Treatment Considerations in Women with Schizophrenia

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ABSTRACT

Schizophrenia is a challenging and complex psychiatric disorder. It is a chronic disorder of thought, affect, and cognition that significantly disturbs the individual’s ability to function in society and develop interpersonal relationships. The clinical presentation can be extremely varied, with symptoms including delusional thinking, disorganized thoughts and speech, hallucinatory behavior, and negative symptoms (e.g., blunted affect, avolition, alogia, anhedonia). Approximately 1% of the population is affected by schizophrenia worldwide, and women may experience different symptoms, have a later age of onset, may respond to different treatments, and may be more concerned about specific side effects than men. Women with schizophrenia traditionally have been treated in the same way as men and have generally had poorer comprehensive medical care. With the introduction of many new antipsychotic medications in recent years, this review focuses on sex differences in schizophrenia, with an emphasis on differences in treatment and side effects. Additionally, it presents patient counseling issues in sexuality and health outcomes.

INTRODUCTION

Schizophrenia is a challenging and complex psychiatric disorder. It is a chronic disorder of thought, affect, and cognition that significantly disturbs the individual’s ability to function in society and develop interpersonal relationships. The clinical presentation can be extremely varied, and despite attempts in the media to portray a stereotype, the stereotypic individual with schizophrenia does not exist. It is a markedly heterogeneous disorder, with symptoms including delusional thinking, disorganized thoughts and speech, hallucinatory behavior, and negative symptoms (e.g., blunted affect, avolition, alogia, anhedonia). People with this disorder may be uncooperative and hostile, have impairments in self-care, and have difficulty initiating or maintaining employment. Nevertheless, a woman with schizophrenia must not be defined in terms of her disease; she requires and deserves comprehensive, individualized treatment and care.

The formal diagnostic criteria for schizophrenia are listed in Table 1.1

THE GENDER FACTOR

Epidemiology

Considerable and convincing evidence suggests that there are sex differences in schizo-
phrenia. There has recently been a resurgence in attention to sex differences in schizophrenia, reflecting the important contribution of these differences to the heterogeneity of schizophrenia phenomenology. Most data have focused on sex differences in the epidemiology and clinical expression of schizophrenia. Many studies note an overall prevalence of schizophrenia at approximately 1%, consistently reporting a 2–3-fold higher incidence of schizophrenia with an onset before age 45 years in men vs. women. Men with schizophrenia also exhibit more negative symptomatology than do women, whereas women often experience more depressive and paranoid symptoms. Men typically experience their first psychotic symptoms by 17–20 years of age, whereas women may not experience symptoms until 20 years of age (3–5 years later). Onset can also occur in postmenopausal women, although new cases typically do not occur in older men. Schizophrenia is still primarily a disease of the reproductive years. Women generally have better clinical outcomes than do men, that is, higher levels of social functioning, shorter hospital stays, and lower relapse rates, and this may partially account for the lower rates of inpatient hospitalization in women than men for treatment of schizophrenia.

**Physiology**

Another area of study addressing sex differences in schizophrenia involves biological and neuroanatomical deficits. It is believed that male subjects with schizophrenia exhibit more structural brain abnormalities than do women with schizophrenia. Key neuroanatomical abnormalities include larger ventricle/brain ratios, reduced gray matter volume (particularly in temporolimbic structures), and a lack of normal asymmetry. Males with schizophrenia also display a higher rate of minor physical anomalies and neurological soft signs than do female patients. In general, men show a greater disadvantage than do women across neuropsychological tests of cognitive function. More recent reports, however, have determined that women with schizophrenia have poorer verbal/spatial memory and visual processing and more conceptual impairments than men. Most impor-
tant, however, are the differences in therapy and side effects that apply to the management of this devastating illness in women.

**THERAPEUTIC CONSIDERATIONS**

*Pharmacological treatment*

As early as the 1960s, significant sex differences in response to phenothiazine agents were noted. Other studies continued to suggest a superior response in women taking conventional antipsychotic medications, such as chlorpromazine and haloperidol, although these early studies did not generally take into account baseline differences, such as age of onset, when reporting results, and diagnostic misclassifications were likely. A more recent double-blind, randomized study that matched clinical and demographic variables between men and women failed to find any differences in outcomes between the sexes when treating with conventional antipsychotics. In contrast, other studies that controlled for baseline variables have reported that women are more likely to respond to these medications, so women may have some benefits over men in this area. No consensus has been reached. The second-generation antipsychotics (SGAs) risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole are now recommended as first-line therapy for both men and women, but none of these antipsychotics has demonstrated an advantage over the others in comparative clinical trials to date. One study showed no appreciable gender differences in efficacy for risperidone, and another trial with olanzapine found a significantly greater response in women than in men. Thus, antipsychotic efficacy is not generally different between the sexes. Although women may have a more robust response than men independent of the specific drug, the most important consideration is the side effect profiles of the individual antipsychotics.

Such factors as genetics, height, weight, age, lean/fat ratio, comorbid conditions, smoking, and diet can contribute to differences in drug response and dosing. Because men and women often differ on all these variables, disparities may be evident. As a group, women have higher plasma levels of antipsychotics than men at the same dosage. This difference in plasma levels is most evident with clozapine and olanzapine, which are both metabolized primarily by the cytochrome (CY) P450-1A2 enzyme. This enzyme is known to be less active in women than in men. Additionally, smoking affects plasma levels of clozapine and olanzapine, and smokers may have 40% lower plasma levels because of the induction of liver enzymes from cigarette smoke. Plasma levels of the newer antipsychotics do not appear to differ significantly with monotherapy in men vs. women, but women may need lower doses of clozapine and olanzapine.

Women are more likely than men to be using antidepressants and mood stabilizers that may interact with antipsychotic metabolism, potentially leading to increased/decreased antipsychotic plasma levels. For example, antiepileptic drugs have been shown to produce steady-state haloperidol levels that are almost 30% lower than values in those not taking antiseizure drugs. Carbamazepine has been found to reduce the concentration/dose ratio of olanzapine by almost 40%. Selective serotonin reuptake inhibitors (SSRIs) may lead to 4-fold increases in plasma levels of risperidone via competitive inhibition of the CYP450-2D6 enzyme. Because no therapeutic range has been established for plasma concentrations of newer antipsychotics (except for clozapine at >350 ng/mL), sex-based dosage adjustments are not always pertinent. However, adjustment may be required if side effects are evident in women that may be due to higher plasma levels. Lower doses may be appropriate for women who are nonsmokers, or in the presence of interacting medications that inhibit metabolism.

Adipose tissue may lead to drug accumulation, and adult women generally have an average adiposity of 33% compared with 20% in men. As most antipsychotics are lipophilic and have large volumes of distribution, maintenance depot injections of conventional antipsychotics should be used less frequently in women than in men.

*Side effects*

Women may be at increased risk of adverse drug reactions from antipsychotic therapy, with a 1.5–1.7-fold greater risk of side effects compared with men. The incidence and severity of antipsychotic side effects most likely depend on drug plasma levels, so the factors that affect serum concentrations may contribute to the risk of side effects. As a class, the conventional antipsychotics (e.g., haloperidol, fluphenazine,
chlorpromazine) are relatively similar in their side effect profiles, with the most troubling adverse effects being extrapyramidal symptoms and tardive dyskinesia. Acute dystonia was long thought to be more prevalent among younger men under treatment, but a 10-week study at equivalent doses reported higher rates of dystonia in first-episode women. Furthermore, elderly women generally have a higher risk of tardive dyskinesia from conventional antipsychotics. The newer class of antipsychotics (i.e., clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole) are more heterogeneous in their side effect profiles, and each is associated with unique pharmacological profiles in women (Table 2).

**Weight gain and metabolic complications**

Antipsychotic-induced side effects may have different significance for men and women. Women tend to be more distressed by effects that detract from their appearance. Obesity is particularly problematic for women, and drug-related weight gain may be more prevalent in women than in men. Long-term morbidity and mortality from obesity and other metabolic effects of antipsychotics (e.g., type 2 diabetes, cardiovascular disease, hyperlipidemia) affect both men and women, and family and individual risk factors should be considered in overall management. Clozapine and olanzapine are associated with the greatest risk for weight and metabolic consequences, with an estimated average weight gain in 10 weeks of 4–5 kg. Risperidone and quetiapine are associated with somewhat lower weight gain and risk for metabolic effects, and there is little evidence of an association for ziprasidone and aripiprazole. African American women may represent a high-risk group for diabetes occurrence with new medications. Monitoring guidelines have been developed, as this concern has become significant.

**Cardiac effects**

Some antipsychotics have effects on electrocardiographic findings, especially on the corrected QT interval (QTc). Extending from the beginning of ventricular depolarization (QRS complex) to the end of repolarization (T wave), the QT interval is shorter with faster heart rates, and longer with slower heart rates. Therefore, a correction for rate (QTc) is applied to make the reporting of the interval more meaningful. The QTc intervals are generally considered to be prolonged if they are >450 milliseconds in men or >470 milliseconds in women. In both sexes, QTc prolongation >500 milliseconds may increase the risk of *torsades de pointes*. Women have longer QTc intervals at baseline, which may predispose them to these phenomena. Postmenopausal women using estrogen therapy have significantly longer QTc intervals than nonusers. Drug-induced QTc prolongation was found in one study to be higher during ovulation than in the luteal phase of the menstrual cycle, corresponding to higher estrogen levels. Other factors that may predispose patients to a longer QTc interval are metabolic abnormalities (hypokalemia, hypomagnesemia, hypothyroidism, hypocalcemia), hyperglycemia, alcoholism, bradycardia, and cardiac disease. Moreover, QTc prolongation occurs at routine doses to some degree with all the antipsychotics. Increases have been reported at 20 milliseconds for ziprasidone, 30 milliseconds for thioridazine, and 7–15 milliseconds for the other newer antipsychotics and haloperidol. Women

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Weight gain</th>
<th>Diabetes risk</th>
<th>Worsening lipid profile</th>
<th>Prolactin elevations</th>
<th>Sedation</th>
<th>Extrapyramidal side effects</th>
<th>Gastrointestinal effects</th>
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<tbody>
<tr>
<td>Clozapine</td>
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<td>Quetiapine</td>
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<td>Ziprasidone</td>
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<td>Aripiprazole</td>
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*a*, increased effect; –, no effect; D, discrepant results.

bFewer drugs with limited long-term data.

Adapted from Allison and Casey.
with risk factors and concurrent medications that inhibit ziprasidone metabolism may do best to avoid this drug as first-line therapy.

Prolactin elevations

One of the most prominent sex differences in antipsychotic side effects is the degree of prolactin elevations in women. Literature reviews indicate that prolactin concentrations can rise as high as 10 times normal levels in women during antipsychotic treatment; as a consequence, 75% or more of the women in some studies experienced amenorrhea with or without galactorrhea. Antipsychotics with stronger dopamine-binding properties (e.g., haloperidol, fluphenazine, risperidone) are associated with a higher risk of prolactin elevation. Women taking medications that raise prolactin levels show decreased bone mineral density (BMD). Additionally, drug-related secondary hypoestrogenism resulting from hyperprolactinemia may lead to osteoporosis. In women with long-term use of dopamine-blocking antipsychotics and other risk factors for osteoporosis (e.g., family history, poor diet, smoking, lack of exercise), it may be beneficial to consider treatment with a prolactin-sparing antipsychotic. A potential relationship has been theorized between prolactin elevations and breast cancer, but no controlled data have been reported. Sexual dysfunction can also be related in part to elevations in prolactin. Approximately 50% of both men and women using antipsychotics report sexual dysfunction when questioned directly. Men tend to be more disturbed by decreased sexual performance than do women, but questioning patients about sexual function is an important component of treatment and outcomes. Prolactin-sparing antipsychotics that do not produce sustained elevations include clozapine, quetiapine, aripiprazole, and ziprasidone.

PSYCHOSOCIAL ISSUES AND PATIENT COUNSELING

Sexuality

Sexuality is a natural part of human behavior, and the nature of sexual behavior in the normal population has been well addressed. In contrast, sexual functioning has received little attention in the management of schizophrenia. Both male and female patients report that one of the areas with the highest proportion of unmet needs is counseling about intimate relationships. Studies addressing sexual issues have generally concluded that schizophrenia patients are prepared and willing to discuss sexual activity. Thus, sex education should be an integral part of the comprehensive treatment plan for patients with schizophrenia. The primary care physician may be the patient’s only nonpsychiatric medical contact and should always ask the patient if she has any questions or needs in this area.

Compared with emotionally healthy controls, women with schizophrenia have been found to have significantly less reproductive and contraceptive knowledge. In addition, schizophrenia patients often have poor judgment and may be more likely to engage in risky sexual behaviors that can increase their exposure to HIV and other sexually transmitted diseases (STDs). A history of sexual and physical abuse women with schizophrenia is estimated to be 50%. Women with schizophrenia whose condition has been stabilized with medication may have questions and concerns about childbearing. There is some evidence of a hereditary component in schizophrenia, and genetic counseling may be appropriate. There may be reduced fertility secondary to drug-induced hyperprolactinemia. The SGAs are less likely to affect fertility, although patients and their families often are unaware of this. As patients switch to these medications and regain libido, sexual function, and fertility, more pregnancies may occur; there are several cases in which switching patients from traditional antipsychotics to SGAs has resulted in unplanned pregnancy. The advent of newer treatments that may increase fertility adds yet another reason for providing appropriate education and counseling to women with schizophrenia.

Contraceptive use in women with schizophrenia has not been well characterized. Oral contraceptives (OCs) have been tried, although compliance is an issue in this population. The newer antipsychotics generally do not interact with OCs, but women with schizophrenia often use anticonvulsants and mood stabilizers that may decrease the effectiveness of OCs. Therefore, a full medication review is necessary before prescribing OCs, and dosage adjustments may be required. Women with schizophrenia receive significantly fewer gynecological services than do other women, which also requires redress.
The use of antipsychotics in pregnancy and lactation remains a risk/benefit decision. The risk of psychotic relapse may be more detrimental to the mother and baby than the risks of drug use, and antipsychotics are often continued throughout pregnancy and postpartum. Essentially all of the antipsychotic medications pass through the placenta, and if possible, stopping antipsychotic use for the first trimester is desirable. However, women who experience a relapse in their psychotic symptoms during pregnancy are at greater risk for birth complications. Therefore, the danger of psychiatric relapse must be weighed against the risks of fetal drug exposure for individual medications. Most newer antipsychotic drugs pose little fetal risk, which appears to be no higher than in a non-schizophrenic comparison groups. Lower birth weights do occur, and spontaneous abortions, stillbirths, and a small, non-specific risk for organ malformations has been reported. Antipsychotics are all excreted in breast milk, but breastfeeding is generally permissible with many of the first-line antipsychotics.

**Medical comorbidities/overall health concerns**

Women with schizophrenia have increased risks of several chronic physical illnesses, and have a shorter life expectancy than women in the general population. Approximately 50% of individuals living with schizophrenia have been found to have serious co-occurring physical illness. Hypertension, epilepsy, lung diseases, diabetes, and hepatitis are the most commonly occurring comorbid medical disorders, contributing to the increased mortality rate of persons with schizophrenia. This mortality rate is estimated to be 2–3 times higher than that of the general population. A meta-analysis of mortality rates showed that patients with schizophrenia have a higher rate of death from natural and unnatural causes than patients with other mental disorders. Deaths from cardiovascular-related events are believed to occur more than 4 times more frequently in patients with schizophrenia than in the normal population. It is believed that medical comorbidity may be rising as a result of newer treatments and that poor lifestyle habits contribute as well to increases in morbidity and mortality in people with schizophrenia. These habits include lack of exercise and sedentary lifestyle, poor diet and related obesity, smoking and related lung disease, and other types of substance abuse. Therefore, women should be counseled about appropriate lifestyle choices such as diet and exercise, and realistic goals should be set. Attempts to help women with schizophrenia manage problems with substance abuse and smoking is an important step in improving overall health concerns.

**CONCLUSIONS**

Caring for women with schizophrenia presents a difficult challenge to the clinician. Women will most likely experience symptoms at a later age and may have a better prognosis than men. Women are also more likely to have concomitant depressive symptoms. Treatment should be individualized in terms of patient risk and drug side effect profiles (Table 3). Most importantly for women, consideration should be given to weight gain, risk of cardiovascular disease and type 2 diabetes, hormonal disturbances and sexual dysfunction, and other factors, such as concomitant

**Table 3. Guidelines for Prescribing Antipsychotics in Women**

- Women generally require lower doses than men
- Depot doses should be given at longer intervals in women than in men
- Prolactin levels are higher in women
- Obesity and weight gain are more of a problem in women
- Women need regular mammography, electrocardiography, and bone densitometry
- Women need diabetes and cardiovascular workups
- Women need regular monitoring of lipid and glucose levels and weight
- Dosages need to be modulated in aging women
- Women require education in family planning and genetic counseling
- Contraception should be offered to women with schizophrenia
- During pregnancy and lactation, treatment must be subjected to risk/benefit analysis.

Adapted from Seeman.
medications and pharmacokinetic issues. Finally, a discussion of sexuality and overall health concerns should be an integral part of treatment in women with this disorder.

CONFLICT OF INTEREST

Dr. Kelly has served as an advisor for Solvay, Bristol Myers Squibb, and Janssen. She has received grant support from Astra-Zeneca and Abbott.

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