implication of progesterone in the overall emotion processing, the significant correlations between this steroid hormone and cerebral activations during affective task are not unexpected. What remains surprising, however, is that there was no association between progesterone and emotional processing in either healthy or schizophrenia women, despite progesterone's role in mood regulation of female subjects (in both human and animal studies) [4, 28, 29].

Animal studies have shown that progesterone receptors are present in several limbic and corticolimbic structures (traditionally associated with affect and emotion processing), including hypothalamus, thalamus, amygdala, hippocampus, prefrontal cortex, olfactory bulb and cerebellum [30–32]. Moreover, one postmortem study in women revealed

concentrations of progesterone and its metabolites in the prefrontal, temporal, and parietal cortex, as well as in some subcortical structures including amygdala, hippocampus, caudate, putamen, thalamus, nucleus accumbens, substantia nigra, hypothalamus, and cerebellum [33]. Therefore, our findings of significant correlations between progesterone levels and brain activations in orbitofrontal cortex in male participants are somewhat consistent with those receptor binding and postmortem studies.

Several studies have shown that progesterone and its derivative, allopregnanolone, have a modulating effect on neurotransmitters systems involved in the regulation of emotion, such as serotonin and noradrenalin [34, 35]. Traditionally, progesterone has been investigated in the context of the female menstrual cycle, contraception, or breast cancer. However, our results show that, at least in the case of cerebral activations during emotional processing, this hormone appears to be more important for men than for women. In other words, although progesterone plays a primary role in the female reproductive function, it may be also important for the brain function in males.

Thus despite the fact that our principal motivation for the present study was to examine differences between schizophrenia patients and healthy controls, our most intriguing finding was the similar pattern of sex differences in both groups (i.e., progesterone had a significant association with cerebral activations in men but not women). It should be added that this relationship was more pronounced in healthy men than in schizophrenia men.

Although intriguing, this data is preliminary and warrants further investigation. For example, it is possible that with greater number of female participants we would also find a significant association between progesterone and brain activation during emotional processing, though the pattern of these results might differ. The findings emphasize the importance of including both sexes (and investigating them separately) in neuroendocrine and neuroimaging studies of schizophrenia and other psychiatric disorders that show sex differences in epidemiological, clinical, or neurobiological profile (e.g., major depression, autism, and ADHD).

Conflict of Interests

The authors would like to declare no conflict of interests.

Acknowledgments

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References

[1] J. M. Andreano and L. Cahill, "Menstrual cycle modulation of medial temporal activity evoked by negative emotion," *NeuroImage*, vol. 53, no. 4, pp. 1286–1293, 2010.

[2] V. G. Guapo, F. G. Graeff, A. C. T. Zani, C. M. Labate, R. M. dos Reis, and C. M. Del-Ben, "Effects of sex hormonal levels and phases of the menstrual cycle in the processing of emotional faces," *Psychoneuroendocrinology*, vol. 34, no. 7, pp. 1087–1094, 2009.

[3] M. Zitzmann, "Testosterone and the brain," *Aging Male*, vol. 9, no. 4, pp. 195–199, 2006.

[4] G. A. van Wingen, L. Ossewaarde, T. Bäckström, E. J. Hermans, and G. Fernández, "Gonadal hormone regulation of the emotion circuitry in humans," *Neuroscience*, vol. 191, pp. 38–45, 2011.

[5] J. R. Bostwick, S. K. Guthrie, and V. L. Ellingrod, "Antipsychotic-induced hyperprolactinemia," *Pharmacotherapy*, vol. 29, no. 1, pp. 64–73, 2009.

[6] V. Hendrick, L. L. Altshuler, and V. K. Burt, "Course of psychiatric disorders across the menstrual cycle," *Harvard Review of Psychiatry*, vol. 4, no. 4, pp. 200–207, 1996.

[7] D. R. Rubinow and P. J. Schmidt, "The neuroendocrinology of menstrual cycle mood disorders," *Annals of the New York Academy of Sciences*, vol. 771, pp. 648–659, 1995.

[8] E. S. Leblanc, J. Janowsky, B. K. S. Chan, and H. D. Nelson, "Hormone replacement therapy and cognition: systematic review and meta-analysis," *Journal of the American Medical Association*, vol. 285, no. 11, pp. 1489–1499, 2001.

[9] R. D. Brinton, R. F. Thompson, M. R. Foy et al., "Progesterone receptors: form and function in brain," *Frontiers in Neuroendocrinology*, vol. 29, no. 2, pp. 313–339, 2008.

[10] American Psychiatric Association, *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR Fourth Edition*, American Psychiatric Press, Washington, DC, USA, 1994.

[11] R. C. Oldfield, "The assessment and analysis of handedness: the Edinburgh inventory," *Neuropsychologia*, vol. 9, no. 1, pp. 97–113, 1971.

[12] Census, The National Occupational Classification and the Career Handbook, 23: pp. 56–62, 2001, http://www5.hrsdc.gc.ca/noc/English/CH/2001/IntroductionNOCandCH.aspx.

[13] R. L. Spitzer, J. B. Williams, M. Gibbon, and M. B. First, "The structured clinical interview for DSM-III-R (SCID), I: history, rationale, and description," *Archives of General Psychiatry*, vol. 49, no. 8, pp. 624–629, 1992.

[14] S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophrenia Bulletin*, vol. 13, no. 2, pp. 261–276, 1987.

[15] S. W. Woods, "Chlorpromazine equivalent doses for the newer atypical antipsychotics," *Journal of Clinical Psychiatry*, vol. 64, no. 6, pp. 663–667, 2003.

[16] P.J. Lang, A. Öhman, and D. Vaitl, *The International Affective Picture System (Photographic Slides)*, Center for Research in Psychophysiology, University of Florida, Gainesville, Fla, USA, 1988.

[17] K. J. Friston, "Commentary and opinion: II. Statistical parametric mapping: ontology and current issues," *Journal of Cerebral Blood Flow and Metabolism*, vol. 15, no. 3, pp. 361–370, 1995.

[18] K. L. Phan, T. Wager, S. F. Taylor, and I. Liberzon, "Functional neuroanatomy of emotion: a meta-analysis of emotion activation studies in PET and fMRI," *NeuroImage*, vol. 16, no. 2, pp. 331–348, 2002.

[19] E. M. Reiman, R. D. Lane, G. L. Ahern et al., "Neuroanatomical correlates of externally and internally generated human emotion," *American Journal of Psychiatry*, vol. 154, no. 7, pp. 918–925, 1997.

[20] M. Liotti, H. S. Mayberg, S. K. Brannan, S. McGinnis, P. Jerabek, and P. T. Fox, "Differential limbic-cortical correlates of sadness and anxiety in healthy subjects: implications for affective disorders," *Biological Psychiatry*, vol. 48, no. 1, pp. 30–42, 2000.

[21] U. Habel, M. Klein, T. Kellermann, N. J. Shah, and F. Schneider, "Same or different? Neural correlates of happy and sad mood in healthy males," *NeuroImage*, vol. 26, no. 1, pp. 206–214, 2005.

[22] A. Bartels and S. Zeki, "The neural basis of romantic love," *NeuroReport*, vol. 11, no. 17, pp. 3829–3834, 2000.

[23] M. Beauregard, J. Lévesque, and P. Bourgouin, "Neural correlates of conscious self-regulation of emotion," *The Journal of Neuroscience*, vol. 21, no. 18, Article ID RC165, 2001.

[24] X. Protopopescu, H. Pan, M. Altemus et al., "Orbitofrontal cortex activity related to emotional processing changes across the menstrual cycle," *Proceedings of the National Academy of Sciences of the United States of America*, vol. 102, no. 44, pp. 16060–16065, 2005.

[25] G. Northoff, A. Richter, M. Gessner et al., "Functional dissociation between medial and lateral prefrontal cortical spatiotemporal activation in negative and positive emotions: a combined fMRI/MEG study," *Cerebral Cortex*, vol. 10, no. 1, pp. 93–107, 2000.

[26] J. O'Doherty, E. T. Rolls, S. Francis, R. Bowtell, and F. McGlone, "Representation of pleasant and aversive taste in the human brain," *Journal of Neurophysiology*, vol. 85, no. 3, pp. 1315–1321, 2001.

[27] J. F. Monroe, M. Griffin, A. Pinkham et al., "The fusiform response to faces: explicit versus implicit processing of emotion," *Human Brain Mapping*. In press.

[28] O. S. Gbadebo, "Reduced maladaptive behavior and improved social function in a child with PDD-NOS treated with progesterone," *Clinical Medicine and Research*, vol. 9, no. 2, pp. 100–102, 2011.

[29] D. S. Reddy, B. W. O'Malley, and M. A. Rogawski, "Anxiolytic activity of progesterone in progesterone receptor knockout mice," *Neuropharmacology*, vol. 48, no. 1, pp. 14–24, 2005.

[30] C. Guerra-Araiza, A. Coyoy-Salgado, and I. Camacho-Arroyo, "Sex differences in the regulation of progesterone receptor isoforms expression in the rat brain," *Brain Research Bulletin*, vol. 59, no. 2, pp. 105–109, 2002.

[31] J. Kato, S. Hirata, A. Nozawa, and N. Yamada-Mouri, "Gene expression of progesterone receptor isoforms in the rat brain," *Hormones and Behavior*, vol. 28, no. 4, pp. 454–463, 1994.

[32] C. Guerra-Araiza, O. Villamar-Cruz, A. González-Arenas, R. Chavira, and I. Camacho-Arroyo, "Changes in progestrone receptor isoforms content in the rat brain during the oestrous cycle and after oestradiol and progesterone treatments," *Journal of Neuroendocrinology*, vol. 15, no. 10, pp. 984–990, 2003.

[33] M. Bixo, A. Andersson, B. Winblad, R. H. Purdy, and T. Bäckström, "Progesterone, 5 α-pregnane-3,20-dione and 3 α-hydroxy-5 α-pregnane- 20-one in specific regions of the human female brain in different endocrine states," *Brain Research*, vol. 764, no. 1-2, pp. 173–178, 1997.

[34] C. L. Bethea, M. Pecins-Thompson, W. E. Schutzer, C. Gundlah, and Z. N. Lu, "Ovarian steroids and serotonin neural function," *Molecular Neurobiology*, vol. 18, no. 2, pp. 87–123, 1998.

[35] C. N. Epperson, K. L. Wisner, and B. Yamamoto, "Gonadal steroids in the treatment of mood disorders," *Psychosomatic Medicine*, vol. 61, no. 5, pp. 676–697, 1999.

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Research Article

Gender Differences in Remission and Recovery of Schizophrenic and Schizoaffective Patients: Preliminary Results of a Prospective Cohort Study

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The aim of the paper was to evaluate rates of clinical remission and recovery according to gender in a cohort of chronic outpatients attending a university community mental health center who had been diagnosed with schizophrenia and schizoaffective disorder according to DSM-IV-TR. A sample of 100 consecutive outpatients (70 males and 30 females) underwent comprehensive psychiatric evaluation using the Structured Clinical Interview for Diagnosis of Axis I and II DSM-IV (SCID-I and SCID-II, Version R) and an assessment of psychopathology, social functioning, clinical severity, subjective wellbeing, and quality of life, respectively by means of PANSS (Positive and Negative Syndrome Scale), PSP (Personal and Social Performance), CGI-SCH (Clinical Global Impression—Schizophrenia scale), SWN-S (Subjective Well-being under Neuroleptics—scale), and WHOQOL (WHO Quality of Life). Rates of clinical remission and recovery according to different criteria were calculated by gender. Higher rates of clinical remission and recovery were generally observed in females than males, a result consistent with literature data. Overall findings from the paper support the hypothesis of a better outcome of the disorders in women, even in the very long term.

1. Introduction

The importance of gender differences in psychiatry is widely acknowledged, given its relevance for a better understanding of biological and psychosocial risk factors, time course, outcome, and response to treatments of major mental disorders, in particular schizophrenia and psychotic spectrum disorders [1–4]. Moreover, gender differences may play a crucial role in the early diagnosis and treatment of schizophrenia [5–7]. Indeed, a significant body of data revealed gender differences in terms of incidence rates, neurobiological factors, familial transmission, age of onset, clinical features, course and outcome, treatment response, compliance, and tolerability of drug treatments [2, 3, 8, 9]. According to the majority of authors, males manifest the disease earlier [2, 10, 11] and display more severe premorbid dysfunctions, intellectual impairment, and social deficits [10, 12–15], although data present in the literature are somewhat conflicting at times [5]. However, course and outcome of the illness [2, 10, 16], as well as the first episode of psychosis itself, are usually more severe and disabling in males [17–19]. On the contrary, women manifest onset symptoms later in life [2, 10, 11, 17], complete their studies, get married, or establish intimate relationships more frequently than males, showing less frequently negative [6, 7, 12, 13, 20–22] and affective [6, 10, 23] symptoms. Furthermore, women show a lower tendency towards substance abuse and antisocial behavior [24–27], better response to treatment [10, 28], higher rate of compliance, but an increased vulnerability to side effects of drugs [29]. A higher age of onset, better premorbid functioning, and a more favorable course of the disease may justify the better clinical and social outcome generally observed in women [10]. Notwithstanding the large amount of data relating to clinical and psychosocial outcome in schizophrenia and related disorders, only a limited number of studies to date have evaluated clinical outcome using

operational criteria for clinical and functional remission [30, 31]. Moreover, social outcome has prevalently been assessed by means of social-demographic parameters (marital status, occupation, and level of autonomy) or other nonspecific measures [31]. As a consequence, the existence of gender differences with regard to rates of clinical or psychosocial remission and recovery remains a matter of debate in the light of the conflicting evidence reported [31–39]. These contrasting results are partly due to relevant methodological differences, particularly criteria used in the definition of either remission or recovery. Taking into account the limited number of studies conducted on psychotic patients in community settings and evaluated by means of operationalized criteria, the present study aimed to evaluate rates of clinical remission and recovery according to gender in a cohort of chronic outpatients with a diagnosis of schizophrenia and schizoaffective disorder who were attending a community mental health center.

2. Methods

2.1. Sample. In the context of a prospective follow-up study, all patients with a diagnosis of schizophrenia or schizoaffective disorder according to DSM-IV-TR attending a university community mental health centre between 1 January and 31 December 2010 were enrolled consecutively. Patients with other comorbid disorders were also included in the study, although those affected by comorbid mental retardation or organic brain diseases were excluded. A sample of 100 consecutive outpatients (70 males, mean age 42.49 ± 7.75 yrs; 30 females; mean age 44.70 ± 11.76 yrs) who met the above-mentioned inclusion/exclusion criteria was studied. All patients were submitted to standard care provided in community mental health centers in Italy (pharmacological treatment, clinical monitoring at least on a monthly basis, home care when required, and psychosocial and rehabilitation interventions tailored to patient's needs).

2.2. Ratings. All patients underwent comprehensive psychiatric evaluation by means of the Structured Clinical Interview for Diagnosis of Axis I DSM-IV (SCID-I Research Version) [40] and for Axis II of DSM-IV (SCID-II) [41], after having signed an informed consent form. Interviews were conducted by residents in psychiatry trained in the use of the instruments by a specialist; interrater reliability, assessed using Cohen's K before the study, was higher than 0.80.

Personal and social data, and clinical history were collected on the basis of a structured interview purpose-developed for the present study. Severity of symptoms was evaluated by means of PANSS (Positive and Negative Syndrome Scale) [42] and Clinical Global Impression—Schizophrenia scale (CGI-SCH) [43]; functioning, subjective wellbeing and quality of life were, respectively, evaluated by means of PSP (Personal and Social Performance) [44], Subjective Wellbeing under Neuroleptics (SWN-S) [45], and WHO Quality of Life Brief questionnaire (WHOQOL-Brief) [46].

PANSS (Positive and Negative Syndrome Scale) consists of 30 items grouped into 3 distinct clusters (positive symptoms, negative symptoms, general psychopathological symptoms). The manual accompanying the scale provides a detailed explanation of individual items and criteria of quantification of symptoms that are rated on a 7-point scale.

PSP (Personal and Social Performance Scale), developed from SOFAS (Social Occupational Functioning Scale), assesses social functioning of patients with schizophrenia on 4 main areas: social activities, personal and social relationships, self-care and disturbing/aggressive behaviors. The PSP must be completed on the basis of data provided by the patient, family, or staff-member in charge of the patient. For each area a score ranging from 0 (no disability) to 5 (very severe disability) is attributed according to specific criteria. A comprehensive overall score ranging from 1 (maximum dysfunction) to 100 (maximum functioning) is attributed, based on score obtained at each single area.

CGI-SCH is the adapted version of the CGI (Clinical Global Impression Rating Scale) [43], one of the main rating scales currently used in the comprehensive assessment of psychopathology. The CGI scale comprises 3 main scores: severity of illness, global improvement, and efficacy index. The CGI-SCH, as adapted for use in schizophrenia, provides for the assessment of severity and improvement of positive, negative, cognitive, symptoms and depression over the week before the visit.

SWN (Subjective Wellbeing under Neuroleptic Treatment) is a self-administered rating scale developed by Naber in 1995, aimed at evaluating the psychological and physical wellbeing of patients treated with neuroleptics. For the purpose of the study the short version (20 items, including 5 subscales: mental functions, self-control, physical function, emotional control, and social capability) was used.

The WHOQOL (World Health Organization Quality of Life Scale) is a self-evaluated questionnaire developed by the World Health Organization (WHO QOL Group) to assess subjective quality of life. In the present study the 26-item short version (WHOQOL-BRIEF) was used, allowing us to obtain four subscores focusing on the quality of life in 4 areas, respectively (physical, psychological, social relationships, and environment).

2.3. Criteria for Clinical Remission and Recovery. To evaluate clinical remission, criteria developed by the "Remission of Schizophrenia Working Group" [30] based on ratings at 8 focal symptoms in positive, negative, and general psychopathology subscales of PANSS (P1, P2, P3, N1, N4, N6, G5, G9) were applied. The patient is judged to be in clinical remission when scores obtained at each of these items are less than or equal to 3 over a six-month period. Due to the fact that baseline data from an ongoing, prospective follow-up study was used, as suggested by the Remission of Schizophrenia Working Group severity was adopted in evaluating clinical remission, whilst duration was not taken into account. Moreover, to define a state of clinical remission [47], a CGI-SCH score equal or less than 3 was required. Given that the criteria published by Andreasen for clinical remission are based on eight selected items from PANSS, thus excluding all items which significantly contribute towards overall clinical picture and quality of life, such as depressive

and other symptoms [48], we decided to apply other more restrictive criteria. For the purpose of this study therefore, clinical remission was defined as (a) the meeting of both Andreasen's and CGI-SCH criteria; (2) achieving a score equal or less than 3 at each item of the Positive and Negative Scale of PANSS (extended PANSS criterion); (3) obtaining a score equal to or less than 3 at all items of PANSS (overall PANSS criterion).

In view of the lack of consensus in literature as to the definition and criteria of recovery [49], we adopted specific criteria purpose-developed for the present study. Recovery was primarily defined as the simultaneous fulfillment of Andreasen's criteria for clinical remission together with the presence of a "functional remission" as evaluated by PSP (score equal or greater to 70) and a "subjective remission," in terms of a full subjective wellbeing according to SWN scale (score equal or greater than 80). Secondary criteria for recovery were defined as (1) clinical remission plus functional remission and (2) clinical remission plus subjective remission. Criteria for clinical remission and recovery are summarized in Table 1.

2.4. Statistical Analysis. Categorical data were analyzed using Pearson's χ^2 test (chi-square) or Fisher's exact test; continuous variables were assessed by means of Student's t-test for independent samples. Data analyses were performed using SPSS 19.0. Level of significance was set at a P value ≤ 0.05 for two-tailed hypothesis

3. Results

3.1. Sociodemographic Characteristics and Clinical History according to Gender. Significant gender differences were detected with regard to marital status. No other differences in sociodemographic characteristics were found (Table 2).

Females were more frequently married ($\chi^2 = 13.280$, $df = 2$, $P = 0.001$) and with children than males ($\chi^2 = 7.563$, $df = 1$, $P = 0.012$). The age at onset of psychosis was higher in women (26.10 ± 12.26 years) than in men (21.61 ± 7.67 years) although the difference did not achieve statistical significance ($t = -1.854$, $df = 39.082$, $P = 0.071$). Age at first treatment for psychotic disorder was higher in women (30.90 ± 12.23 yrs) than in men (24.93 ± 8.04 yrs; $t = -2.455$, $df = 40.172$, $P = 0.018$). No gender differences were found in mean number of hospitalizations (1.29 ± 1.185 in men and 1.63 ± 1.732 in women; $t = -0.977$, $df = 41.458$, $P = 0.334$). However, men were characterized by a higher number of months since the last hospitalization (124.13 ± 108.52) than women (71.84 ± 66.43) ($t = 2.392$, $df = 53.325$, $P = 0.020$). No significant differences were revealed in duration of untreated psychosis (DUP), considered as average time in months between the onset of psychotic symptoms and the first treatment: 20.90 ± 40.27 mo. in men versus 44.55 ± 91.17 mo. in women ($t = -1.342$, $df = 32.757$, $P = 0.189$); the type of course (episodic with complete remission, episodic with residual symptoms or continuous; Table 3); percentage of patients having undergone at least one hospitalization in their lifetime (69.6%, $n = 48$ males and 63.3%, $n = 19$ females; $\chi^2 = 0.371$, $df = 1$, $P = 0.641$) and who had attempted suicide or manifested self-harming behaviors (27.5%, $n = 19$ males and 37.9%, $n = 11$ females; $\chi^2 = 1.039$, $df = 1$, $P = 0.342$). The proportion of patients who had committed crimes was higher in males (11.6%, $n = 8$) than females (0%; $\chi^2 = 3.661$, $df = 1$, $P = 0.053$).

3.2. Axis I and II Diagnosis according to Gender. On the basis of data obtained at SCID-I interviews, a higher frequency of schizophrenia was found among males (M = 48.8%; F = 26.7%) while a more frequent diagnosis of schizoaffective disorder was detected among females (M = 51.4%; F = 73.3%; $P = 0.042$).

No significant gender differences were observed in Axis I comorbidity: comorbid anxiety disorders were diagnosed in 21.5% males and 20% females; other disorders were found in 5.7% males and 6.7% females. At SCID II 22.9% of males and 30.0% of females were diagnosed as having a personality disorder, although the difference was not statistically significant. Moreover, no relevant differences among genders were found with regard to personality clusters, with the sole exception of personality disorder not otherwise specified, more frequently represented in females (23.3%) than males (8.6%; $P = 0.056$).

3.3. Treatment Prescribed. The large majority of patients were on psychopharmacological treatment without any significant difference according to gender (males = 100%; females = 96.6%). Similarly, no difference was found in type of drug treatment (typical or atypical antipsychotics, antidepressants, mood stabilizers, and anticholinergics), with the exception of benzodiazepines, prescribed somewhat more frequently to males (64.3%) than females (43.3%; $P = 0.052$).

More women (23.3%) than men (7.2%) underwent individual psychotherapeutic treatment ($P = 0.024$) while no significant differences were detected with regard to group therapies and family interventions. 18.8% of males and 30.0% of females were undergoing rehabilitation treatment, the difference not being statistically significant; however, female patients were more frequently involved in expressive therapies (art therapy; 23.3%) than males (7.2%; $P = 0.024$).

3.4. Psychopathological Severity according to Gender. No significant differences were found among genders in mean scores achieved at PANSS total scale, general psychopathology scale, and positive and negative scales. Moreover, no significant gender differences were detected in mean scores on the overall severity scale and each one of the subscales (positive symptoms, negative symptoms, depressive symptoms, and cognitive deficits) of CGI-SCH. When focusing on individual items of PANSS, significant gender differences were found only for items N7 (stereotyped thinking; males = 1.60 ± 1.027, females = 1.23 ± 0.679, $P < 0.05$); G3 (feelings of guilt; males = 1.37 ± 0.871; females = 1.90 ± 1.348, $P < 0.05$), and G5 (postural mannerisms; males = 1.09 ± 0.329; females = 1.00 ± 0.000, $P < 0.05$).

Table 1: Clinical remission and recovery criteria.

	Psychopathology	Functioning	Subjective wellbeing
Clinical remission criteria			
Andreasen's criteria	Score ≤3 in items P1, P2, P3, N1, N4, N6, G5, G9 of PANSS		
CGI-SCH criteria	Overall score ≤3 at the CGI-SCH		
Andreasen's criteria + CGI-SCH criteria	Score ≤3 in items P1, P2, P3, N1, N4, N6, G5, G9 of PANSS, overall score ≤3 at the CGI-SCH		
Extended PANSS criteria	Score ≤3 at each one item of the Positive and Negative Scale of PANSS		
Overall PANSS criteria	Score ≤3 at all the items of PANSS		
Recovery criteria			
Clinical + functional + subjective wellbeing remission	Score ≤3 in items P1, P2, P3, N1, N4, N6, G5, G9 of PANSS	Score ≥70 at PSP Scale	Score ≥80 at SWN Scale
Clinical + functional remission	Score ≤3 in items P1, P2, P3, N1, N4, N6, G5, G9 of PANSS	Score ≥70 at PSP Scale	
Clinical + subjective wellbeing remission	Score ≤3 in items P1, P2, P3, N1, N4, N6, G5, G9 of PANSS		Score ≥80 at SWN Scale

Table 2: Sociodemographic characteristics of the sample according to gender.

	Males	Females	Statistics		*df*	*P* value
			t value	χ^2 test		
Age (mean years ± sd)	42.49 ± 7.751	44.70 ± 11.765	−0.947		98	0,350
Education (mean years ± sd)	10.37 ± 3.800	12.00 ± 4.235	−1.897		98	0,061
Marital status				13.280	2	0,001
Married (*N*, %)	5 (7.1)	6 (20.0)				
Separated (*N*, %)	1 (1.4)	5 (16.7)				
Widowed (*N*, %)	—	—				
Single (*N*, %)	64 (91.4)	19 (63, 3)				
Employment status				8.914	5	0,113
Employed	17 (24.33)	4 (13, 3)				
Housewives	—	2 (6.7)				
Students	2 (2.9)	2 (6.7)				
Retired	9 (12.9)	7 (23.3)				
Disability pension	32 (45.7)	10 (33.3)				
Unemployed	10 (14.3)	5 (16.7)				

3.5. Social Functioning according to Gender. Males displayed significantly higher mean scores than females on PSP "disturbing and aggressive behaviors" (males = 0.38 ± 0.75; females = 0.13 ± 0.434; $P = 0.046$). With regard to PSP total score, a greater dysfunction was detected in males (46.07 ± 26.449) than in females (33.93 ± 31.858), although this difference was not significant from a statistical point of view ($P = 0.073$). Taking into account patients with a PSP score equal to or higher than 70, 10% of males and 30% of females were considered "functionally remitted" in view of their adequate functioning, a difference devoid of statistical significance.

3.6. Subjective Wellbeing according to Gender. Women showed significantly higher scores (18.66 ± 3.243) than males (16.81 ± 4.044) at the "self-control" subscale of SWN ($P = 0.020$). Considering patients with an SWN total score equal to or higher than 80, no significant gender differences were found. 65.7% of males and 70% of females were considered in "subjective remission" (true subjective wellbeing).

3.7. Quality of Life according to Gender. No significant gender differences were revealed in subjective quality of life for the four areas considered (physical, psychological, social relationships, and environment) in the WHOQOL-BREF questionnaire.

3.8. Clinical Remission according to Gender. Data obtained according to the different criteria of clinical remission adopted are reported in Table 4. A lower percentage of male (48.6%, $n = 34$) than female patients (60.0%, $n = 18$) were deemed in clinical remission according to the criteria of Andreasen, a finding devoid of statistical significance. Similarly, no significant gender differences emerged when

Table 3: Course of illness according to gender.

Course of illness	Males	Females	χ^2 test	*df*	*P* value
Episodic with full remissions (*n*, %)	11 (16.2)	7 (23.3)	3.990	3	0.262
Episodic with residual symptoms (*n*, %)	14 (20.6)	3 (10.0)			
Continuous (*n*, %)	39 (57.4)	20 (66.7)			
Undefined (*n*, %)	4 (5.9)	—			

Table 4: Clinical remission rates according to gender.

Criteria	Male (*n*, %)	Female (*n*, %)	χ^2 test	*df*	*P* value
Andreasen's criteria	34 (48.6)	18 (60.0)	1.099	1	0.383
CGI-SCH total score	38 (56.7)	13 (48.1)	0.569	1	0.498
CGI-SCH and Andreasen's criteria	28 (41.8)	12 (46.2)	0.145	1	0.816
PANSS (positive and negative items)	22 (31.4)	14 (46.7)	2.116	1	0.175
PANSS (all items)	16 (22.9)	8 (26.7)	0.167	1	0.799

CGI-SCH criteria were used to evaluate clinical remission (males = 56.7%, $n = 38$; females = 48.1%, $n = 13$). When more restrictive criteria were applied (Andreasen's and CGI-SCH criteria combined), once again no difference was detected between genders (41.8% $n = 28$ males and 46.2% $n = 13$ females). On applying more restrictive criteria to evaluate clinical remission (a score less than or equal to 3 for all items of the PANSS positive and negative scales), clinical remission was observed in 31.4% of males ($n = 22$) and 46.7% of females ($n = 14$), although devoid of statistical significance. Even following the use of extremely restrictive criteria to define clinical remission (scores less than or equal to 3 for all PANSS items), no difference was found between genders, given that 22.9% of males ($n = 16$) and 26.7% of females ($n = 8$) were seen to be in clinical remission using these criteria.

3.9. Recovery in Relation to Gender. Patients who were clinically remitted as established by Andreasen's criteria were viewed as being "recovered," as "adequately functioning" in line with PSP total score and in a state of subjective wellbeing on the basis of SWN total score (Table 5), with a significantly higher proportion of females (16.7%, $n = 5$) than males (2.9%, $n = 2$) among the "recovered" ($P = 0.024$). When basing criteria for "recovery" on clinical remission and "adequate" functioning alone, once again a significantly higher proportion of females (26.7%, $n = 8$) than males (5.7%, $n = 4$) seemed to have "recovered" ($P = 0.006$). Similarly, when considering "recovery" only in terms of clinical remission associated with a true subjective wellbeing, a higher albeit not significant proportion of females (41.4%, $n = 12$) than males (25.7%, $n = 18$) were "recovered"($P = 0.123$).

4. Discussion

The present study provides a cross-sectional picture of a cohort of typical chronic psychotic patients attending a community mental health service in Italy. The patient sample was made up largely of middle aged, low income subjects with a long psychiatric history who lived in the community. As expected, a number of gender differences were revealed in the sample described here. Sociodemographic conditions of women were somewhat better than those of males, as shown by the higher frequency of female patients who were married with children, a finding that is substantially congruent with data present in the literature [8], probably reflecting the later onset of schizophrenia, a better premorbid adjustment [10, 12, 13] and less severe symptoms at onset among females [17]. In the sample studied, a higher proportion of schizoaffective disorders was found among females, a finding partially congruent with literature data reporting a higher frequency of affective symptoms in women [6, 10, 11, 23]. Although statistical significance was not reached, likely due to the limited number of subjects investigated, the younger age at onset of the disorder and the consequent early start of treatment in males observed in this study is fully in agreement with previous findings [2, 10, 11]. The more frequent prevalence of male offenders found in our study, together with a higher rate of disturbing and aggressive behaviors as evaluated by means of PSP, tend to confirm data from the literature reporting a stronger association of violent crimes in mental disorders with the male gender [49, 50]. No substantial gender differences were detected with regard to duration of untreated psychosis, a result which is partly congruent with literature data reporting on first-onset psychoses [51], and in contrast with others showing a longer DUI among males [52]. In accordance with literature findings (2) no gender differences were detected in the sample studied in symptom course pattern, although there was a considerable lack of literature studies reporting on clinical course according to DSM-IV criteria.

The absence of gender differences in current pharmacological treatment may indicate that, in spite of a series of literature reports demonstrating substantial differences between the genders in terms of response to and tolerability of treatments, in clinical practice males and females are treated in a comparable manner, thus reflecting the lack

Table 5: Recovery rates according to gender.

Recovery criteria	Male (n, %)	Female (n, %)	χ^2 test	df	P value
Clinical* + functional + subjective wellbeing remission	2 (2.9)	5 (16.7)	6.152	1	0.024
Clinical* + functional remission	4 (5.7)	8 (26.7)	8.730	1	0.006
Clinical* + subjective wellBeing remission	18 (25.7)	12 (41.4)	2.382	1	0.151

* Andreasen's et al. criteria [30].

of gender-specific treatment guidelines [4]. In this study, female patients more frequently underwent individual psychotherapy, a finding which might be interpreted as the consequence of a higher propensity compared to males to resort to psychological interventions rather than to actual differences in therapeutic needs. Interestingly, no differences were detected in the frequency of rehabilitation activities between genders, with the sole exception of art therapies, which were more frequent among female patients. These findings are partly in contrast with literature data, underlining how women are less involved in rehabilitation activities, probably due to the lower degree of disability generally attributed to the female sex, and to lower needs of clinical and psychosocial care [53, 54]. Moreover, women are reportedly less involved in job placement or educational programs [8], although no significant gender differences were observed in the present sample with regard to these interventions. The data obtained in this study showed substantially similar levels and quality of psychopathology, as revealed by PANSS and CGI-SCH, in males and females; these findings are in contrast with data present in the literature, generally reporting a higher incidence of negative symptoms in males, and affective symptoms in females [6, 23, 31]. However, in the present study the more frequent observation of schizoaffective disorders in women may reflect a higher frequency of mood symptoms in females throughout the longitudinal course of the illness.

Following application of Andreasen's et al. [30] criteria, higher rates of clinical remission were detected for women than for men, although differences were not statistically significant; likewise, similar results emerged when other criteria were used. However, as expected rates of remission progressively decreased when more restrictive sets of criteria were considered. Moreover, a higher albeit not significant percentage of women showed an adequate functioning and were considered in "functional remission". Furthermore, compared to males, women more frequently report a condition of subjective wellbeing on SWN scale, with statistically significant differences in the "self-control" subscale. Recent studies utilizing operational criteria to define clinical and functional remission show contrasting results. A study by Galderisi et al. [31] failed to find a statistically significant difference in rates of clinical remission between genders and higher rates of functional remission in females, a difference at the limits of statistical significance; Brugnoli et al. [55] found a higher frequency of clinical remission among females, while no difference between the sexes was found by Karow et al. [56].

When taking into account the main criteria adopted in the present study, that is, a state of clinical remission together with an adequate functioning and a true subjective wellbeing, "recovery" was significantly more frequent among female patients; similar results were obtained when recovery was only based on clinical remission and functional status. These results are fundamentally congruent with evidence from the literature. Indeed, in a longitudinal prospective study lasting 20 years Grossman et al. [32] revealed a trend for a better overall outcome and higher rates of recovery among women with schizophrenia and other psychotic disorders, thus disconfirming the hypothesis advanced by some authors that in women with schizophrenia outcome worsened over time, largely resembling that observed in men [33–35]. The SOHO study [30] reported a higher frequency of full recovery among females, presenting a lower global severity, less negative symptoms, and better social functioning at baseline. Similarly, Albert et al. [37] found that recovery was predicted, among other factors, by female sex.

Prior to the drawing of any conclusion from the data collected in the present study, a series of limitations should be taken into account, including the cross-sectional nature of the study, the limited number of cases included, the exclusion of cases of mental retardation and organic brain disorders, the exclusion of duration criteria in defining clinical remission. On the other hand, the use of structured interviews to define diagnoses and of standardized methods in the evaluation of clinical and psychosocial variables, thus allowing remission and recovery to be assessed in a reliable manner should be considered strengths of the study. The overall data provided by this study of a cohort of chronic outpatients who were highly representative of typical psychotic patients attending community mental health centers in Italy, tend to confirm a best prognosis and lower overall severity of schizophrenic spectrum disorders in women than in men [2, 10, 14]. In particular, our data appear to demonstrate a better outcome not only in the short and middle term, but likewise in the long term in schizophrenic and schizoaffective women. This improved outcome is likely the result of both an intrinsic, less severe nature of the disorder and to a series of other positive factors related to treatment (i.e., better response, higher compliance) and psychosocial environment (i.e., higher social support) among women.

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References

[1] M. Afifi, "Gender differences in mental health," *Singapore Medical Journal*, vol. 48, no. 5, pp. 385–391, 2007.

[2] H. Häfner, "Gender differences in schizophrenia," *Psychoneuroendocrinology*, vol. 28, supplement 2, pp. 17–54, 2003.

[3] S. Š. Ivezić and N. John, "Gender and shizoprenia," *Psychiatria Danubina*, vol. 21, supplement 1, pp. 106–110, 2009.

[4] F. Pinna, V. Mattana, and B. Carpiniello, "Schizophrenia spectrum disorders and sex differences: results of a study on clinical and therapeutical aspects in an outpatient sample," *Italian Journal of Psychopathology*, vol. 11, no. 4, pp. 417–427, 2005.

[5] S. M. Cotton, M. Lambert, B. G. Schimmelmann et al., "Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis," *Schizophrenia Research*, vol. 114, no. 1–3, pp. 17–24, 2009.

[6] A. Køster, M. Lajer, A. Lindhardt, and B. Rosenbaum, "Gender differences in first episode psychosis," *Social Psychiatry and Psychiatric Epidemiology*, vol. 43, no. 12, pp. 940–946, 2008.

[7] A. Thorup, L. Petersen, P. Jeppesen et al., "Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study," *Journal of Nervous and Mental Disease*, vol. 195, no. 5, pp. 396–405, 2007.

[8] M. V. Seeman, "Women and schizophrenia," *Medscape Women's Health*, vol. 5, no. 2, p. 2, 2000.

[9] E. H. Nasser, N. Walders, and J. H. Jenkins, "The experience of schizophrenia: what's gender got to do with it? A critical review of the current status of research on schizophrenia," *Schizophrenia Bulletin*, vol. 28, no. 2, pp. 351–362, 2002.

[10] A. Leung and P. Chue, "Sex differences in schizophrenia, a review of the literature," *Acta Psychiatrica Scandinavica*, vol. 101, no. 401, pp. 3–38, 2000.

[11] J. Usall, E. Busquets, S. Araya, S. Ochoa, and A. Gost, "Gender differences in schizophrenia. A literature review," *Actas Españolas de Psiquiatría*, vol. 28, no. 3, pp. 178–185, 2000.

[12] V. A. Morgan, D. J. Castle, and A. V. Jablensky, "Do women express and experience psychosis differently from men? Epidemiological evidence from the Australian National Study of Low Prevalence (Psychotic) Disorders," *Australian and New Zealand Journal of Psychiatry*, vol. 42, no. 1, pp. 74–82, 2008.

[13] N. J. Preston, K. G. Orr, R. Date, L. Nolan, and D. J. Castle, "Gender differences in premorbid adjustment of patients with first episode psychosis," *Schizophrenia Research*, vol. 55, no. 3, pp. 285–290, 2002.

[14] J. Addington, S. van Mastrigt, and D. Addington, "Patterns of premorbid functioning in first-episode psychosis: initial presentation," *Schizophrenia Research*, vol. 62, no. 1-2, pp. 23–30, 2003.

[15] M. L. Silverstein, G. Mavrolefteros, and D. Close, "Premorbid adjustment and neuropsychological performance in schizophrenia," *Schizophrenia Bulletin*, vol. 28, no. 1, pp. 157–165, 2002.

[16] J. Usall, S. Ochoa, S. Araya, and M. Márquez, "Gender differences and outcome in schizophrenia: a 2-year follow-up study in a large community sample," *European Psychiatry*, vol. 18, no. 6, pp. 282–284, 2003.

[17] R. Marvin, C. Rosen, J. L. Reilly, H. Solari, and J. A. Sweeney, "Diagnostic and gender differences in first episode psychosis," *Schizophrenia Bulletin*, vol. 33, p. 241, 2007.

[18] H. Naqvi, M. M. Kahn, and A. Faizi, "Gender differences in age at onset of schizophrenia," *Journal of the College of Physicians and Surgeons Pakistan*, vol. 15, no. 6, pp. 345–348, 2005.

[19] A. Barajas, I. Baños, S. Ochoa et al., "Gender differences in incipient psychosis," *European Journal of Psychiatry*, vol. 24, no. 3, pp. 176–194, 2010.

[20] N. Hayashi, Y. Igarashi, M. Yamashina, and K. Suda, "Is there a gender difference in a factorial structure of the positive and negative syndrome scale? A test by structural equation modeling," *Psychopathology*, vol. 35, no. 1, pp. 28–35, 2002.

[21] J. Usall, S. Ochoa, S. Araya, A. Gost, E. Busquets, and Grupo NEDES, "Sintomología y género e la esquizofrenia," *Actas Españolas de Psiquiatría*, vol. 28, no. 4, pp. 219–223, 2000.

[22] M. A. Roy, M. Maziade, A. Labbé, and C. Mérette, "Male gender is associated with deficit schizophrenia: a meta-analysis," *Schizophrenia Research*, vol. 47, no. 2-3, pp. 141–147, 2001.

[23] A. C. Altamura, R. Bassetti, S. Bignotti, R. Pioli, and E. Mundo, "Clinical variables related to suicide attempts in schizophrenic patients: a retrospective study," *Schizophrenia Research*, vol. 60, no. 1, pp. 47–55, 2003.

[24] D. A. Regier, M. E. Farmer, D. S. Rae et al., "Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) study," *Journal of the American Medical Association*, vol. 264, no. 19, pp. 2511–2518, 1990.

[25] J. L. Ayuso-Gutiérrez and J. M. D. R. Vega, "Factors influencing relapse in the long-term course of schizophrenia," *Schizophrenia Research*, vol. 28, no. 2-3, pp. 199–206, 1997.

[26] T. K. Larsen, I. Melle, B. Auestad et al., "Substance abuse in first-episode non-affective psychosis," *Schizophrenia Research*, vol. 88, no. 1–3, pp. 55–62, 2006.

[27] J. Rabinowitz, E. J. Bromet, J. Lavelle, G. Carlson, B. Kovasznay, and J. E. Schwartz, "Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients," *Psychological Medicine*, vol. 28, no. 6, pp. 1411–1419, 1998.

[28] M. V. Seeman, "Gender differences in treatment response in schizophrenia," in *Gender and Psychopathology*, M. V. Seeman, Ed., pp. 227–251, American Psychiatric Press, Washington, DC, USA, 1995.

[29] M. V. Seeman, "Gender differences in the prescribing of antipsychotic drugs," *American Journal of Psychiatry*, vol. 161, no. 8, pp. 1324–1333, 2004.

[30] N. C. Andreasen, W. T. Carpenter, J. M. Kane, R. A. Lasser, S. R. Marder, and D. R. Weinberger, "Remission in schizophrenia: proposed criteria and rationale for consensus," *American Journal of Psychiatry*, vol. 162, no. 3, pp. 441–449, 2005.

[31] S. Galderisi, P. Bucci, A. Üçok, and J. Peuskens, "No gender differences in social outcome in patients suffering from schizophrenia," *European Psychiatry*. In press.

[32] L. S. Grossman, M. Harrow, C. Rosen, R. Faull, and G. P. Strauss, "Sex differences in schizophrenia and other psychotic disorders: a 20-year longitudinal study of psychosis and recovery," *Comprehensive Psychiatry*, vol. 49, no. 6, pp. 523–529, 2008.

[33] H. Jonsson and A. K. Nyman, "Predicting long-term outcome in schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 83, no. 5, pp. 342–346, 1991.

[34] D. Loyd, J. C. Simpson, and M. T. Tsuang, "Are there sex differences in the long-term outcome of schizophrenia?

Comparisons with mania, depression, and surgical controls," *Journal of Nervous and Mental Disease*, vol. 173, no. 11, pp. 643–649, 1985.

[35] S. Opjordsmoen, "Long-term clinical outcome of schizophrenia with special reference to gender differences," *Acta Psychiatrica Scandinavica*, vol. 83, no. 4, pp. 307–313, 1991.

[36] D. Novick, J. M. Haro, D. Suarez, E. Vieta, and D. Naber, "Recovery in the outpatient setting: 36-month results from the Schizophrenia Outpatients Health Outcomes (SOHO) study," *Schizophrenia Research*, vol. 108, no. 1–3, pp. 223–230, 2009.

[37] N. Albert, M. Bertelsen, A. Thorup et al., "Predictors of recovery from psychosis. Analyses of clinical and social factors associated with recovery among patients with first-episode psychosis after 5 years," *Schizophrenia Research*, vol. 125, no. 2-3, pp. 257–266, 2011.

[38] L. Petersen, A. Thorup, J. Øqhlenschlæger et al., "Predictors of remission and recovery in a first-episode schizophrenia spectrum disorder sample: 2-year follow-up of the OPUS trial," *Canadian Journal of Psychiatry*, vol. 53, no. 10, pp. 660–670, 2008.

[39] J. M. Haro, A. Ciudad, J. Alonso et al., "Remission and relapse in the ambulatory treatment of patients with schizophrenia. Outcomes at 3 years," *Actas Españolas de Psiquiatría*, vol. 36, no. 4, pp. 187–196, 2008.

[40] M. B. First, R. L. Spitzer, J. B. W. Williams, and M. Gibbon, *Structured Clinical Interview for DSM IV Axis I Disorders-Research Version (SCID-I, Version 2. 0)*, Biometrics Research Department, New York State Psychiatric Institute, New York, NY, USA, 1996.

[41] M. B. First, M. Gibbon, R. L. Spitzer, J. B. W. Williams, and L. Benjamin, *Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II, Version 2. 0)*, Biometrics Research Department, New York State Psychiatric Institute, New York, NY, USA, 1996.

[42] S. R. Kay, A. Fiszbein, and L. A. Opler, "The positive and negative syndrome scale (PANSS) for schizophrenia," *Schizophrenia Bulletin*, vol. 13, no. 2, pp. 261–276, 1987.

[43] J. M. Haro, S. A. Kamath, S. Ochoa et al., "The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia," *Acta Psychiatrica Scandinavica*, vol. 107, no. 416, pp. 16–23, 2003.

[44] P. L. Morosini, L. Magliano, L. Brambilla, S. Ugolini, and R. Pioli, "Development, reliability and acceptability of a new version of the DSM-IV Social Occupational Functioning Assessment Scale (SOFAS) to assess routine social functioning," *Acta Psychiatrica Scandinavica*, vol. 101, no. 4, pp. 323–329, 2000.

[45] D. Naber, S. Moritz, M. Lambert et al., "Improvement of schizophrenic patients' subjective well-being under atypical antipsychotic drugs," *Schizophrenia Research*, vol. 50, no. 1-2, pp. 79–88, 2001.

[46] S. M. Skevington, M. Lotfy, and K. A. O'Connell, "The World Health Organization's WHOQOL-BREF quality of life assessment: psychometric properties and results of the international field trial a report from the WHOQOL group," *Quality of Life Research*, vol. 13, no. 2, pp. 299–310, 2004.

[47] M. Jäger, T. Messer, G. Laux et al., "Standardized remission criteria in schizophrenia: descriptive validity and comparability with previously used outcome measures," *Pharmacopsychiatry*, vol. 41, no. 5, pp. 190–195, 2008.

[48] S. Majadas, J. Olivares, J. Galan, and T. Diez, "Prevalence of depression and its relationship with other clinical characteristics in a sample of patients with stable schizophrenia," *Comprehensive Psychiatry*. In press.

[49] R. Emsley, B. Chiliza, L. Asmal, and K. Lehloenya, "The concepts of remission and recovery in schizophrenia," *Current Opinion in Psychiatry*, vol. 24, no. 2, pp. 114–121, 2011.

[50] C. Wallace, P. Mullen, P. Burgess, S. Palmer, D. Ruschena, and C. Browne, "Serious criminal offending and mental disorder: case linkage study," *British Journal of Psychiatry*, vol. 172, pp. 477–484, 1998.

[51] A. Thorup, L. Petersen, P. Jeppesen et al., "Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study," *Journal of Nervous and Mental Disease*, vol. 195, no. 5, pp. 396–405, 2007.

[52] W. C. Chang, J. Y. M. Tang, C. L. M. Hui et al., "Gender differences in patients presenting with first-episode psychosis in Hong Kong: a three-year follow up study," *Australian and New Zealand Journal of Psychiatry*, vol. 45, no. 3, pp. 199–205, 2011.

[53] G. Thornicroft, M. Leese, M. Tansella et al., "Gender differences in living with schizophrenia. A cross-sectional European multi-site study," *Schizophrenia Research*, vol. 57, no. 2-3, pp. 191–200, 2002.

[54] S. Ochoa, J. Usall, J. M. Haro et al., "Comparative study of the needs of patients with schizophrenia," *Actas Españolas de Psiquiatría*, vol. 29, no. 3, pp. 165–171, 2001.

[55] R. Brugnoli, D. Novick, J. M. Haro, D. Suarez, A. Rossi, and S. Frediani, "Incidence and characteristics of remission in schizophrenic patients: analysis of the results of a three year SOHO study in Italy (Schizophrenia Outpatients Health Outcomes)," *Italian Journal of Psychopathology*, vol. 14, no. 3, pp. 243–251, 2008.

[56] A. Karow, S. Moritza, M. Lambert, D. Schöttle, and D. Naber, "Remitted but still impaired? Symptomatic versus functional remission in patients with schizophrenia," *European Psychiatry*. In press.

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Review Article

Intervention to Prevent Child Custody Loss in Mothers with Schizophrenia

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Depending on jurisdiction, time period studied, and specifics of the population, approximately 50 percent of mothers who suffer from schizophrenia lose custody of their children. The aim of this paper is to recommend interventions aimed at preventing unnecessary custody loss. This paper reviews the social work, nursing, psychology, psychiatry, and law literature on mental illness and custody loss, 2000–2011. Recommendations to mothers are to (a) ensure family health (b) prevent psychotic relapse, (c) prepare in advance for crisis, (d) document daily parenting activities, (e) take advantage of available parenting resources, and f) become knowledgeable about legal issues that pertain to mental health and custody. From a policy perspective, child protection and adult mental health agencies need to dissolve administrative barriers and collaborate. Access to appropriate services will help mothers with schizophrenia to care appropriately for their children and allow these children to grow and develop within their family and community.

1. Intervention to Prevent Child Custody Loss in Mothers with Schizophrenia

A psychotic illness can, but does not need to, interfere with an individual's ability to be a good parent. Given well-timed, appropriate, and adequate education and resources, many individuals with psychotic illness succeed in parenting their children. This is not always recognized by child welfare workers who may continue to be influenced by outdated views of psychotic illness as intractable and parenting with schizophrenia as impossible [1]. Without effective intervention, parents who suffer from psychotic illness too often lose custody of their children [2], an unfortunate outcome that can be avoided by early intervention [3–5]. The emphasis in this clinical review is on *mothers* with a diagnosis of schizophrenia (because there is very little literature on fathers and effects on children merit a separate paper).

2. Method

This paper used the following grouped search terms in Google Scholar (which includes MEDLINE, EMBASE, PsycINFO, and SOCINDEX, as well as the nursing and legal literature) for the years 2000–2011: schizophrenia/diagnosis/custody; schizophrenia/impact/custody; schizophrenia/postpartum/custody; schizophrenia/termination parental rights. Following the literature review and case illustrations (from which identifying facts have been removed), recommendations are made for mothers, care providers, and policy makers.

3. Prevalence of Custody Loss in Mothers with Psychosis

Studying reports published in the last ten years, it appears that approximately 50% of women with schizophrenia who are mothers lose custody of their children, either temporarily or permanently, although the percentage varies by jurisdiction. For instance, a report from Canada indicates that 84% of parents treated for schizophrenia by a community treatment team were not living with their children at the time of interview [6], but this figure includes both male and female parents, so is probably higher than it would be for women alone. In London, UK, Howard and colleagues [7]

established that 63% of women with psychosis (but only 26% of men) were parents. Hollingsworth [8] studied 322 women with serious mental illness and found that 26% had lost custody at some point in the child's life. A survey of mothers in psychiatric rehabilitative services [9] reported that 68% had been permanently separated from at least one child under the age of 18, often with little subsequent contact. The number of women with schizophrenia who experience custodial loss of their children is probably diminishing with time, as stigma lessens and interventions improve. Nevertheless, it remains high and effective intervention at the earliest stage of psychosis is warranted.

4. The Impact of Diagnosis on Custody Loss

Mothers with serious mental illness, as a group, fear that schizophrenia is equated in the mind of the public with parental incompetence or, worse, with parental neglect or violence [10]. This may well be the case because mothers with schizophrenia are often given relatively little opportunity to prove their parenting competence. Ackerson [11] has commented that parents with a diagnosis of psychosis are victimized twice first, by psychotic illness, then by protective removal of their children.

5. The Impact of Custody Loss on Mothers

Removing a child from a mother's care causes grief and distress to both. It is especially difficult for the mother when she has had little say in the process or when the event occurs at a time when she is too ill to understand what is happening. Diaz-Caneja and Johnson [12], in their qualitative study of 22 women with schizophrenia who were mothers, conclude that fear of losing child custody or access is always uppermost in the minds of severely mentally ill women, making it problematic to disclose to their care providers parenting difficulties that they may experience. Sands and colleagues [13] have reported that mothers with mental illness whose children are apprehended by child protection agencies are usually bewildered by events and confused about what steps to take in order to regain custody. Without psychiatric and legal guidance, they find it difficult to maintain contact with their children.

6. Postpartum Vulnerability to Custody Loss

The postpartum period is a particularly vulnerable time for women at risk of losing custody. Psychotic symptoms may emerge for the first time during this period and, for mothers with a prior history of mental illness, the risk of relapse is high during this reproductive phase [14, 15], bringing with it a very real threat of protective removal of children from the mother's care. Newborns are the most vulnerable members of society, and child protection legislation is therefore biased, as it needs to be, towards their needs rather than to the needs of the mother, however vulnerable she may also be. In order to meet the demands of competent infant care and retain custody of their infants, young mothers with severe postpartum psychiatric illness require substantial support and advocacy [16].

7. Composite Case Example of Unnecessary Children's Aid Involvement in Postpartum Psychosis

Patient A. was admitted to hospital for a postpartum psychotic episode. She had never been ill before. While she was in hospital, her infant was looked after at home by her parents. The baby's father was also involved in the child's care. Before the patient's hospital discharge, the psychiatric resident contacted Children's Aid, as a preventive measure, in order to notify the agency that Ms. A. might need help with mothering. Ms. A. had by then recovered and was functioning well. Psychiatric followup had been arranged, in addition to which several adults at home expressed willingness and availability to help look after the baby. The decision to call Children's Aid was solely determined by the fact that the patient had suffered a psychosis, placing her "on the books" of Children's Aid. While this could be perceived as a safety precaution for the family, it could also become a problem for the mother should, for example, the baby's father decide in the future to sue for sole custody of the child.

8. Causes of Termination of Parental Rights

The central moral and legal issue involved in temporary or permanent cessation of parental rights is the child's safety. When an environment is unsafe, the child must be removed until the situation changes [17, 18]. For small children, the safety of the environment is generally judged on the presence/absence of abuse and neglect. The parent must be able to provide basic care (shelter, nutrition, hygiene, clothing, and medical care) and security (protection from dangers, including unsafe people). As the child grows older, other domains of the parental environment take precedence. Brockington et al. [18] categorize these as the parent's ability to provide: *emotional warmth* (comfort, praise, and affection), *encouragement of learning* (through play, language, support of schooling, and social opportunities), *guidance and setting consistent limits (teaching consideration of others, self-discipline,* and *internal moral values),* and *a stable family base* for engagement with the wider world.

Assessing competent parenting requires skill and experience. While it is relatively easy to ascertain the presence of gross neglect or abuse, the more subtle qualities of parenting are harder to evaluate. Parent competency instruments are imperfect; they tend to focus on deficits rather than on strengths, and they are subject to cultural biases, since parental norms differ among cultures [19, 20].

9. Overrepresentation of Psychiatric Patients in Parental Termination Hearings

Besides parental competence, conditions such as physical and mental disability, side effects of medications, hospitalization history, quality and permanence of living arrangements,

employment record, and socioeconomic status enter into decision making about custody. These variables are all intimately associated with mental illness, and, as a result, parents with psychiatric diagnoses are overrepresented in parental termination proceedings. In an Australian study, parental psychiatric illness was the most prevalent condition at such court hearings [21]. Marital status is also important—unmarried women (and this describes the majority of women with a diagnosis of schizophrenia) are more likely to lose custody than their married peers [22]. Social integration in a network of family, friends, and community members, often deficient in women with schizophrenia, is also relevant [8]. The more dense a social network is, the less likely it is for children to be apprehended by child protection services. The diagnosis of schizophrenia in itself undermines a woman's chances of retaining custody, so does the substance abuse that frequently accompanies mental illness [7]. Recent studies have shown that substance abuse is perhaps the most important contributory factor [23, 24], although there are many interacting factors that determine out-of-home placements. Young mothers suffering from psychosis find it very hard to disentangle themselves and their children from the web of problems in which they become caught.

10. Preventing Custody Loss: Recommendations for Mothers and Care Providers

There are several ways in which mothers with severe mental illness can reduce the risk of child apprehension. It is the responsibility of care providers to provide mothers with this information and training in order to help them to preserve the integrity of their family [25].

10.1. Maintaining Mental Health. In trying to provide for their children, mothers often neglect their own health and yet maintenance of personal health is a crucial first step toward ensuring child custody. This includes proper diet, a healthy sleep schedule, an exercise program, regular physician and mental health visits, and adherence to a prescribed regimen of medication. When questioned, most mothers with schizophrenia do understand that custody can be lost if prescribed treatment for their condition is not adhered to [26].

When women deny psychiatric illness, the intense desire to retain custody of their children can be used as a form of leverage, a controversial but effective strategy [26–28].

11. Case Example

Patient B., the sole caregiver of a 5-year old son, sought treatment for psychotic symptoms but refused antipsychotic medication. She was hospitalized against her will after she was verbally abusive to another mother at her son's school. During her hospitalization, her son was placed in the care of a cousin. In hospital, Ms. B. continued to refuse medication. She asked for a lawyer to represent her so that she could leave hospital and return to her son. The lawyer advocated for her with hospital staff and persuaded Ms. B. to agree to community treatment orders (outpatient commitment), which included monthly depot antipsychotic injections. The lawyer convinced her that this would be her best recourse in order to regain custody of her son. Ms. B. had an excellent therapeutic response to the antipsychotic and soon went home. Her son returned to her care, and, when the 6-month community treatment order expired, Ms. B. continued the injections voluntarily because she felt so much better. Child protection worked collaboratively with legal and mental health agencies to help this family stay together. Followup after many years showed that Ms. B. has succeeded as a parent. She has had no further hospitalizations, and her son remains in good health.

As symptoms of psychosis decline, parenting stress is reduced and the quality of parenting inevitably improves [29]. Addressing symptoms alone is never sufficient [30], but does show the court that mothers are taking responsibility for this aspect of their recovery.

11.1. Self-Monitoring for Signs of Relapse. Avoiding recurrence of symptoms and the possibility of hospitalization is important for continuity of parental care, which means that psychiatric crises need to be avoided through anticipatory planning and self-monitoring. Mothers can be advised to maintain a written list of personal relapse triggers and early warning signs (sleeplessness, lapsed hygiene, increased suspiciousness, and so on) and to be knowledgeable about their medications. A requirement for dose changes whenever relapse threatens should be thoroughly discussed between mothers and care providers; the mother needs to know when and how she can increase (or decrease) her prescription to prevent a crisis. She needs to document what has worked in previous predicaments of a similar nature and what she can do to avert them. She needs ready access to crisis help. Evidence of self-monitoring convinces the court that mothers recognize that they suffer from a potentially relapsing illness and are doing their best to prevent recurrence.

11.2. Developing a Crisis Plan. Should hospitalization become necessary, it is important for mothers to be prepared for this disruption in their ability to care for their children. Several crisis plan templates are available electronically for parents with mental illness, none of which have as yet been evaluated for effectiveness [31]. It is best for all family members and all care providers to be involved in developing the crisis plan. The aim is to negotiate what needs to occur in an emergency and to clarify the responsibility of each member of the support network. Older children need to be part of the response team as they may be the first to notice their mother's early illness symptoms and they need to know whom to turn to under such circumstances. It is important, however, not to overburden children with the responsibility of looking after an ill parent.

The phone numbers and addresses of surrogate caregivers must be made available to children and also to care providers. Thought should be given to establishing backup caregivers in case of the unavailability of first choices.

The plan should be written down, shared, and periodically updated because names and details will change. It should include critical information about the children's needs: their doctor, dentist, teachers, allergies, food and activity preferences, favorite toys, bedtime routines, and physical and psychological history. Plans for family pets should be included. Reupert and colleagues [31] report that it typically takes 6–12 months to develop a comprehensive crisis plan because all the necessary interagency meetings take that long to organize. Such a plan indicates to the court that mothers place their parental responsibilities above all else.

11.3. Taking Advantage of Parenting Resources. Depending on the community, parenting skills classes, parenting mutual aid or support groups, parent coaches, parenting warm lines, home visiting, and respite services may all be available resources [32–34]. An online parenting course has even been developed in The Netherlands [35]. Well-trained care providers should be able to point mothers in the right directions to access the best resources [36]. Upgrading parental skills demonstrates to the court that mothers are trying their best to be responsible parents.

11.4. Documenting Household and Child Care Routines. When asked by a judge to give evidence of good parenting, many mothers do not know what to say, especially because such questions are not usually asked of mothers unless they suffer from mental illness. The judge, however, is entitled to ask about safety issues and about issues pertaining to domains of parenting competence similar to those outlined by Brockington et al. [18] Mothers can be helped to document the day to day manner in which they address their child's instrumental and emotional problems, how they help their children resolve conflicts, how they set limits, and how they help to socialize their children. They need to build a record detailing their parenting strengths and the quality of the bonds that exist with their children. Care providers should be able to provide guidance for the mother so that she is not at a loss when questions about her parenting emerge in court.

11.5. Navigating the Legal System. Mothers need to understand the mandated child abuse reporting laws of their jurisdictions. They need to connect with attorneys who understand mental illness and family law and the family court system and who can act as strong advocates. Policies intended to promote a speedy resolution for children in out-of-home care may unintentionally discriminate against parents with mental illness because they fast-track the termination of parental rights, allowing only a brief time period for new parents to meet the goals set by child protection agencies. Attorneys and care providers need to help mothers achieve these goals as quickly as possible by ensuring access and legal rights to the necessary supports and services. Collaboration is important between child protection and lawyers who represent parents in custody and termination proceedings. It is not an easy collaboration, however, because child welfare professionals and court professionals come from two distinct cultures, the first a culture of care and concern, the second an adversarial system that, above all else, values individual rights [37]. There is a definite need for mental health education of judges and court professionals.

12. Recommendations for Policy Makers

Early intervention services, adult mental health services, and child protection services often act in competition rather than in cooperation [38]. It is crucial to develop a philosophy and care system that cooperatively addresses the needs of the whole family. There is now a promising evidence base of effectiveness of wraparound services for families impacted by serious mental illness [39].

The term, "wraparound," is increasingly being used to describe a family-driven, strengths-based approach that uses an array of both formal services and natural supports [40]. Another phrase often used is "system of care." A system of care is a network of structures and relationships that is held together by shared values and that operates across administrative and funding jurisdictions [41, 42]. A family-driven system of care is based on the needs of children, parents, and extended family. It supports choice, ongoing evaluation, and accountability and promotes partnerships between families and professionals, collaboration between multiple agencies and service sectors, and individualized services that are sensitive to cultural differences. The cultural sensitivity of a service refers to the ability of its staff to understand, value, and incorporate the perspective of the family into service provision and, whenever possible, provide services in the family's language of choice.

In a wraparound system, there is a single point of entry for the many services that are provided. Among these are early identification and prevention strategies, attention to reproductive and child health, substance abuse counseling, case management, liaison with schools and the legal system, financial support, crisis management, housing, transportation aid, vocational help, spiritual, cultural, and recreational guidance, and respite care. Ideally, the services are open ended and sensitive to the stigma associated with mental illness. Cook and Steigman [43] advocate supports specifically designed to preserve the parental relationship. They identify assessment of parenting strengths and needs, birth control counseling, pregnancy decision-making support, trauma and abuse counseling, peer support, parent mentoring, self-help, support groups for children, and medication management as important aspects of a system of care for families with a mentally ill member. Specific counseling around benefits and entitlements is also critical for low-income mothers, some of whom may be intermittently homeless and require housing support [44]. Administrative policies, training opportunities for service providers, and hard work on the part of mothers themselves are all needed to ensure that

children of mentally ill parents grow up, whenever possible, in their family of origin.

References

[1] S. E. Mason and R. Miller, "Stigma and schizophrenia: directions in student training," *Journal of Teaching in Social Work*, vol. 26, no. 1-2, pp. 73–91, 2006.

[2] C. Mason, S. Subedi, and R. B. Davis, "Clients with mental illness and their children: Iimplications for clinical practice," *Issues in Mental Health Nursing*, vol. 28, no. 10, pp. 1105–1123, 2007.

[3] A. Reupert and D. Maybery, "Programmes for parents with a mental illness," *Journal of Psychiatric and Mental Health Nursing*, vol. 18, pp. 257–264, 2011.

[4] C. A. Clark, P. R. Smith, and P. Smith, "Promoting collaborative practice for children of parents with mental illness and their families," *Psychiatric Rehabilitation Journal*, vol. 33, no. 2, pp. 95–97, 2009.

[5] B. R. Hinden, K. Biebel, J. Nicholson, A. Henry, and J. Katz-Leavy, "A survey of programs for parents with mental illness and their families: identifying common elements to build the evidence base," *Journal of Behavioral Health Services and Research*, vol. 33, no. 1, pp. 21–38, 2006.

[6] R. Gewurtz, T. Krupa, S. Eastabrook, and S. Horgan, "Prevalence and characteristics of parenting among people served by assertive community treatment," *Psychiatric Rehabilitation Journal*, vol. 28, no. 1, pp. 63–65, 2004.

[7] L. M. Howard, R. Kumar, and G. Thornicroft, "Psychosocial characteristics and needs of mothers with psychotic disorders," *British Journal of Psychiatry*, vol. 178, pp. 427–432, 2001.

[8] L. D. Hollingsworth, "Child custody loss among women with persistent severe mental illness," *Social Work Research*, vol. 28, no. 4, pp. 199–209, 2004.

[9] H. Dipple, S. Smith, H. Andrews, and B. Evans, "The experience of motherhood in women with severe and enduring mental illness," *Social Psychiatry and Psychiatric Epidemiology*, vol. 37, no. 7, pp. 336–340, 2002.

[10] I. Savvidou, V. P. Bozikas, S. Hatzigeleki, and A. Karavatos, "Narratives about their children by mothers hospitalized on a psychiatric unit," *Family Process*, vol. 42, no. 3, pp. 391–402, 2003.

[11] B. J. Ackerson, "Parents with serious and persistent mental illness: Issues in assessment and services," *Social Work*, vol. 48, no. 2, pp. 187–195, 2003.

[12] A. Diaz-Caneja and S. Johnson, "The views and experiences of severely mentally ill mothers—a qualitative study," *Social Psychiatry and Psychiatric Epidemiology*, vol. 39, no. 6, pp. 472–482, 2004.

[13] R. G. Sands, N. Koppelman, and P. Solomon, "Maternal custody status and living arrangements of children of women with severe mental illness," *Health and Social Work*, vol. 29, no. 4, pp. 317–325, 2004.

[14] N. R. Matevosyan, "Pregnancy and postpartum specifics in women with schizophrenia: a meta-study," *Archives of Gynecology and Obstetrics*, vol. 283, no. 2, pp. 141–147, 2011.

[15] S. N. Vigod and L. E. Ross, "Epidemiology of psychotic symptoms during pregnancy and postpartum in women with schizophrenia," *Current Women's Health Reviews*, vol. 6, no. 1, pp. 17–21, 2010.

[16] M. Lagan, K. Knights, J. Barton, and P. M. Boyce, "Advocacy for mothers with psychiatric illness: a clinical perspective," *International Journal of Mental Health Nursing*, vol. 18, no. 1, pp. 53–61, 2009.

[17] A. Monds-Watson, R. Manktelow, and M. McColgan, "Social work with children when parents have mental health difficulties: acknowledging vulnerability and maintaining the 'rights of the child'," *Child Care in Practice*, vol. 16, no. 1, pp. 35–55, 2010.

[18] I. Brockington, P. Chandra, H. Dubowitz et al., "WPA guidance on the protection and promotion of mental health in children of persons with severe mental disorders," *World Psychiatry*, vol. 10, pp. 1–10, 2011.

[19] R. Kuersten-Hogan, C. Benjet, and S. T. Azar, "Evaluating the parental fitness of psychiatrically diagnosed individuals: advocating a functional-contextual analysis of parenting," *Journal of Family Psychology*, vol. 17, no. 2, pp. 238–251, 2003.

[20] M. V. Seeman, "Cross-cultural evaluation of maternal competence in a culturally diverse society," *American Journal of Psychiatry*, vol. 165, no. 5, pp. 565–568, 2008.

[21] G. Llewellyn, D. McConnell, and L. Ferronato, "Prevalence and outcomes for parents with disabilities and their children in an Australian court sample," *Child Abuse and Neglect*, vol. 27, no. 3, pp. 235–251, 2003.

[22] S. Strega, C. Fleet, L. Brown, L. Dominelli, M. Callahan, and C. Walmsley, "Connecting father absence and mother blame in child welfare policies and practice," *Children & Youth Services Review*, vol. 30, no. 7, pp. 705–716, 2008.

[23] D. Jones, R. L. Macias, P. B. Gold, P. Barreira, and W. Fisher, "When parents with severe mental illness lose contact with their children: are psychiatric symptoms or substance use to blame?" *Journal of Loss and Trauma*, vol. 13, no. 4, pp. 261–287, 2008.

[24] L. Lewin and A. Abdrbo, "Mothers with self-reported axis I diagnoses and child protection," *Archives of Psychiatric Nursing*, vol. 23, no. 3, pp. 200–209, 2009.

[25] L. B. Kundra and L. B. Alexander, "Termination of parental rights proceedings: legal considerations and practical strategies for parents with psychiatric disabilities and the practitioners who serve them," *Psychiatric Rehabilitation Journal*, vol. 33, no. 2, pp. 142–149, 2009.

[26] A. Busch and A. D. Redlich, "Patients' perception of possible child custody or visitation loss for nonadherence to psychiatric treatment," *Psychiatric Services*, vol. 58, no. 7, pp. 999–1002, 2007.

[27] J. Monahan, A. D. Redlich, J. Swanson et al., "Use of leverage to improve adherence to psychiatric treatment in the community," *Psychiatric Services*, vol. 56, no. 1, pp. 37–44, 2005.

[28] J. Nicholson, "Use of child custody as leverage to improve treatment adherence," *Psychiatric Services*, vol. 56, no. 3, pp. 357–358, 2005.

[29] S. K. Kahng, D. Oyserman, D. Bybee, and C. Mowbray, "Mothers with serious mental illness: when symptoms decline does parenting improve? " *Journal of Family Psychology*, vol. 22, no. 1, pp. 162–166, 2008.

[30] M. W. Wan, S. Moulton, and K. M. Abel, "A review of mother-child relational interventions and their usefulness for mothers with schizophrenia," *Archives of Women's Mental Health*, vol. 11, no. 3, pp. 171–179, 2008.

[31] A. E. Reupert, K. T. Green, and D. J. Maybery, "Care plans for families affected by parental mental illness," *Families in Society*, vol. 89, no. 1, pp. 39–43, 2008.

[32] E. A. Craig, "Parenting programs for women with mental illness who have young children: a review," *Australian and New Zealand Journal of Psychiatry*, vol. 38, no. 11-12, pp. 923–928, 2004.

[33] M. V. Seeman, "Parenting issues in mothers with schizophrenia," *Current Women's Health Reviews*, vol. 6, no. 1, pp. 51–57, 2010.

[34] P. D. Zeanah, J. A. Larrieu, N. W. Boris, and G. A. Nagle, "Nurse home visiting: perspectives from nurses," *Infant Mental Health Journal*, vol. 27, no. 1, pp. 41–54, 2006.

[35] R. A. P. van der Zanden, P. A. M. Speetjens, K. S. E. Arntz, and S. A. Onrust, "Online group course for parents with mental illness: development and pilot study," *Journal of Medical Internet Research*, vol. 12, no. 5, article e50, 2010.

[36] A. Reupert and D. Maybery, "Families affected by parental mental illness: a multiperspective account of issues and interventions," *American Journal of Orthopsychiatry*, vol. 77, no. 3, pp. 362–369, 2007.

[37] M. Han, S. Carnochan, and M. J. Austin, "The challenges to promoting collaboration between child protection services workers and court professionals: an exploratory study of case records," *Journal of Public Child Welfare*, vol. 1, no. 3, pp. 115–131, 2007.

[38] Y. Darlington, J. A. Feeney, and K. Rixon, "Practice challenges at the intersection of child protection and mental health," *Child and Family Social Work*, vol. 10, no. 3, pp. 239–247, 2005.

[39] M. L. Kessler and B. J. Ackerson, "Wraparound services: an effective intervention for families impacted by severe mental illness," *Journal of Family Social Work*, vol. 8, no. 4, pp. 29–45, 2005.

[40] N. C. Winters and W. P. Metz, "The wraparound approach in systems of care," *Psychiatric Clinics of North America*, vol. 32, no. 1, pp. 135–151, 2009.

[41] E. J. Bruns and J. S. Walker, "Defining practice: flexibility, legitimacy, and the nature of systems of care and wraparound," *Evaluation and Program Planning*, vol. 33, no. 1, pp. 45–48, 2010.

[42] S. Hodges, K. Ferreira, N. Israel, and J. Mazza, "Systems of care, featherless bipeds, and the measure of all things," *Evaluation and Program Planning*, vol. 33, no. 1, pp. 4–10, 2010.

[43] J. Cook and P. Steigman, "Experiences of parents with mental illnesses and their services needs," *Journal of National Association for the Mentally (NAMI) California*, vol. 11, no. 2, pp. 21–23, 2000.

[44] L. Weinreb, J. Nicholson, V. Williams, and F. Anthes, "Integrating behavioral health services for homeless mothers and children in primary care," *American Journal of Orthopsychiatry*, vol. 77, no. 1, pp. 142–152, 2007.