REVIEW ARTICLE
Key Words: schizophrenia, psychosocial, antipscyhotics, hypoestrogenism

Gender and Schizophrenia

By Carla M. Canuso, MD and Gahan Pandina, PhD

ABSTRACT *~ What are the important gender differences seen in men and women with schizophrenia? Although schizophrenia affects men and women with equal frequency, the illness is expressed differently between the sexes. Women with schizophrenia tend to have better premorbid functioning, a later age at onset, a distinct symptom profile and better course of illness, and different structural brain abnormalities and cognitive deficits. Additionally, premenopausal women appear to have a superior response to typical antipsychotics compared to men and postmenopausal women. These gender differences are thought to arise from the interplay between hormonal and psychosocial factors. It has been hypothesized that estrogen, with effects on both neurodevelopment and neurotransmission, may play a protective role in women with schizophrenia and account for some of the gender differences observed in the disorder. Despite the potential benefit of estrogen in this population, women with schizophrenia appear to be at risk for hypoestrogenism, either as a consequence of antipsychotic-induced hyperprolactinemia or, possibly, as a manifestation of the illness itself. The mechanism and consequences of hypoestrogenism in women with schizophrenia, as well as the role for hormonal therapies in this population, require further study.* Psychopharmacology Bulletin. *2007;40(4):178-190.*

INTRODUCTION

Increasingly, medical research has given attention to the role of gender in the expression of disease. Within psychiatry, the study of gender differences provides an "ideal window through which to look at the interplay of biological and psychosocial factors."[1] Women and men with schizophrenia display many important clinical differences, including dissimilarities in premorbid function, age at onset, symptomatology, course of illness, and response to typical antipsychotic medications, as well as possible differences in neuroanatomical abnormalities and cognitive deficits. Several authors have proposed that such differences arise from the inter-relationship between gonadal hormones and neurodevelopmental and psychosocial differences.[2–4]

Clinical evidence, supported by studies from the basic neurosciences, suggests estrogen may account for some of the differences observed in schizophrenia and may confer a clinical advantage to female patients. Likewise, social and psychological factors may contribute to a more favorable course of illness in women. This paper reviews some of the established gender differences in schizophrenia and summarizes the clinical and relevant pre-clinical evidence implicating estrogen's role in modifying neurodevelopment and disease expression. In light of estrogen's potentially

Dr. Canuso and Dr. Pandina are associate directors of clinical development for Janssen Pharmaceutica, Inc., in Titusville, NJ.

To whom correspondence should be addressed: MedWorks Media, 1048 17th Street, Santa Monica, CA 90403, USA; Tel: 310 829 4290; fax: 310 829 4289; E-mail: mthase@medworksmedia.com

beneficial role in women with schizophrenia, additional attention is given to the neuroendocrine side-effects of antipsychotic medication in women, as well as to possible hormonal manifestations of schizophrenia itself.

GENDER DIFFERENCES IN SCHIZOPHRENIA

Epidemiology, Premorbid Function and Age at Onset

Schizophrenia, occurring in approximately 1% of the global population, is thought to affect men and women with equal frequency.[5] Although more recent studies suggest, depending on the diagnostic criteria used, there is a trend towards a higher annual incidence in males,[6] the cumulative lifetime risk for schizophrenia appears to be the same for men and women.[7]

Women who develop schizophrenia tend to have better premorbid functioning than men, as reflected by the nature of their social relationships and marriage rates, and by indicators such as IQ, attention, and school and work functioning.[8–11]

Throughout the global schizophrenia literature, age at onset is consistently reported to occur approximately three to five years earlier in men than women.[12] In men age at onset peaks between ages 18-25, whereas in women this peak occurs between ages 25-35.[13] Unlike men, women appear to have an additional, smaller peak period of onset after the age of 40.[7,14] Moreover the preponderance of late-onset schizophrenia, defined as illness beginning after the age of 45, occurs in women.[15,16] However, the overall difference in age of onset appears to be accounted for by sporadic, but not familial schizophrenia – males and females with strong genetic loading have similarly early onsets.[3] Likewise, Meltzer and coworkers[17] reported a later age of onset in treatment responsive female patients, a difference not seen among non-responsive patients.

Symptom Expression and Course of Illness

Most, but not all, studies suggest that mood symptoms and specific positive symptoms (eg, paranoia, persecutory delusions, and auditory hallucinations) are common in women with schizophrenia, while negative symptoms (eg, social withdrawal, blunted affect, and amotivation) tend to be more predominant in men.[18–21] Inconsistency within these findings may relate to inadequate methodology as well as the absence of operational criteria and standardized interviews.[7] Additionally, because women tend to have more affective, cyclical, and atypical symptoms, there is less diagnostic concordance for women than men.[3]

In women with schizophrenia, symptoms tend to be relatively mild early in the course of illness. However as women age, these symptoms are apt to become more severe, whereas in men they tend to diminish.[22]

Additionally, women with late-life schizophrenia are inclined to develop a more severe form of the illness than their male counterparts.[2,23]

Irrespective of sex differences in symptomatology, women appear to have a more favorable course of illness and better psychosocial outcome than men, manifested by lower rehospitalization rates and shorter lengths of stay, longer time to relapse, and better social adjustment and rehabilitative capacity.[1,24–26] Women tend to receive better care, even when there are no differences in symptom severity or psychosocial factors; they attend outpatient appointments more frequently and receive more psychological, psychotherapeutic, and social rehabilitative care.[1] Although women with schizophrenia have lower suicide and overall mortality rates than their male counterparts,[27] female patients may experience more medical comorbidity.[28] The poorer social course of schizophrenia in men appears to relate to 1) their lower level of premorbid function; 2) the impact of their earlier age at onset on social development; and 3) their greater tendency to engage in socially adverse illness behavior (self neglect, treatment noncompliance, and substance abuse).[2,25] Additionally, families of male patients tend to be more critical, and males are more susceptible to relapse as a consequence of a "high expressed emotion" family environment.[29]

Neuroanatomy and Neuropsychological Function

Although less consistently reported, some studies indicate that women with schizophrenia have fewer and less severe structural brain abnormalities and cognitive deficits than men with the illness.[30,31] More specifically, males (but not females) have shown enlarged ventricles,[31,32] decreased temporal lobe volumes,[33] decreased volume in language-associated regions,[34] and more asymmetries.[35–37] While fewer studies show no difference or greater structural brain abnormality in women,[38] there may still be differential patterns of neurological impairment by gender.[39,40]

Studies of sex differences in neuropsychological performance in schizophrenia show conflicting results, possibly due to methodological limitations such as sampling bias and lack of adequate controls.[41] Perhaps the most consistent finding is better verbal performance in women than men,[42–45] though this difference may be mediated by sex differences in normal laterality of neuropsychological functioning.[46] Several studies demonstrate either no difference[47–49] or worse performance in females than males,[50–54] although some of the women in these samples were described as more impaired due to early onset or overall poorer outcome than average.

Antipsychotic Treatment Response

Many, though not all, studies suggest that, irrespective of body weight, pre-menopausal women with schizophrenia require lower doses and

TABLE 1

	MEN TEND TO HAVE	WOMEN TEND TO HAVE
Premorbid Functioning	Worse	Better
Age and Pattern of Onset	Peak at 18–25	Peak at 25–23
	No peak after 40	Second peak after 40
Symptom Expression	More mood symptoms	More negative symptoms
Course of Illness	More relapses	Fewer relapses
	More substance abuse	More medical comorbidity
Treatment Response		
Typical Antipsychotics	Higher dose requirements	Lower dose requirements
	Less favorable, but stable with age	Initially favorable, but reverses with age
Atypical Antipsychotics	Similar to women?	Similar to men?

Canuso and Pandina *Psychopharmacology Bulletin*. Vol. 40. No. 4. 2007.

achieve higher drug levels of typical antipsychotic medications, and have a better and more rapid treatment response than their male counterparts.[55–60] While better medication compliance among female patients may contribute to differences in dose requirements and treatment response,[60] it is important to note that as women approach menopause, these gender differences seem to disappear, or even reverse.[62] Since the typical antipsychotics exert their mechanism of action through dopamine D2 blockade, many have suggested that estrogen, through its antidopaminergic properties (see below), may enhance the effect of these drugs and explain the lower doses and better pharmacological response seen in pre-menopausal, but not postmenopausal, women.[55,62] Additionally, the reduction of cerebral blood flow with age may be a factor in the inferior treatment response seen in older compared to younger women, and a slower rate of dopamine D2 receptor decay in aging females compared to similarly aged men, may also contribute to the poorer response seen in older women relative to their male counterparts.[3]

Less is known about the differential response of women and men to atypical antipsychotic medications. Although studies of clozapine in treatment refractory schizophrenia reported a less favorable response in female compared to male patients,[63] it has been suggested that such results may have been confounded by sampling bias, as female patients with refractory illness may represent a more severely ill subset of women compared with men with the disorder.[41] Interestingly, in studies of atypical antipsychotics conducted in less severely ill populations, compared to men, women appear to respond similarly to risperidone and quetiapine, and perhaps better to olanzapine.[64–66] Since the antipsychotic effect of the atypical agents is thought to be related to their high affinity for the serotonin 5-HT_{2A} receptor relative to dopamine D2 receptor blockade, it is possible the antidopaminergic properties of estrogen do not

add as appreciable a benefit to the overall antipsychotic efficacy of these drugs as compared to the typical antipsychotics.

ROLE OF ESTROGEN IN SCHIZOPHRENIA

A later and bimodal pattern of onset, a relatively mild but progressive course of illness, and an initially favorable but dissipating response to typical antipsychotics are all characteristics of women with schizophrenia. Such clinical observations have led investigators to hypothesize that estrogen may play a protective role in women with schizophrenia and may account for some of the gender differences observed in the disorder.[4,67] Estrogen, present during the premenopausal years, may increase the threshold of susceptibility for schizophrenia, while the loss of estrogen after menopause may relate to an increased risk for development or worsening of the disorder. This hypothesis is further supported by studies of the relationship between the presence of estrogen and clinical symptoms in women with schizophrenia, as well as by the pre-clinical evidence of estrogen's effects on neurodevelopment and neurotransmission.

Estrogen and Clinical Symptoms of Schizophrenia

A variety of indirect clinical studies suggest a protective effect of estrogen in women with schizophrenia. For example, age at onset in women with schizophrenia appears to be inversely related to age at menarche, suggesting estrogen exposure may forestall early onset.[68] Additionally, an increased risk of relapse has been reported during the luteal phase of the menstrual cycle, during the postpartum period, and after menopause,[69] when estrogen levels are relatively low or absent. Conversely, women with recurrent psychosis have been noted to have fewer symptoms during pregnancy.[70] While few studies have directly assessed the relationship of serum estrogen levels and clinical symptoms, data suggest an inverse relationship between estrogen levels and psychotic symptoms,[71] and a positive relationship between cognitive performance and estrogen levels in menstruating women with schizophrenia.[72] Even less well studied than the effects of estrogen in women with schizophrenia are those of progesterone, which has been shown to have anxiolytic effects.[73]

Based on these observations, and studies of the effects of estrogen on dopamine transmission (see below), it has been suggested that estrogen may have antipsychotic-like effects.[67] Indeed, case reports, retrospective reviews, and preliminary studies of the adjunctive use of estrogen in the treatment of women with schizophrenia are beginning to emerge within the literature.[74–76] A small (n = 17), open study found that patients receiving a combination of transdermal estradiol (0.02 mg) and a typical antipsychotic (n = 11) showed a more rapid improvement in psychotic symptoms than patients receiving antipsychotic treatment alone.[76] To date

however, there are no published controlled trials to establish the effects of estrogen on psychotic symptoms in women with schizophrenia.

Estrogen and the Brain: Implication for Women with Schizophrenia

Sex hormones, present during fetal life, differentially impact central nervous system (CNS) development and permanently alter the structure and function of male and female brains.[77] Since schizophrenia is thought to be a neurodevelopmental disorder, with origins during fetal life, the role of these hormones on the normal sexual dimorphism in brain development may be relevant to gender differences in the expression of schizophrenia.[78,79]

In addition to permanent prenatal effects, sex hormones have transient neuroregulatory effects within the CNS.[80] Preclinical studies indicate that estrogen modulates a variety of neurotransmitter systems, particularly dopamine pathways.[81] In animal studies, estrogen has been shown to have antidopaminergic effects within the anterior pituitary and the striatum.[82,83] Given acutely, estrogen appears to reduce behavioral changes in animals treated with apomorphine (a D2 agonist), and enhances behavioral changes in animals treated with the D2receptor-blocking antipsychotic haloperidol.[67,81] Additionally, estrogen exposure in rodents decreases gene transcription of tyrosine hydroxylase, essential in the synthesis of dopamine and other catecholamines.[84] While not all studies support these findings,[85] taken together the literature suggests that estrogen results in an overall down-regulation of dopamine transmission. Additionally, estrogen has been shown to modulate other neurotransmitter systems, including serotonergic[86] and glutamatergic[87] pathways, thought to be relevant in the pathophysiology of schizophrenia.[86,88]

Neuroendocrine Function in Women with Schizophrenia

Given the potential benefit of estrogen in women with schizophrenia, it is important to recognize that women with schizophrenia may be at increased risk for hypoestrogenism, either as a consequence of antipsychotic-induced hyperprolactinemia, or perhaps of the illness itself.[89]

Antipsychotic-Induced Hyperprolactinemia

Typical antipsychotic medications and the atypical antipsychotic risperidone elevate serum prolactin levels through their potent blockade of dopamine D2 receptors in the tuberoinfundibular area of the brain.[90–92] Antipsychotic-induced hyperprolactinemia appears to be of greater magnitude in women compared to men,[93] and has long been considered a major factor in the high rates of menstrual dysfunction and, possibly, diminished estrogen levels observed in women with schizophrenia.[92,94] This topic has become of greater clinical interest since the availability of

several atypical antipsychotics with less potential to elevate prolactin.[95–98] While these new agents have been used to treat female patients with antipsychotic-induced hyperprolactinemia,[99,100] studies of the relationship between antipsychotic-induced hyperprolactinemia and ovarian function in women with schizophrenia are rather limited.

Although menstrual abnormalities have been cited in up to 50-75% of women treated with antipsychotics,[101–105] these reports do not describe the relationship of such abnormalities to serum prolactin levels. More recent studies designed to examine this relationship have failed to show significant differences in the prolactin levels of female patients with and without menstrual dysfunction.[89,94,106–108] Additionally, even studies of risperidone, which may have the most potential to elevate prolactin,[109,110] found no correlation between treatment-induced hyperprolactinemia and the emergence of prolactin-related side effects, including amenorrhea.[111,112] While one study[113] reported an inverse relationship between prolactin and estrogen levels in female patients with schizophrenia, other studies found no correlation between prolactin and estrogen levels in this patient population.[89,114] Although there does not appear to be a clear relationship between prolactin and estrogen levels in these patients, a number of recent studies,[71,72,89,94,114,115] as well as a carefully conducted study from the pre-neuroleptic era,[116] have suggested that women with schizophrenia do have diminished estrogen levels.

Osteoporosis is associated with both hyperprolactinemia and hypoestrogenism.[117,118] Several authors have suggested that patients with schizophrenia are at increased risk for osteoporosis, due possibly to antipsychotic-induced hyperprolactinemia as well as other associated risk factors such as cigarette smoking, polydipsia, and lack of exercise.[119,120] Since hyperprolactinemic bone loss appears to be related to the duration of prolactin elevation rather than to the absolute levels,[121] it will be important for future research to establish the extent to which antipsychotic-induced hyperprolactinemia, per se, contributes to the risk of osteoporosis in this population requiring chronic treatment.

Galactorrhea, a classic clinical manifestation of hyperprolactinemia, has been reported in 19-50% of female patients treated with antipsychotic medications.[122,123] While galactorrhea is a benign condition, the long-term effect of prolactin elevation on breast tissue is unknown. Although theories of breast cancer development stress the role of estrogen, rather than prolactin, as a risk factor, whether chronic treatment with antipsychotics increase risk for breast cancer has been a matter of some concern. A study using mammography to compare the incidence of breast cancer in chronic psychiatric patients to patients at a general medical clinic reported a 3.5 times higher incidence of breast cancer in the psychiatric population.[124] Although such findings are concerning, it

is not known whether the purported increased cancer rate is related to the use of prolactin-elevating medication. In addition, results from epidemiologic studies are equivocal; the majority of studies show no increased prevalence in breast cancer among antipsychotic-exposed females with schizophrenia,[125–127] or a small increase in females exposed to typical antipsychotics in an uncontrolled sample.[128]

The long-term consequences of antipsychotic-induced hyperprolactinemia are unknown. While there may be differential liability for various antipsychotics to elevate serum prolactin, the risk of hyperprolactinemia must be weighed against the risk of other clinically significant effects such as weight gain and altered glucose and lipid metabolism.[129,130]

Hypothalamic-Pituitary-Ovarian Manifestations of Schizophrenia

Based on several studies reporting high rates of menstrual dysfunction and/or diminished estrogen levels, irrespective of prolactin levels, we have speculated that ovarian dysfunction may be a neuroendocrine manifestation of schizophrenia in women. Since dopamine plays an important role in regulating the hypothalamic-pituitary-ovarian axis,[131] the dopamine dysregulation thought to underlie psychosis may also impair ovarian function.[89] Further research is necessary to assess whether such ovarian dysfunction is primarily related to the schizophrenic process and whether hormone replacement therapy or selective estrogen receptor modulators might provide clinical benefit to women with the disorder.

CONCLUSION

The literature suggests that women and men with schizophrenia manifest the illness differently. Women with schizophrenia tend to have better premorbid functioning, a later age and distinct pattern of onset, a more favorable course of illness, different cognitive deficits, and during the premenopausal years, a superior treatment response to typical antipsychotics compared to men. Such differences are thought to arise from an interaction between sex hormones and psychosocial factors. Estrogen, perhaps through its effects on dopamine transmission, may modulate symptom expression and may confer a clinical advantage for premenopausal women with schizophrenia. Despite the potential benefits of estrogen, women with schizophrenia appear to be at risk for hypoestrogenism, perhaps due to the prolactin-elevating effects of some antipsychotic medications or to the illness itself. Further studies are necessary to determine the long-term consequences of antipsychotic-induced hyperprolactinemia and clarify the mechanism of hypoestrogenism in women with schizophrenia. Additionally, further research on the safety and clinical utility of hormonal therapies to enhance outcome

and potentially reverse some consequences of hypoestrogenism in these patients is warranted. ✤

REFERENCES

1 Riecher-Rossler A, Hafner H. Gender aspects in schizophrenia: bridging the boarder between social and biological psychiatry. *Acta Psychiatr Scand*. 2000;102(suppl. 407):58-62.
2. Hafner H. Gender differences in schizophrenia. *Psychoneuroendocrinol*. 2003;28:17-54.
3. Leung A, Chue P. Sex differences in schizophrenia, a review of the literature. *Acta Psychiatr Scand*. 2000;101:3-38.
4. Seeman MV, Lang M. The role of estrogen in schizophrenia gender differences *Schizophr Bull*. 1990; 16(2):185-94.
5. Robins LN, Helzer JE, Weissman MM, Orvaschel H, Gruenberg E, Burke JD, et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry*. 1984;41(10):949-58.
6. Hambrect M, Maurer K, Hafner H. Gender differences in schizophrenia in three cultures. Results of the WHO cccollaborative study on psychiatric disability. *Soc Psychiatry Psychiatr Epidemiol*. 1992;27:117-21.
7. Hafner H, Maurer K, Loffler W, Riecher-Rossler A. The influence of age and sex on the onset and early course of schizophrenia. *Br J Psychiatry*. 1993;162:80-6.
8. Aylward E, Walker E, Bettes B. Intelligence in schizophrenia. *Schizophr Bull*. 1984;10(3):430-59.
9. Erlenmeyer-Kimling L, Kestingbaum C, Bird H, Hildoff U. Asssement of the New York high-risk project subjects in sample A who are now clinical deviants. In: Watt N, Anthony EJ, Wynne LC, Rolf eds. *Children at Risk for Schizophrenia: A Longitudinal Prospective*. 1984. Cambridge MA, Cambridge Press.
10. Larsen TK, McGlashan TH, Johannessen JO, Vibe-Hansen L. First-episode schizophrenia. II. Premorbid patterns of gender. *Schizophr Bull*. 1996;22(2):257-69.
11. Mednick SA, Schulsinger F, Teasdale TW, Schulsinger H, Venables PH, Rock D. Schizophrenia in high risk children: Sex differences and predisposing factors. In: Serban, G ed. *Cognitive Defects in the Development of Mental Illness*. 1978. New York, Brunner/Mazel, 169-97.
12. Jablensky A, Sartoriuos N, Ernberg G, Anker M, Korten A, Cooper JE, et al.Schizophrenia: manisfestations, incidence and course in different culutures. A World Health Organization ten-country study. *Psychol Med*. 1992;20(suppl. 20):1-97.
13. Angermeyer MC, Kuhn L. Gender differences in age at onset of schizophrenia. *Eu Arch Psychiatry Neurol Sci*. 1988;237:351-64.
14. Lindamer LA, Lohr JB, Harris MJ, Jeste DV. Gender, estrogen, and schizophrenia. *Psychophamacol Bull*. 1997;33(2):221-8.
15. Castle DJ, Murray RM. The epidemiology of late-onset schizophrenia. *Schizophr Bull*. 1993;19:691-700.
16. Jeste DV, Harris MJ, Krull A, et al. Clinical and neuropsychological characteristics of patients with late-onset schizophrenia. *Am J Psychiatry*. 1995;152:722-30.
17. Meltzer HY. Rabinowitz J. Lee MA. Cola PA. Ranjan R. Findling RL. Thompson PA. Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry*. 1997;154(4):475-82.
18. Addington D, Addington J, Patten S. Gender and affect in schizophrenia. *Can J Psychiatry*. 1996;41: 265-8.
19. Goldstein JM, Link B. Gender and the expression of schizophrenia. *J Psychiatric Res*. 1988;22(2):141-55.
20. Rector NA, Seeman MV. Auditory hallucinations in women and men. *Schizophr Bull*. 1992;7;233-6.
21. Ring N, Tantum D, Montague L, Newby D, Balack D, Morris J. Gender differences in incidence of definite schizophrenia and atypical psychosis: Focus on negative symptoms in schizophrenia. *Acta Psychiatry Scand*. 1991;84:489-96.
22. Ciompi L. The influence of aging on schizophrenia. *Triangle*. 1993;32:25-31.
23. Lindamer LA. Lohr JB. Harris MJ. McAdams LA. Jeste DV. Gender-related clinical differences in older patients with schizophrenia. *J Clin Psychiatry*. 1999;60(1):61-7.
24. Angermeyer MC, Goldstein JM, Kuhn L. Gender differences in schizophrenia: rehospitalization and community survival. *Psychol Med*. 1989;19:365-82.
25. Goldstein JM. Gender differences in the course of schizophrenia. *Am J Psychiatry*. 1988;145:684-9.
26. Salokangas RK. Prognostic implications of the sex of schizophrenic patients. *Br J Psychiatry*. 1983;142:145-51.
27. Goldstein JM, Santangelo SL, Simpson J, Tsuang MT. Gender and mortality in schizophrenia: Do women act like men? *Psychol Med*. 1993;23:941-8.
28. Sajatovic M, Sultana D, Bingham CR, Buckley P, Donenwirth. Gender related differences in clinical characteristics and hospital based resource utilization among older adults with schizophrenia. *Int J Geriatr Psychiatry*. 2002;17:542-48.

29. Hogarty G. Expressed emotion and schizophrenic relapse: Implications from the Pittsburgh study. In Alpert M, ed. *Controversies in Schizophrenia*. New York: Guilford Press, 1985;345-63.
30. Reite M, Sheeder J, Teal P, Adams M, Richardson D, Simon J, Jones RH, Rojas DC. Magnetic source imaging evidence of sex differences in cerebral lateralization in schizophrenia. *Arch Gen Psychiatry*. 1997;54:433-40.
31. Nopoulos P, Flaum M, Andreasen NC. Sex differences in brain morphology in schizophrenia. *Am J Psychiatry*. 1997;154:1648-54.
32. Narr K, Thompson P, Sharma T, Moussai J, Blanton R, Anvar B, Edris A, Krupp R, Rayman J, Khaledy M, Toga A. Three-dimensional mapping of temporo-limbis regions and the lateral ventribles in schizophrenia: gender effects. *Biol Psychiatry*. 2002;50:84-97.
33. Bryant NL, Buchanan RW, Vladar K, Breir A, Rothman M. Gender differences in temporal lobe structures of patients with schizophrenia: a volumetric MRI study. *Am J Psychiatry*. 1999;156:603-9.
34. Schlaepfer TE, Harris GJ, Tien AY, Peng L, Lee S, Pearlson GD. Structural differences in the cerebral cortex of healthy female and male subjects: a magnetic resonance imaging study. *Psychiatry Res*. 1995;61:129-135.
35. DeLisi LE, Hoff AL, Neale C, Kushner M. Asymmetries in the superior temporal lobe in male and female first-episode schizophrenic patients: measures of the planum temporale and superior temporal gyrus by MRI. *Schizophr Res*. 1994;12:19-28.
36. Gur RC. Turetsky BI. Matsui M. Yan M. Bilker W. Hughett P. Gur RE. Sex differences in brain gray and white matter in healthy young adults: correlations with cognitive performance. *J Neurosc*. 1999;19(10):4065-72.
37. McDonald B, Highley JR, Walker MA, Herron BM, Cooper SJ, Esiri MM, Crow TJ. Anomalous asymmetry of fusiform and parahippocampal gyrus gray matter in schizophrenia: a postmortem study. *Am J Psychiatry*. 2000;157:40-7.
38. Flaum M, Swayze V, O'Leary D, Yuh W, Ehrhardt J, Arndt S, Andreasen N. Effects of diagnosis, laterality, and gender on brain morphology in schizophrenia. *Am J Psychiatry*. 1995;152:704-14.
39. Gur RE, Turetsky BI, Cowell PE, Finkelman C, Maany V, Grossman RI, Arnold SE, Bilker WB, Gur RC. Temporolimbic volume reductions in schizophrenia. *Arch Gen Psychiatry*. 2000;57:769-75.
40. Goldstein J, Seidman L, O'brien L, Horton N, Kennedy D, Makris N, Caviness V, Faraone S, Tsuang M Impact of normal sexual domorphisms on sex differences in structural brain abnormalities in schizophrenia assessed by magnetic resonance imaging. *Arch Gen Psychiaty*. 2002;59:154-64.
41. Goldstein J. Sampling biases in studies of gender and schizophrenia: a reply. *Schizophr Bull*. 1993; 19(1):109-14.
42. Albus M, Hubmann W, Mohr F, Scherer J Sobizack N, Franz U, Hecht S, Borrmann M, Walheim C. Are there gender differences in neuropsychological performance in patients with first episode schizophrenia? *Schizophr Res*. 1997;28:39-50.
43. Goldstein J, Seidman L, Santangelo S, Knapp P, Tsuang M. Are schizophrenic men at higher risk for developmental deficits than schizophrenic women? Implications for adult neuropsychological functions. *J Psychiatr Res*. 1994;28(6):483-98.
44. Goldstein J, Seidman L, Goodman J, Koren D, Lee H, Weintraub S, et al. *Am J Psychiatry*. 1998;155: 1437-9.
45. Amminger G, Edwards J, Brewer W, Harrigan S, McGorry P Duration of untreated psychosis and cognitive deterioration in first-episode schizophrenia. *Schizophr Res*. 2002;54(3):223-30.
46. Ragland J, Gur R, Klimas B, McGrady N, Gur R. Neuropsychological laterality indices of schizophrenia: interactions with gender. *Schizophr Bull*. 1999;25(1):79-89.
47. Goldstein J, Gold J, Torrey E, Weinberger D. Lack of sex differences in the neuropsychological performances of patients with schizophrenia. *Am J Psychiatry*. 1995;152(6):883-8.
48. Moriarty PJ, Lieber D, Bennett A, White L, Parrella M, Harvey PD, Davis KL. Gender differences in poor outcome patients with lifelong schizophrenia. *Schizophr Bull*. 2001;27(1):103-13.
49. Scully PJ, Coakley G, Kinsella A, Waddington JL. Executive (frontal) dysfunction and negative symptoms in schizophrenia: apparent gender differences in 'static' v. 'progressive' profiles. *Br J Psychiatry*. 1997; 171:154-8.
50. Cadenhead KS, Geyer MA, Butler RW, Perry W, Sprock J, Braff DL. Information processing deficits of schizophrenia patients: relationship to clinical ratings, gender and medication status. *Schizophr Res*. 1997;28(1):51-62.
51. Friis S, Sundet K, Rund B, Vaglum P, McGlashan T. Neurocognitive dimensions characterising patients with first-episode psychosis. *Br J Psychiatry*. 2002;43(suppl):s85-s90.
52. Lewine R, Walker E, Shurett R, Caudle J, Haden C. Sex differences in neuropsychological functioning among schizophrenic patients. *Am J Psychiatry*. 1996;153(9):1178-84.
53. Perlick D, Mattis S, Stastny P, Teresi J. Gender differences in cognition in schizophrenia. *Schizophr Res*. 1992;8(1):69-73.

54. Weiser M, Reichenberg A, Rabinwitz J, Kaplan Z, Mark M, Nahon M, Davidson M Gender differences in premorbid cognitive performance in a national cohort of schizophrenic patients. *Schizophr Res*. 2002;45:185-90.
55. Chouinard G, Annable L. Pimozide in the treatment of newly admitted schizophrenic patients. *Psychopharmacol (Berl)*. 1982;76:13-9.
56. Glick M, Mazure CM, Bowers MB, Zigler E. Premorbid social competence and the effectiveness of early neuroleptic treatment. *Comp Psychiatry*. 1993;34:396-401.
57. Meltzer HY, Busch DA, Fang VS. Serum neuroleptic and prolactin levels in schizophrenic patients and clinical response. *Psychiatry Res*. 1983;9:271-83.
58. Pinals DA, Malhotra AK, Missar CD, Pickar D, Breier A. Lack of gender differences in neuroleptic response in patients with schizophrenia. *Schizophr Res*. 1996;22:215-22.
59. Salokangas RK. Gender and the use of neuroleptics in schizophrenia. Further testing of the estrogen hypothesis. *Schizophr Res*. 1995;16(1):7-16.
60. Seeman MV. Interaction of sex, age, and neuroleptic dose. *Compr Psychiatry*. 1983; 24:125-8.
61. Yonkers KA, Kando JC, Cole JO, Blumenthal S. Gender differences in pharmacokinetics and pharmacodynamics of psychotropic medication. *Am J Psychiatry*. 1992;149(5):587-95.
62. Seeman MV. The role of estrogen in schizophrenia. *J Psychiatry Neurosci*. 1996;21:123-7.
63. Szymanski S, Lieberman J, Pollack S, et al. Gender differences in neuroleptic nonresponsive clozapine-treated schizophrenics. *Biol Psychiatry*. 1996;39:249-54.
64. Goldstein JM, Cohen LS, Horton NJ, Lee H, Andersen S, Tohen M, Crawford A, Tollefson G. Sex differences in clinical response to olanzapine compared with haloperidol. *Psychiatry Res*. 2002;110(1): 27-37.
65. Labelle A. Light M. Dunbar F. Risperidone treatment of outpatients with schizophrenia: no evidence of sex differences in treatment response. *Can J Psychiatry*. 2001;46(6):534-41.
66. Reinstein M, et al. Poster presented at Annual Meeting of the APA, 1999. Washington, DC.
67. Hafner H, Behnens S, Devry J, Gattaz WF. An animal model for the effects of estradiol on dopamine-mediated behavior: Implications for sex differences in schizophrenia. *Psychiatry Res*. 1991;38:125-34.
68. Cohen RZ. Seeman MV. Gotowiec A. Kopala L. Earlier puberty as a predictor of later onset of schizophrenia in women. *Am J Psychiatry*. 1996;156(7):1059-64.
69. Hallonquist J, Seeman M, Lang M, Rector N. Variations in symptom severity over the menstrual cycle of schizophrenics. *Biol Psychiatry*. 1993;33:207-9.
70. Krener P, Simmins MK, Hansen RL, Treat JN. Effects of pregnancy on psychosis: life circumstances and psychiatric symptoms. *Int J Psychiatry Med*. 1989;19:65-84.
71. Riecher-Rossler A, Hafner H, Dutsch-Strobel A, Stunbaum M. Gonadal function and its influence on psychopathology: A comparison of schizophrenia and non-schizophrenic female inpatients. *Arch Women Ment Health*. 1998;1:15-26.
72. Hoff AL. Kremen WS. Wieneke MH. Lauriello J. Blankfeld HM. Faustman WO. Csernansky JG. Nordahl TE. Association of estrogen levels with neuropsychological performance in women with schizophrenia. *Am J Psychiatry*. 2001;158(7):1134-9.
73. Majewska MD. Neurosteroids: endogenous modulators of the GABA-A receptor: mechanism of action and physiological significance. *Prog Neurobiol*. 1992:38:379-95.
74. Korhonen S, Saarijarvi S, Alto M. Successful estradiol treatment of psychotic symptoms in the premenstrual phase: a case report. *Acta Psychiatr Scand*. 1995;92:237-8.
75. Lindamer LA, Buse DC, Lohr JB, Jeste DV. Hormone replacement therapy in postmenopausal women with schizophrenia: positive effect on negative symptoms? *Biol Psychiatry*. 2001;49(1):47-51.
76. Kulkarni J, de Castella A, Smith D Taffe J, Keks N, Copolov D. A clinical trial of the effects of estrogen in acutely psychotic women. *Schiz Res*. 1996;20:247-52.
77. Pilgrim C, Reisert L. Differences between male and female brains – development mechanisms and implications. *Horm Metab Res*. 1993;24:353-9.
78. Goldstein JM. Sex differences in schizophrenia: epidemiology, genetics, and the brain. *Int Rev Psychiatry*. 1997;9:339-408.
79. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry*. 1987; 44:660-9.
80. McEwen BS, Parsons B. Gonadal steroid action on the brain: neurochemistry and neuropharmacology. *Annu Rev Pharmacol Toxicol*. 1982;22:555-98.
81. DiPaolo T. Modulation of brain dopamine transmission by sex steroids. *Rev Neurosci*. 1994;5:27-42.
82. Raymond V, Beaulieu M, Labbrie F, Bossier JR. Potent antidopaminergic activity of estradiol at the level of prolactin release. *Science*. 1978;200:1173-5.
83. Di Paolo T, Poyet P, Labrie F. Effect of chronic estradiol and haloperidol treatment on striatal dopamine receptors. *Eur J Pharmacol*. 1981;73:1105-6.

84. Blum M, McEwen BS, Roberts JL. Transcriptional analysis of tyrosine hydroxylase gene expression in the tuberoinfundibular dopaminergic neurons of the rat arcuate nucleus after estrogen treatment. *J Biol Chem*. 1987;262:817-21.
85. Nausieda PA, Koller WC, Weiner WJ, Klawans HL. Modification of postsynaptic dopaminergic sensitivity by female sex hormones. *Life Sci*. 1979;25:521-6.
86. Fink G, Sumner BEH, McQueen JK, Wilson H, Rosie R. Sex steroid control of mood, mental state and memory. *Clin Exp Pharmacol Physiol.* 1998;25:764-75.
87. McEwen BS, Alves SE, Bulloch K, Weiland NG. Ovarian steroids and the brain: implications for cognition and aging. *Neurology.* 1997;48(suppl7):S8-S15.
88. Tamminga CA. Schizophrenia and glutamatergic transmission. *Crit Rev Neurobiol.* 1998;12(1-2):21-36.
89. Canuso C, Goldstein J, Wojcik J, Dawson R, Brandman D, Klibanski A, Schildkraut J Green A. Antipsychotic medication, prolactin elevation, and ovarian function in women with schizophrenia and schizoaffective disorder. *Psychiatry Res*. 2002;111:11-20.
90. Ereshefsky L, Lacombe S. Pharmacological profile of risperidone. *Can J Psychiatry.* 1993;38(supp): S80-S88.
91. Green AI, Brown WA. Prolactin and neuroleptic drugs. *Neurol Clinics*. 1988;6:213-32.
92. Meltzer HY. Long-term effects of neuroleptic drugs on the neuroendocrine system. In: Kremali D, Racagni G, editors. *Chronic Treatments in Neuropsychiatry: Advances in Biochemical Psychopharmacology*. Raven Press,1985; pp 59-68.
93. Kuruvilla A, Peedicayil J, Srikrishna G, Kuruvilla K, Kanagasabapathy AS. A study of serum prolactin in schizophrenia: comparison of males and females. *Clin Experiment Pharmacol Physiol.* 1992;19:603-6.
94. Riecher-Rossler A, Hafner H, Stunbaum M, Maurer K, Schmidt R. Can estradiol modulate schizophrenic symptomatology? *Schizophr Bull*. 1994;20:203-14.
95. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol: acute phase results in the North American double-blind olanzapine trial. *Neuropsychpharmacol*. 1996;14:111-23.
96. Casey DE. 'Seroquel' (quetiapine): preclinical and clinical findings of a new atypical antipsychotic. Exp Opin Invest Drugs 1996;5:939-57
97. Daniel DG, Copeland LF. Ziprasidone: comprehensive overview and clinical use of novel antipsychotic. *Exp Opin Invest Drugs.* 2000;9(4):819-28.
98. Kane JM, Cooper TB, Sachar EJ, Halpern FS, Bailine S. Clozapine: plasma levels and prolactin response. *Psychopharmacol*. 1981;73:184-7.
99. Bunker MT, Marken PA, Schneiderhan ME, Ruehter VL Attenuation of antipsychotic-induced hyperprolactinemia with clozapine. *J Child Adol Psychopharmacol*. 1997;7:65-9.
100. Canuso CM, Hanau M, Jhamb KK, Green AI. Olanzapine use in women with antipsychotic-induced hyperprolactinemia. *Am J Psychiatry*. 1998;155:1458.
101. Akhtar S, Thomson, JA Jr. Schizophrenia and sexuality: a review and a report of twelve unusual cases – Part 2. *J Clin Psychiatry*. 1980;41:166-74.
102. Beaumont PJV, Gelder MG, Friesen HG, Harris GW, MacKinnon PCB, Mandelbrote BM, Woles DH. The effects of phenothiazines on endocrine function: I. *Br J Psychiatry*. 1974;124:413-19.
103. Polishuk WZ, Kulcsar S. Effects of chlorpromazine on pituitary function. *J Clin Endocrinol*. 1956; 16:292-3.
104. Sandison RA, Whitelaw E, Currie JD. Clinical trials with mellaril (TP21) in the treatment of schizophrenia: a two year study. *J Ment Sci*. 1960;106:732-41.
105. Sullivan G, Lukoff D. Sexual side effects of antipsychotic medication: evaluation and interventions. *Hosp Com Psychiatry*. 1990;41:1238-41.
106. Ghadirian AM, Chouinard G, Annable L. Sexual dysfunction and plasma prolactin levels in neuroleptic-treated schizophrenic outpatients. *J Nervous Ment Dis*. 1982;170:463-7.
107. Magharious W, Goff DC, Amico E. Relationship of gender and menstrual status to symptoms and medication side effects in patients with schizophrenia. *Psychiatry Res*. 1998;77(3):159-66.
108. Prentice DS, Deakin JFW. Role of neuroleptic drugs and organic mechanisms in the etiology of menstrual irregularities in schizophrenic women. *Schizophr Res*. 1992;6:114.
109. Dickson RA, Dalby JT, Williams R, Edwards A. Risperidone-induced prolactin elevations in premenopausal women with schizophrenia. *Am J Psychiatry*. 1995;152:453-5.
110. Kinon BJ, Gilmore JA, Liu H, Halbreich UM. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. *Psychoneuroendocrin*. 2003;28(2):55-68.
111. Kleinberg DL, Davis JM, de Coster R, Van Baelen B, Brecher M. Prolactin levels and adverse events in patients treated with risperidone. *J Clin Psychopharmacol*. 1999;19(1):57-61.

112. Conley R, Mahmoud R. A randomized, double blind study of risperidone and olanzapine in the treatment of schizophrenia and schizoaffective disorder. *Am J Psychiatry*. 2001;158:765-74.
113. Smith S, Wheeler MJ. Murray R, O'Keane V. The effect of antipsychotic-induced hyperprolactinemia on the hypothalamic-pituiutary-gonadal axis. *J Clin Psychopharmacol*. 2002;22:109-14.
114. Huber TJ, Rollnik J, Wilhelms J, von zur Muhlen A, Emrich HM, Schneider U. Estradiol levels in psychotic disorders. *Psychoneuroendocrin*. 2001;26:27-53.
115. Oades RD, Schepker R. Serum gonadal steroid hormones in young schizophrenic patients. *Psychoneuroendocrin*. 1994;19(4):373-85.
116. Ripley HS, Papanicolaou GN. The menstrual cycle with vaginal smear studies in schizophrenia, depression and elation. *Am J Psychiatry*. 1941;98(4):567-73.
117. Klibanski A, Neer R, Beitins I, Ridgway EC, Zervas NT, McArthur JW. Decreased bone density in hyperprolactinemic women. *N Engl J Med*. 1980;303(26):1511-4.
118. Schlechte J, Walkner L, Kathol M. A longitudinal analysis of premenopausal bone loss in healthy women and women with hyperprolactinemia. *J Clin Endocrinol Metab*.1992;75:698-703.
119. Abraham G, Friedman, RG, Verghese C. Osteoporosis demonstrated by dual energy X-ray absorptiometry in chronic schizophrenia patients. *Biol Psychiatry*. 1996;40(5):430-1.
120. Halbreich U, Palter S. Accelerated osteoporosis in psychiatric patients: possible pathophysiological processes. *Schizophr Bull*. 1996; 22:447-54.
121. Greenspan SL, Neer RM, Ridgway EC, Klibanski A. Osteoporosis in men with hyperprolactinemic hypogonadism. *Ann Intern Med*. 1986;104:777-82.
122. Apostolakis M, Kapetanskis S, Lazos G, Madena-Pyrgaki A. In: Lactogenic Hormones Wolstenholme GEW, Knight J, eds. 1972. Churchill Livingstone.
123. Windgassen K, Wesselmann U, Schulze-Monking H. Galactorrhea and hyperprolactinemia in schizophrenic patients on neuroleptics: frequency and etiology. *Neuropsychobiol*. 1996;33:142-146.
124. Halbreich U, Shen J, Panaro V. Are chronic psychiatruc patients at increased risk for developing breast cancer? *Am J Psychiatry*. 1996;153:559-60.
125. Goode DJ, Corbett WT, Schey HM, Suh SH, Woodies, B, Morris DL, Morrisey L. Breast cancer in hospitalized psychiatric patients. *Am J Psychiatry*. 1981;138:804-6.
126. Love RR, Rose DR, Su rawicz TS, Newc omb P. Prolactin and growth horm one levels in premenopausal women with breast cancer and healthy women with a strong family history of breast cancer. *Cancer*. 1991;68(6):1401-5.
127. Wang DY, De Stavola BL, Bulbrook RD, Allen DS, Kwa HG; Fentiman IS, Hayward JL, Millis RR. Relationship of blood prolactin levels and the risk of subsequent breast cancer. *Int J Epidemiol*. 1992; 21(2):214-21.
128. Wang P, Walker AM, Tsuang M, Orav EJ, Glynn RJ, Levvin R, Avorn J. Dopamine antagonists and the development of breast cancer. *Arch Gen Psychiatry*. 2002;59:1147-54.
129. Allison DB, Meentore JL, Heo M, Chandler LP, Cappellari JC, Infante MC, Weiden PJ. Antipsychotic induced weight gain: a comprehensive research synthesis. *Am J Psychiatry*. 1999;156:1686-96.
130. Lindenmayer JP, Czobor P, Volavka J, Citrome L, Sheitman ,. McEvoy JP, Cooper TB, Chakos M, Lieberman JA. Changes in glucose and cholesterol levels in patients with schizophrenia treated with typical or atypical antipsychotics. *Am J Psychiatry*. 2003;160(2):290-6.
131. Ferin M, Jewlewicz R, Warren M. The neuroendocrine component: The hypothalamic-pituitary unit. In: *The Menstrual Cycle Physiology, Reproductive Disorders, and Infertility*. 1993; Oxford University Press, New York, pp. 8-24.