Review Paper

The Role of Estrogen in Schizophrenia: Implications for Schizophrenia Practice Guidelines for Women

Sophie Grigoriadis, PhD, MD[1], Mary V Seeman, MDCM, FRCPC, FACP[2]

Objective: The objective of this paper is to integrate what is known about estrogen effects on symptoms and treatment response into a global understanding of schizophrenia. The aim is to expand Canadian schizophrenia guidelines to include the specific needs of women.

Method: We searched the Medline database; keywords included estrogen, estrogen replacement therapy, schizophrenia, psychosis, treatment, tardive dyskinesia (TD), and women. We examined reference lists from relevant articles to ensure that our review was complete. We review the evidence for the effects of estrogen in schizophrenia and we make recommendations for the next revision of official practice guidelines.

Results: The epidemiologic evidence suggests that, relative to men, women show an initial delay in onset age of schizophrenia, with a second onset peak after age 44 years. This points to a protective effect of estrogen, confirming animal research that has documented both neurotrophic and neuromodulatory effects. Clinical research results indicate that symptoms in women frequently vary with the menstrual cycle, worsening during low estrogen phases. Pregnancy is often, though not always, a less symptomatic time for women, but relapses are frequent postpartum. Some work suggests that in the younger age groups women require lower antipsychotic dosages than men but that following menopause they require higher dosages . Estrogen has been used effectively as an adjunctive treatment in women with schizophrenia. Estrogen may also play a preventive role in TD.

Conclusions: Symptom evaluation and diagnosis in women needs to take hormonal status into account. Consideration should be given to cycle-modulated neuroleptic dosing and to careful titration during pregnancy, postpartum, and at menopause. We recommend that discretionary use of newer neuroleptic medication and adjuvant estrogen therapy be considered.

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Clinical Implications

- Clinical assessment in women with schizophrenia must include questions about hormonal status.
- Treatment in women needs to consider hormonal status.
- The longitudinal course of illness in women is different from that in men.

Limitations

- Clinical studies have been few and have included limited numbers of subjects.
- Atypical antipsychotics and adjuvant estrogen pose their own health risks.

Key Words: *women, schizophrenia, estrogen, practice guidelines*

Numerous sex differences have been reported in schizophrenia, and it is now evident that men and women experience and manifest psychosis differently. Briefly, women show a superior premorbid adjustment, relative to men: their symptoms begin later in life, and outcome is usually superior (at least in the first 15 years after onset) (1). Women also show a second paramenopausal peak onset not seen in men (2). Mood symptoms such as depression are more common in women, whereas apathy, flat affect, paucity of speech, and social isolation are more often seen in men (3), although this dif-

ference in symptoms is not always seen (1). More brain structure impairment has been reported in men (4). Premenopausal women may respond at lower antipsychotic dosages than do men (5). Although the etiology of the sex differences is not entirely understood, hormone-gene interactions probably account for part of the variance. The first part of this paper reviews the literature on studies examining the influence of estrogen in schizophrenia. This review is based on a Medline database search and a review of relevant reference lists. To optimize diagnosis and treatment of schizophrenia in women, the second half of this paper suggests modifications of practice guidelines, based on the evidence of estrogen effects. To date, guidelines for the treatment of schizophrenia have not directly distinguished between the sexes.

Estrogen Hypothesis

The association between estrogen and schizophrenia in women is not a 20th century phenomenon. Early clinicians referred to many women with schizophrenia as suffering from "hypoestrogenism." Schizophrenic psychosis was said to be influenced by the natural variation of estrogen levels, both over a woman's cycle and over her lifetime (6). The early observations are especially important because they were made before the advent of modern antipsychotics that, via dopamine blockade and subsequent release of prolactin inhibition, result in high prolactin serum levels with downstream inhibition of ovarian estrogen secretion; that is, secondary hypoestrogenism.

The modern "estrogen hypothesis" postulates that estrogen exerts a protective effect against schizophrenia and that this partly explains the observed sex differences in premorbid adjustment, onset age, treatment response, and illness course. Evidence for the role of estrogen in schizophrenia comes from many sources, including epidemiologic data, effects of pubertal age on schizophrenia onset, the changing severity of symptoms over a woman's reproductive life, and the results of treatment studies.

Estrogen Effects

Animal studies show estrogens to have organizational effects on developing neurons and activational effects on mature neurons. Estrogens affect neurite growth and synapse formation; interact with nerve growth factor and other neurotrophins; and modulate many neurotransmitters systems, including the dopamine, serotonin, norepinephrine, acetylcholine, and glutamate systems. Table 1 presents estrogens' multiple other protective effects (7).

Estrogen and Schizophrenia

Epidemiological Studies

Several studies have established that schizophrenia has later onset in women. Typically, women present at age 25 to 29 years, as opposed to men, who usually first present at age 20 to 24 years (2). In addition, a second smaller peak of onset exists for women after age 44 years, around the perimenopause and menopause (8).

Puberty and the Menopause

Earlier age at menarche is associated with later onset of schizophrenic symptoms (9). In contrast to what happens after puberty, prepubertal onset is earlier in girls than in boys (10). These 2 findings taken together suggest that pubertal hormones delay onset in women. At the other end of life, symptom severity increases with age in women only (11).

Symptom Variation Across the Menstrual Cycle, During Pregnancy, and Postpartum

Forty-seven percent of psychiatric admissions occur during the paramenstrual phase, when estrogen levels are lowest (12). Hallonquist and others looked at 5 outpatients over 2 consecutive menstrual cycles and found global symptom scores to be significantly lower during high estrogen phases (13). A more recent study with a larger sample confirmed these findings (14). Riecher-Rossler and others showed a significant association between estradiol levels and psychosis scores, with psychopathology improving when estradiol levels rose (15). Hoff and others studied a group of 22 inpatients and found a positive association between estrogen levels and cognitive performance (16). Taken together, these studies suggest a modulating effect of estrogen on both symptoms and cognition: the higher the estrogen levels, the less severe the symptoms, and the more intact the cognitive abilities.

Chang and Renshaw reported an amelioration of symptoms during pregnancy (17). Krener and others found that women with schizophrenia received and required less medication to control their thought disorder when they were pregnant (18).

Table 1 The effects of estrogens

- Increase sensory perception
- Decrease seizure threshold
- Reduce acute phase inflammatory response
- Possess antioxidant effects
- Increase cerebral blood flow
- Augment cerebral glucose utilization
- Blunt hypothalamic-pituitary-adrenal axis reactivity
- Enhance verbal episodic memory
- May delay the onset and risk of Alzheimer's disease
- Reduce formation of B-amyloid
- Enhance mood state
- Mediate pain perception

Kendall and others noted that relapses tended to occur postpartum, when estrogen levels were low (19).

Estrogen and Neuroleptic Medication

One study showed that women with schizophrenia admitted during the low-estrogen phases of their menstrual cycle required significantly lower mean daily dosages of neuroleptic medication (325 mg chlorpromazine [CPZ], SD 203 mg) than did a high-estrogen phase admission group (414 mg CPZ , SD 204 mg; $P < 0.05$) (20). From this study, Gattaz and others concluded that the antidopaminergic effects of estradiol modulate the vulnerability threshold for psychosis. In a 3-year survey of the neuroleptic maintenance requirements of 101 outpatients suffering from chronic schizophrenia, Seeman found that younger women (age 20 to 39 years) were maintained on lower dosages than were men, but the reverse was true after age 40 years (5). Not all studies agree, however. Although Szymanski and others found a greater pharmacologic response in female patients with first-episode schizophrenia, compared with male patients in one study (21), treatment-refractory women did not fare better then men on clozapine in a subsequent study (22).

Estrogen as Treatment

Direct evidence for the estrogen hypothesis comes from studies that have used estrogen to treat psychotic symptoms. In a 28-day double-blind randomized controlled trial (RCT), Kulkarni and others found dramatic improvement in psychotic symptoms beginning at day 4 (23). In this study, 36 women were randomly assigned either a 100 mcg estrogen patch, a 50 mcg estrogen patch, or placebo, in addition to standardized antipsychotic medication. The women in the 100 mcg group were significantly better at the end of the trial. In an earlier open clinical trial, Kulkarni and others gave 0.02 mg of estradiol in addition to regular neuroleptic treatment to 11 women with acute psychotic symptoms (24). Their response was compared with that of 7 women with similar symptom severity receiving neuroleptic treatment alone. The group receiving the estradiol adjunct showed more rapid improvement in psychotic symptoms, although both groups reached similar levels of recovery by the final week of the study (week 8). Lindamer and others presented a case report of estradiol augmentation in a postmenopausal woman with schizophrenia (25). They administered 0.05 mg of Estraderm in addition to perphenazine and found a reduction in the patient's positive symptoms while on estrogen. Once the patient discontinued the estrogen, she returned to near-baseline levels of positive symptoms. Korhonen reported that estradiol therapy alone alleviated psychotic symptoms occurring in the premenstrual phase of a woman diagnosed with schizoaffective disorder (26). This patient was given 3.0 mg of percutaneous estradiol for 5 months. She was able to discontinue her regular medications 1 month after starting estradiol. Taken together, the results of these studies suggest that estradiol demonstrates antipsychotic properties or acts as a catalyst for neuroleptic responsiveness (or both) in women with schizophrenia. Similarly, Ahokas and others were able to successfully treat 10 women with postpartum psychosis with 17β-estradiol alone (27). Scores on the Brief Psychiatric Rating Scale improved from a mean of 78 (SD 7.7) to 19 (SD 6.9) after the first week of treatment. This study also showed the link between low serum estradiol concentrations and clinical response to estradiol treatment. Although the women in the study suffered from postpartum psychosis and not schizophrenia, estradiol was shown to have a direct antipsychotic effect.

Estrogen and Tardive Dyskinesia

Given that over the age of 70 years the prevalence of tardive dyskinesia (TD) is higher for women than for men (49.1% vs 24.4%), and that this differential rate is similar to the differential rate of osteoporosis in the group over age 70 years, it has been suggested that estrogen withdrawal may in part be implicated in TD (as it is in osteoporosis) (28). Turrone and others reviewed the literature for the potential influences of estrogen on TD in humans and concluded that estrogen may play a role in ameliorating or preventing symptoms of TD (29).

Comments on the Evidence

Despite the interest in this area since the late 1800s, more research is needed to further elucidate the exact role of estrogen in schizophrenia. To date, there have been few studies; and most are descriptive, correlational, or case studies with small sample sizes. The first RCT had a small sample size and awaits replication (23). Moreover, not all studies have been replicated—for example, Salokangas did not find a consistent increase in the daily dosage of neuroleptics after menopause in a sample of patients followed over 3 years (30). A convincing study would need to control for weight, smoking status, substance abuse, and concomitant medications. Castle and others argue that the sex differences are not due to hormonal effects, but rather to sex-specific forms of schizophrenia subtypes (31). Thus, the estrogen hypothesis is not universally held, and it is far from certain whether women and men require different dosing, especially with the newer antipsychotics. There is general consensus, however, that a woman's hormonal status needs to be considered for optimal assessment and treatment.

Implications for Future Research

When designing estrogen treatment studies, the various types and preparations of estrogen need to be kept constant so that results can be compared. When comparing antipsychotic response, the metabolic pathways of specific neuroleptics need to be considered, because estrogen has differential effects on

hepatic enzymes. Future studies need to monitor both estrogen levels and drug plasma levels. Treatment with estrogen has been limited by the potential side effects associated with all estrogens—the most ominous being breast and uterine cancer. The advent of Selective Estrogen Receptor Modulators (SERMS) has allowed more extensive and relatively risk-free investigation of the role of estrogen in the central nervous system (CNS). SERMs are designer estrogens inhibiting or enhancing estrogenic effects in a tissue-specific manner. In Canada, 2 have been released: tamoxifen and raloxifene. Raloxifene has been approved for the prevention of osteoporosis, and has estrogen-like effects on bone, but seems to be an estrogen antagonist in breast and uterine tissue. To date, no data have been released on its effects in treating psychosis, but it does have known CNS effects (32,33).

Assessment and Treatment Implications for Women

The effects of estrogen on schizophrenia have numerous implications that can be incorporated into specific practice guidelines for women. In terms of prevention, closer monitoring and higher suspicion of a schizophrenic illness are needed at different life points in women than in men: the late 20s, postpartum, and menopause are risk periods for women. Relatively good premorbid adjustment or late-onset psychosis do not preclude schizophrenia in women. The menstrual cycle, pregnancy, postpartum, and menopause bring about symptom changes that may require treatment alterations. Clinical monitoring throughout the menstrual cycle, perhaps with the use of diaries, can facilitate both the prevention of exacerbations and the evaluation of treatment response (Table 2). The current *Canadian Clinical Practice Guidelines for the Treatment of Schizophrenia* do not address the monitoring of clinical changes across the menstrual cycle (34). The studies we reviewed on symptom variation across menstrual phases that support this recommendation constitute level 2 ("fair research-based") evidence.

The treatment implications of this review also include cycle-modulated neuroleptic dosing. Higher dosage requirements are expected premenstrually and during menstruation; lower dosage needs are expected mid-cycle. The intent of this recommendation is to avoid perimenstrual exacerbations and to deliver a lower lifetime neuroleptic dosage; that is, fewer side effects and overall optimized treatment. The studies supporting the above recommendation, reviewed in the previous section on estrogen and neuroleptic medication, constitute level 3 ("minimal research-based, but significant clinical") evidence. The estrogen hypothesis argues for higher neuroleptic dosage requirements in menopausal women, which is contrary to the current *Practice Guidelines* recommendation to decreases dosage in the older age groups. Given that there is only level 3 evidence, clinicians should be made aware of the potential need for dosage increments in menopausal women. The benefits of treatment need to be weighed against the potential for increased side effects coincident with advancing age. Adjuvant estrogen therapy should be considered in menopausal and postmenopausal women with schizophrenia where medically indicated, given that estrogen augmentation can help a) ameliorate psychotic symptoms, b) decrease neuroleptic requirements, and c) decrease risk for TD. Although there is only 1 RCT in the schizophrenia literature to support estrogen augmentation (23), there is very good research-based evidence from the medical literature to support the use of estrogen replacement where medically indicated in postmenopausal women.

Although there is no level 1 evidence to support the observation that pregnancy is a less symptomatic period because of higher estrogen levels, given that neuroleptic medication can potentially adversely affect the developing fetus, it is critical to reassess medication dosage during pregnancy. The *Practice Guidelines* do address this issue. The older antipsychotics may increase the risk for congenital anomalies by as much as 4% over baseline. Although double-blind controlled studies are lacking and antipsychotics are considered relatively safe, they, like all drugs, should be avoided between week 4 and 10 postconception. After that period, symptoms should be closely monitored and dosages should be lowered where appropriate. A risk-benefit analysis needs to be considered for

Table 2 Assessing women with schizophrenia: special considerations

- Monitor for symptom changes:
  - Across the menstrual cycle
  - During pregnancy
  - Postpartum
  - At menopause
- Screen for cardiovascular risk factors and family history of
  - Breast cancer
- Screen for sexual side effects:
  - Breast engorgement
  - Galactorrhea
  - Libido
  - Sexual dysfunction
- Screen for Tardive Dyskinesia systematically[a]
- Monitor levels:
  - Prolactin[b]
  - estrogen
  - blood sugar
  - lipid profile[c]

[a]Estrogen withdrawal may be a factor in TD at menopause
[b]Hyperprolactinemia can lead to hypoestrogenism and osteoporosis
[c]Women may be more susceptible to weight gain and lipid abnormalities secondary to antipsychotics

each individual, because untreated illness also poses a risk to the developing fetus: maternal stress and increased glucocorticoid concentrations can adversely affect fetal brain development (35). During the postpartum period, women with schizophrenia are especially vulnerable because of the lowered estrogen levels and because the stresses of child care may be overwhelming. If discontinued prior to delivery, antipsychotic medications should be resumed immediately postpartum and at higher-than-usual dosage for the first 6 weeks (36). Neuroleptic medication concentrates in the lipids of breast milk and, in the past, breast feeding has been discouraged. The benefits of breast feeding are now well known and, currently, most women are encouraged to breast feed; research to date, although scarce, has shown limited risk to the infant of psychotropics in breast milk (37). Guidelines are emerging to help clinicians consider a risk-benefit analysis for their patients (38,39). Recently, concern has been raised that clozapine increases the risk for pulmonary emboli (40). Given that pregnancy and the postpartum state are known risk factors for thromboembolic disease, and that clozapine also puts the infant or fetus at risk for agranulocytosis and seizures, this drug should be avoided where possible during pregnancy and lactation (41). It must, of course, be recognized that clozapine is often a drug of last resort and not easily substituted. Leukocyte counts should be monitored in infants being breast fed by mothers taking clozapine.

Screening for hyperprolactinemia secondary to neuroleptic treatment is especially recommended in women. Although beyond the scope of this paper and controversial, a link has been made between hyperprolactinemia in neuroleptic-treated women and an increased incidence of breast cancer (42). All women are encouraged to conduct regular breast self-examinations; women with schizophrenia, however, may be at increased risk and are often not able to engage in health-promoting behaviour, given the effects of schizophrenia itself. The *Practice Guidelines* state that the most significant consequence of hyperprolactinemia is hypogonadism (or estrogen and testosterone deficiency) and address its management. Some of the newer neuroleptics, such as quetiapine, clozapine, and olanzapine (43), do not increase pituitary prolactin to the same extent as older drugs and thus do not suppress the ovarian secretion of estrogen to the same degree. As a result, women taking these drugs are more fertile than are those on older drugs. Because of this, women need to be instructed in safe contraceptive practice. Current guidelines do not adequately address this issue.

A corollary of the use of the newer drugs is that estrogen levels stay high, and the risk for late effects of hypoestrogenism is lessened. Estrogen deficiency leads to osteoporosis and potentially to cardiovascular disease and cognitive decline (44). Older women on conventional antipsychotics for many years exhibit estrogen deficiency prior to menopause and should be screened for both osteoporosis and cardiovascular disease. Because of this, changing from older to newer neuroleptic medications should be seriously considered in treating women with schizophrenia, although the risk of weight gain and adverse effects on glucose and lipid metabolism need to be seriously weighed against the benefits. A detailed medical family history will help to select the optimal drug. The *Practice Guidelines* do address physical illnesses and their adequate assessment and management, but they do not highlight the particular needs of postmenopausal women. The most efficient and cost-effective strategy would be a joint approach between psychiatrist and primary care provider.

Conclusions

Although more systematic research is needed to understand the etiology of the sex differences in schizophrenia, there is compelling evidence that estrogen plays a major role in the brain. Estrogen has many effects on multiple systems and probably plays a part in amplifying sex differences in schizophrenia. The advent of the designer estrogens holds promise for facilitating further research. There is, however, enough evidence now to incorporate what is known into clinical practice.

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[1]Resident in Psychiatry, University of Toronto, Centre for Addiction and Mental Health, Clarke Division, Toronto, Ontario.
[2]Professor Emeritus, Department Of Psychiatry, University of Toronto, Centre for Addiction and Mental Health, Clarke Division, Toronto, Ontario.
Address for correspondence: Dr S Grigoriadis, University of Toronto, Centre for Addiction and Mental Health, Clarke Division, 250 College Street, Toronto, ON M5T 1R8
e-mail: sophie_grigoriadis@camh.net

Résumé: Le rôle de l'oestrogène dans la schizophrénie : les implications pour les lignes directrices de la pratique pour la schizophrénie chez les femmes

Objectif : Cet article a pour but d'intégrer ce que l'on sait des effets de l'oestrogène sur les symptômes et la réponse au traitement à une compréhension globale de la schizophrénie. Nous entendons ajouter aux lignes directrices canadiennes de la schizophrénie en y incluant les besoins propres aux femmes.

Méthode : Nous avons fait une recherche dans la base de données Medline; les mots clés comprenaient oestrogène, thérapie de substitution de l'oestrogène, schizophrénie, psychose, traitement, dyskinésie tardive (DT) et femmes. Nous avons examiné la bibliographie d'articles pertinents pour faire en sorte que notre revue soit complète. Nous examinons les preuves des effets de l'oestrogène sur la schizophrénie et faisons des recommandations pour la prochaine révision des lignes directrices de la pratique officielles.

Résultats : Les preuves épidémiologiques indiquent que, relativement aux hommes, les femmes présentent un délai initial de l'âge d'apparition de la schizophrénie, avec une deuxième crête d'apparition après l'âge de 44 ans. Cela suggère un effet protecteur de l'oestrogène, confirmant la recherche animale qui a documenté des effets à la fois neurotrophiques et neuromodulatoires. Les résultats de la recherche clinique indiquent que les symptômes chez les femmes varient selon le cycle menstruel et s'aggravent durant les phases faibles en oestrogène. La grossesse est souvent, quoique pas toujours, une période moins symptomatique pour les femmes, mais les rechutes sont fréquentes durant le post-partum. Des travaux suggèrent que dans les groupes d'âge plus jeunes, les femmes nécessitent des doses plus faibles d'antipsychotiques que les hommes, mais qu'elles ont besoin de doses plus fortes après la ménopause. L'oestrogène a été utilisé efficacement comme traitement auxiliaire chez les femmes souffrant de schizophrénie. Il peut aussi jouer un rôle préventif dans la DT.

Conclusions : L'évaluation des symptômes et le diagnostic des femmes doivent tenir compte de l'état hormonal. Il faut se préoccuper du dosage des neuroleptiques modulés par le cycle et du titrage prudent durant la grossesse, le post-partum et à la ménopause. Nous recommandons de songer à l'utilisation discrétionnaire des nouveaux neuroleptiques et de l'oestrogénothérapie auxiliaire.