Gender and Schizophrenia

Carol A. Tamminga, M.D.

Schizophrenia is a chronic psychotic illness that characteristically manifests itself from the early adult years throughout the entirety of life. Its symptoms are well known, its phenomenology has been exhaustively studied, and palliative treatments exist, although they rarely produce complete response. The pathophysiology and the etiology of the illness remain unknown. Clues to the basic understanding of schizophrenia are rare, but they do appear. Gender differences in schizophrenia have always been implicated in the challenge to clearly understand the disorder. Male and female schizophrenics display identical symptomatic features during acute illness, seemingly minimizing the relevance of gender issues. Within the last decade, however, more careful screening has revealed significant gender differences in schizophrenia: in age at onset, premorbid personality, subtype of schizophrenia, psychosocial function, and treatment response. Attention to these differences could be important to answer theoretical and therapeutic questions regarding the disorder.

(J Clin Psychiatry 1997;58[suppl 15]:33–37)

Schizophrenia is a lifelong psychotic illness that features an episodic course and considerable outcome heterogeneity.[1,2] Although it affects men and women with equal incidence, there are several striking gender differences in the illness prodrome, presentation, course, long-term outcome, and treatment response. This article serves to present recent findings in gender and schizophrenia, emphasizing the timely, representative, and methodologically attentive studies. It may be that some of these gender differences, more than reflecting normal sexual dimorphism, reflect aspects of the underlying biology of schizophrenia. In addition, and more practically, differences in the disease manifestation of schizophrenia by gender demand some distinct therapeutic considerations.

Schizophrenia is an illness that demonstrates considerable unexplained heterogeneity in many of its basic characteristics. Patients have widely different types of psychotic symptoms, symptom severities, and courses. Psychologic deficits vary between individuals, as do putative disease subtypes. Response to treatment, both to pharmacologic interventions and interpersonal strategies, differs between affected individuals. Mechanisms to explain this heterogeneity on a biological basis will contribute to studies of the pathophysiology of the illness. That gender differences can explain a significant piece of this variance in schizophrenia is suspected, but the extent of influence is still being studied.[3] This review will attempt to pull together potentially relevant data on the gender differences in schizophrenia in order to better understand its pathophysiology and methods of treatment.

GENDER DIFFERENCES IN PHENOMENOLOGY

Schizophrenia overall is characterized by a variety of psychotic symptoms that manifest themselves in the same way across cultures and throughout a course of illness, even though the expression of these symptoms can vary widely between individuals. Analysis of symptom expression in large clinical populations suggests that most schizophrenic individuals express predominantly one or another of three symptom clusters: hallucinations and delusions, thought disorder and bizarre behavior, or negative symptoms and withdrawal[4]; although primary manifestation of one cluster does not preclude a lesser manifestation of either of the other two symptom groups. These observations have led to the suggestion that there may be biologically meaningful subgroups of schizophrenia, which have definable differences in brain anatomy, biochemistry, and physiology.[4] This is by no means established, but analyses by subgroups of biological or psychologic features are often carried out heuristically. Although both male and female schizophrenics exhibit all the symptoms of schizophrenia, some evidence suggests that there is a shift in prevalence of these symptom clusters by gender even though acute psychotic symptoms seem not to differ.

Symptoms of schizophrenia during acute psychotic episodes, whether at first break[5] or at relapse,[6,7] do not differ

From the Maryland Psychiatric Research Center, University of Maryland at Baltimore.

Presented at the symposium "The Dynamics of Sex: Gender Differences in Psychiatric Disorders," held in conjunction with the 149th annual meeting of the American Psychiatric Association, May 5, 1996, New York, N.Y., and supported by an unrestricted educational grant from Roerig Division of the U.S. Pharmaceuticals Group, Pfizer Inc.

Reprint requests to: Carol A. Tamminga, M.D., Maryland Psychiatric Research Center, University of Maryland at Baltimore, P.O. Box 21247, Baltimore, MD 21228.

between male and female patients, either in type or severity. Several investigators, however, have reported differences in the predominant symptom cluster or subgroup diagnosis by gender. Andia et al.[8] reported a preponderance of female patients with paranoid diagnoses in their sample of 85 consecutive-admission schizophrenic individuals (53 men, 32 women). Szymanski et al.[5] found a lower proportion of primary negative symptoms in female first-break schizophrenics (7%) than in affected males (21%), which confirms earlier reports of more deficit symptoms in male schizophrenic patients.[9,10] Goldstein et al.,[11] in an analysis of 332 schizophrenic outpatients (171 men, 161 women), found that although both genders can express the different subtypes, male schizophrenics are at differential risk for flat affect (negative symptoms), winter birth, and poor premorbid course; female schizophrenics are at differential risk for persecutory delusions and dysphoria. Consistently in these studies, the male schizophrenic is more often afflicted with primary negative symptoms, even at illness onset.

Together, the studies do not support differences in acute symptom profiles between male and female schizophrenics; however, there seems to be a higher proportion of deficit patients who are male and possibly a higher proportion of paranoid individuals who are female.

GENDER DIFFERENCES IN COURSE OF ILLNESS

Schizophrenia is an illness in which a characteristically precipitous drop in psychosocial function occurs over the first several years after illness onset, followed by a relatively flat or stable course thereafter. In later years (in individuals over 50 years old), significant improvement is often evident in symptoms and in function. A clear replicated gender difference exists in schizophrenics in age at onset and in characteristics of illness course. Age at illness onset has consistently differentiated male and female schizophrenic patients, with men having onset at an earlier age than women and poorer premorbid function.[5,12–14] In addition, schizophrenic women have higher overall levels of social functioning across disease course than men.[12]

McGlashan and Bardenstein[15] examined gender differences in a chronic stable group of 163 schizophrenia patients, divided into subgroups of men (N = 80) and women (N = 83). They found the women to more frequently be married (32% of women vs. 15% of men) and have a higher level of premorbid function, despite a slight but significant difference in IQ (108 for women vs. 113 for men). Schizophrenic men were more aggressive and more self-destructive and expressed less dysphoria than schizophrenic women. With respect to outcomes, schizophrenic women spent less time in a psychotic state and had less substance abuse, higher social functioning, greater work competence, and a higher global outcome than schizophrenic men.

Another study[16] of schizophrenics living in a community setting made similar observations: women were more often parents, living with a partner, and heterosexually active than men. They were less often in jail and committed suicide less frequently.

Again, similarly, but in a different first-break schizophrenia sample, phenomenologic features by gender were different.[5] In this first-break group, the prevalence and type of psychotic symptoms were the same across genders; however, the deficit diagnosis was more prevalent in men, as was chronic disease course, whereas women showed higher global social competency scores and less ego impairment. Men's course of illness was more frequently associated with aggressive events, suicide, incarceration, and death than women's course of illness.

Perhaps because treatment response is different by gender, mid-disease course is much more benign for women than for men.[14] Not every course-of-illness study finds that schizophrenic women do better than men; some find no gender difference, but none to date find male patients doing better than female.[17] In a large patient cohort (N = 603), Angermeyer et al.[17] confirmed a lower number of hospitalization days annually and a lower risk for rehospitalization for women with schizophrenia than men with schizophrenia, which were attenuated as age advanced.

The long-term follow-up study[18] of schizophrenics in Vermont was consistent with these other observations of course and confirmed that the substantial differences in mid-life level of function tended to attenuate but not disappear over the very long term. All schizophrenic individuals tended to show significant improvements in symptoms and function after 50 or 55 years of age.

The virulence of schizophrenia is distinct between the genders, with male probands having the worse illness. Not only do schizophrenic women express their disease later, but they have significantly higher psychosocial function than schizophrenic men, despite the lack of remarkable symptomatic differences between genders. While this superior function must surely have a social component as a cause,[7] the differences are too profound to be totally explained on this basis. Thus, biological characteristics to explain these phenomena need to be sought.

GENETICS

Although the number of different studies examining genetics is sparse, some do exist. Goldstein et al.[11] studied 332 consecutive eligible admissions to a midwestern teaching hospital, forming a large and representative sample of schizophrenic individuals. A significantly higher family risk for schizophrenia, schizophreniform disorder, and schizoaffective illness was found in female probands than in male schizophrenics. However, when the diagnostic group within the families was expanded to in-

clude schizotypal personality disorders, atypical psychosis, and paranoid disorders, the female family predominance disappeared, due to the high prevalence of schizotypal disorder in male family members.[11] These data are consistent with the idea that male schizophrenics may be unusually vulnerable to a nongenetic form of the illness. Nonetheless, more studies of this type are needed to develop confidence that male and female schizophrenics differ in their genetic propensity for the illness.

BRAIN STRUCTURE AND FUNCTION

Several interesting gender differences in brain structure and function among normal individuals have been described using modern brain imaging procedures. While it is consistently found that overall brain size is larger in men than in women (both at postmortem examination and with structural imaging analysis),[19] the relative size of several other brain structures is larger in women. Specifically, the size of the corpus callosum and the anterior commissure has been found to be larger in normal women than in men in several, although not all, reports.[20,21] This finding may reflect more extensive interhemisphere communication in women than in men, although this interpretation is speculative.

Women have been found to have a greater volume of cerebral cortex in heteromodal association regions than men, particularly regarding the frontal and superior temporal areas bilaterally.[22,23] These data are consistent with the idea that associational thinking both within and between hemispheres is greater in women. In functional imaging studies, women have been shown to have higher regional cerebral blood flow (rCBF) in cortex and cortical glucose metabolism than men,[24] possibly reflecting a greater concentration of neurons in gray matter into a smaller cortical area. The cognitive state of the subjects determines the magnitude of the differences and is an important variable in these studies.[25]

Gender differences emerge with functional brain imaging *not* during general cognitive tasks[26] but during tasks utilizing language function. Shaywitz et al.[27] reported bilateral middle frontal cortical activation in normal women but only left-sided activation of the same area in normal men performing a language task (i.e., verbalization), whereas when the two groups were performing nonlanguage tasks, no gender differences were apparent. Magnetoencephalography and magnetic source imaging are two higher resolution techniques for functional brain assessment now being applied in interesting paradigms, especially to the question of gender differences.[28]

Studies of the brain structure of schizophrenics have tended to identify more men than women with structural abnormalities[9]; the corpus callosum has been variously identified as the feature with the greatest degree of abnormality.[20,21,29,30] Other than this, previous reports[10] studying gender differences in brain structure in schizophrenia, while not negative, had not been at all consistent and have suggested subtle disease changes. This group has also reported that while no direct gender differences developed in schizophrenics in frontal or temporal cortex volume, gender differences appeared in volume measures as they interacted with the subsymptom profile, although the differences were not great.

With respect to functional imaging studies of gender differences, far fewer studies have been done with schizophrenics than with nonaffected persons. Gur and Gur[31] have reported no significant differences in rCBF between schizophrenics across gender and performance variables. Holcomb et al.,[26] too, found no gender differences in schizophrenic or nonschizophrenic patients despite specific functional changes in the patient group (Figure 1). Neither of these studies involved language tasks, suggesting that in schizophrenics, as in nonaffected individuals,[32] gender differences may emerge only in select tasks, like language skills.

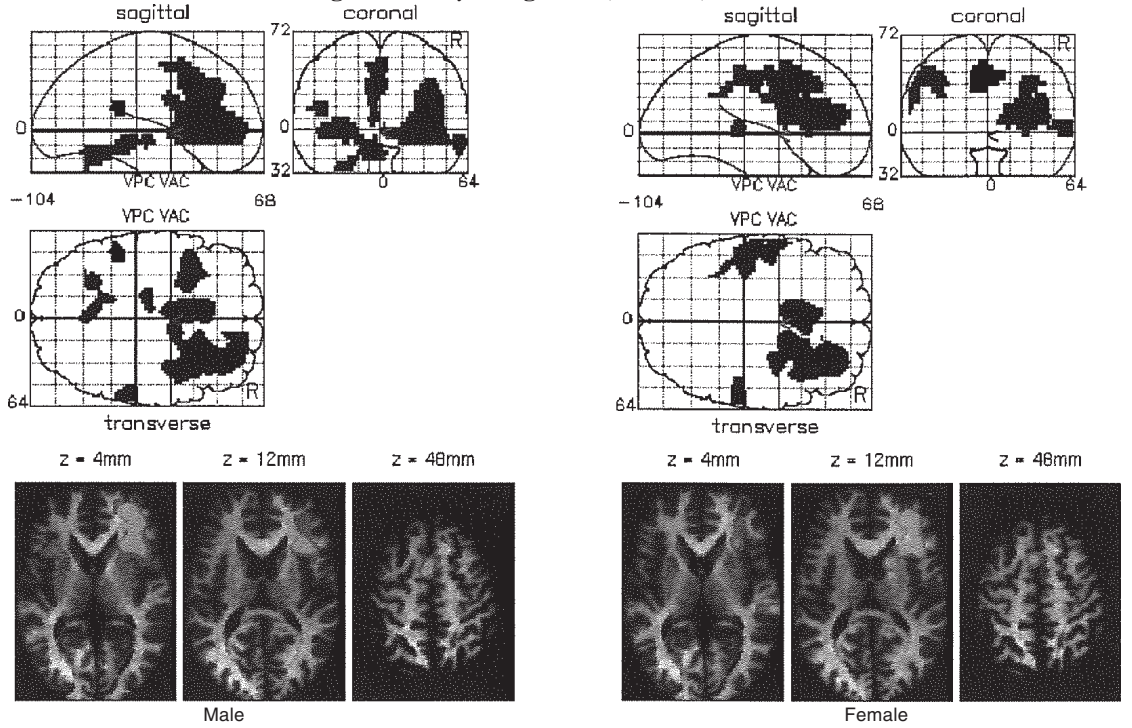
The interesting gender differences emerging from the study of normal individuals with functional imaging are likely to lead to parallel in vivo imaging studies in schizophrenics. This strategy would be promising to apply over time to schizophrenics to search for course determinants.

TREATMENT RESPONSE

Overall treatment response is relatively poor in schizophrenia compared with other treatable diseases like depression, pneumonia, or anemia; treatment for psychosis is often incomplete, requires continuous medication, and is accompanied by prominent treatment side effects. That rather substantial gender differences exist in treatment response is interesting. In a group of first-break schizophrenic patients, treatment response occurred sooner in women (12.1 weeks vs. 42.1 weeks), the frequency of nonremission was higher in male than female schizophrenics (18% vs. 2%), and the dose of neuroleptic required for treatment was lower in women than in men.[5,8] These data suggest that whereas women have the same level of psychopathology as men with acute episodes of psychosis, their response to medication is faster, occurs at a lower dose, and is more extensive than men's response.[33] Not only in first-break samples, but in older, more chronic individuals as well, schizophrenic women are treated with lower neuroleptic doses than men (437 mg, women vs. 812 mg, men; in chlorpromazine equivalents) out of proportion to their weight difference.

Haas et al.[7] examined the influence of psychosocial family training on the treatment response of the patient. The patient plus his or her family was given intensive family training, and outcomes were different depending on the gender of the patient. Families of male schizophrenics were more often late to sessions and were more rejecting

Figure 1. Differences Between rCBF During an Auditory Recognition (Decision) Task*



*This difference is illustrated in a group of normal persons, distinguished by gender in statistical parametric mapping projection images (top) and in difference plots on MRI templates (bottom). There are no gender differences in the nonaffected individuals when performing this auditory recognition task.

of the patient than the women's families. Families of female schizophrenics, after a course of inpatient family intervention (IFI) with hospitalization, more often showed a reduction in rejecting attitudes, whereas families of the men showed no such response. In fact, the IFI treatment outcomes improved over time for the women, but neither an immediate nor delayed effect was seen in men. Despite the gender differences determined in outcomes, no differences were seen in the core symptoms of schizophrenia.

By all parameters, female schizophrenics respond to all treatments better than male schizophrenics. They require less neuroleptic and are more likely to benefit from psychosocial treatment. These observations suggest the usefulness of designing treatment programs with gender-specific aspects in their design. In the current days of decreasing treatment moneys, such programs would be both effective and efficient if correctly done.

CONCLUSION

Consistent gender differences have been described among schizophrenic persons in psychosocial characteristics and treatment response, both in pharmacologic and psychosocial treatments. From a practical perspective, the prominence of these differences should suggest to responsible clinicians the importance of a differential treatment approach by gender for optimal therapeutic response. Female schizophrenics should have lower doses of neuroleptic treatment over a shorter time period and should have more aggressive psychosocial treatments. Male schizophrenics should have more aggressive drug treatments, a treatment focused on modulating interpersonal aggression and controlling addictions, and a concentration on integrating into structured long-term treatment settings. These different emphases for treatment are derived directly from observed gender differences in illness characteristics.

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