

Diagnosing and Managing Schizophrenia in Women

Primary care providers can play a key role in treatment

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Schizophrenia is an illness of unknown etiology that usually begins in the late teens but, in women, may first manifest as late as the perimenopausal years. (Estrogen seems to have a protective effect.) There are a number of ways in which the diagnosis and management of schizophrenia differ in men and women. For example, diagnosis is often more difficult in women. Also, although women tend to be easier to engage in treatment, they are more likely to suffer medication side effects. The importance of good treatment in women is underscored by the fact that our ability to prevent schizophrenia in children is partially influenced by the effectiveness with which we manage the disorder in mothers.

The key to effective treatment is building a therapeutic alliance with the patient, and primary care clinicians are often in a better position to do this than are psychiatrists or other specialists. Although few primary care clinicians may feel comfortable prescribing antipsychotic medications, they can play an important role in the overall treatment of the patient.

This article is designed, therefore, to briefly outline the ways in which the diagnosis and management of schizophrenia differ between men and women. I will

ABSTRACT: Schizophrenia is often harder to diagnose in women than in men and may manifest as late as the perimenopausal years. Symptoms include delusions, hallucinations, incomprehensible speech, disorganized behaviors, social isolation, apathy, and lack of emotional tone. For the diagnosis to be made, these symptoms must be accompanied by social or occupational dysfunction, or both. Women tend to be more open to treatment but are more likely to suffer adverse reactions to antipsychotic drugs. Comprehensive treatment, including close collaboration between psychiatrists and primary care clinicians, is crucial, as is suicide prevention. Hormone fluctuations can worsen the condition. Early intervention for mothers may help protect children, who face a 1:10 risk of the disease themselves. (*Women Health Primary Care* 2002; 5(9):556-563)

begin by reviewing the criteria for diagnosis; I will then discuss today's treatments. I will also explain a number of ways in which management must be tailored to account for menstruation, pregnancy, and menopause, as well as the socioeconomic conditions that women with schizophrenia (and their children) must often confront.

HOW IS SCHIZOPHRENIA DIAGNOSED?

According to the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*, a specific set of symptoms needs to be present for at least one month in order for a diagnosis of schizophrenia to be made.¹ In addition, there must be evidence that these symptoms are interfering with the patient's ability to function.

SYMPTOMS

These are grouped into two main categories:

Delusions are beliefs that are not true and that are based on a false perception or, sometimes, on a real experience that the person misinterprets. For example, the patient might see a large number of people with black leather jackets walking on the street and subsequently jump to the conclusion that those people are part of a conspiracy to follow her, monitor her actions and thoughts, get her into trouble, or perhaps break into her house and cause her physical injury. Deluded

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thoughts can also manifest as magnified ideas of reference—the patient may think that television programs, lyrics to a song, or casual comments made by another person are referring specifically to her. Deluded thoughts can be distinguished from superstitions or mystical thinking by the fact that others within the patient's cultural group do not share the same beliefs.

Patients will hold on to their delusions against all logic. For example, a 65-year-old woman may believe that her doctor is in love with her and that they will have a baby. The doctor does not respond to her overtures and she is too old to conceive, but these facts do not shake her conviction. Instead, a skewed reality may be reinforced for her every day by her interpretation of the words and gestures acted out by her favorite characters in a television series.

Hallucinations are symptoms that alter or exaggerate a patient's perceptions. Often, a patient reports hearing one or more voices addressing her or holding a conversation in her head. Voices that degrade the patient or threaten her are the norm in schizophrenia. Hallucinations that are visual, olfactory, gustatory, or tactile are less common; when they do occur, a thorough neurologic assessment should be conducted to rule out brain tumors, epilepsy, or a cardiovascular event.

The diagnosis of schizophrenia can be considered on the basis of one symptom alone if the delusion or hallucination is sufficiently bizarre or if the voices keep up a running commentary; however, the delusion or hallucination must be present for at least one month. If a single symptom is not that distinctive, at least two symptoms have to last for one month before the diagnosis can be established (Table 1). These symptoms may be delusions or hallucinations, but they can also manifest as:

- ◆ Disorganized speech that makes the patient incomprehensible.
- ◆ Grossly disorganized behavior.
- ◆ A "negative" symptom cluster: apathy, social isolation, and lack of emotional tone.

SOCIAL AND OCCUPATIONAL DYSFUNCTION

The presence of social and occupational dysfunction is the second criterion for a schizophrenia diagnosis. Many people go through life exhibiting disorganized behavior, hard-to-follow logic, a lack of motivation and energy, and even the occasional delusion and hallucination. These people cannot be diagnosed with schizophrenia unless their symptoms are of sufficient magnitude to interfere with every-day function.

Table 1. Acute symptoms of psychosis (one month's duration)

- ◆ Delusions
- ◆ Hallucinations
- ◆ Incomprehensible speech
- ◆ Disorganized behavior
- ◆ "Negative" symptoms (apathy, social isolation, and lack of emotional tone)

Schizophrenia can cause disturbed interpersonal relationships, problems at school, impaired ability to work, and deficient self-care. Obviously, though, a constellation of other disorders (Table 2) can produce similar findings, including substance abuse (especially withdrawal phenomena), medical conditions (eg, thyroid dysfunction, starvation, temporal lobe epilepsy, or brain tumor), and, especially, mood disorders (eg, depression or bipolar illness with psychotic features). These other disorders must be excluded as the root of function loss before a diagnosis of schizophrenia can be considered. However, if these other disorders are

excluded and the dysfunction lasts for six months or more, schizophrenia can be diagnosed.

SEX DIFFERENCES

DSM-IV criteria make it more difficult for women than for men to be diagnosed with schizophrenia, for several reasons² (Table 3):

- ◆ Women display the severe "negative" symptom cluster (apathy, social isolation, and lack of emotional tone) much less frequently than men do.
- ◆ Especially in the interpersonal sphere, women are often able to function well despite serious schizophrenia symptoms.
- ◆ In general, women are more prone than men to express emotional lability, making mood disorders difficult to exclude.
- ◆ Active psychotic symptoms in women often initially persist for less time than the requisite one month.

Diagnoses first given to women who are ultimately diagnosed with schizophrenia include depression, bipolar disorder, brief psychotic disorder, eating disorder (when the delusions are about food and hallucinations can be attributed to starvation), and borderline personality disorder. In addition, psychotic symptoms may be ascribed to short-lived dissociative states resulting from forgotten trauma, such as posttraumatic stress syndrome.

DOES PATHOGENESIS DIFFER BY SEX?

Symptoms of schizophrenia are currently thought to result from neural network disturbances in the developing brain, which may be determined by interactive products of several susceptibility genes. These genes are as yet undiscovered but are thought to be activated during the development of the fetus, perhaps in response to intrauterine factors, such as oxygen deprivation, malnutrition, or viral infection.

Obstetric complications may also play a part in gene activation; they have been correlated with early schizophrenia onset. These complications are known to occur more frequently during the birth of boys than of girls, which may partially explain the earlier onset of schizophrenia in males. In women, pubertal hormones (especially estrogen, which is considered protective) influence the timing of onset.³ Head trauma and substance abuse in adolescence can bring the age of onset forward. Psychologic stress may have a similar effect, but its definition, measurement, and specific role remain controversial.

HOW IS SCHIZOPHRENIA TREATED?

Convincing the patient that she is ill and that medical treatment can help alleviate her distress is the first obstacle in management.⁴ This is not an easy, always accomplished task. The patient experiences her symptoms as if their source is outside herself; it will seem illogical to her that taking medication will alleviate them. For example, if she believes that people in black leather jackets are out to get her, it will be hard for her to believe that a pill will fend them off. Instead, she may reason that the drug's sedative effect will make her more, rather than less, vulnerable to attack. Thus, building a therapeutic alliance is crucial in convincing the patient that she needs treatment (Table 4), and this may be harder for an emergency room clinician or psychiatrist than for the primary care clinician, who may have known the patient and her family for some time.

Another obstacle may be presented if the patient adamantly refuses to allow clinicians to confer with her family, since family support is essential in treatment. Again, primary care clinicians who have an established relationship with the patient may have more

Table 2. Differential diagnosis after six months' deterioration of function

<p>Rule out:</p> <ul style="list-style-type: none"> ◆ Substance abuse <ul style="list-style-type: none"> Toxicity Withdrawal phenomena ◆ Mood disorder <ul style="list-style-type: none"> Depression with psychotic features Bipolar illness with psychotic features ◆ Medical/neurologic conditions <ul style="list-style-type: none"> Thyroid dysfunction Starvation Temporal lobe epilepsy Brain tumor
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success in overcoming this obstacle than specialists would. If all else fails, it may be possible to arrange for the family to relay their observations and concerns to a social worker, who can then confer with the psychiatrist and primary care clinician.

MEDICATIONS

Once the patient has been convinced of the need for treatment, the second step is selecting an appropriate antipsychotic medication at a dose that is likely to address the symptoms and not cause discomfort.⁵ In most cases in the United States, treatment is initiated by a psychiatrist; however, the primary care clinician is often intimately

Table 3. Presentation of schizophrenia in women

<ul style="list-style-type: none"> ◆ Initial episode can occur relatively late in life ◆ Psychotic episode may last less than a month ◆ Mood symptoms may mask psychotic symptoms ◆ Often, interpersonal function is preserved ◆ "Negative symptoms" may be less pronounced than in men
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involved in follow-up.

Of the newer medications, olanzapine is an easy one to start with; a 10-mg evening dose will usually help alleviate the patient's insomnia (making her feel subjectively better) and cause few side effects. Because the therapeutic range for olanzapine is small, a therapeutic dose can be achieved relatively quickly. For long-term use, however, olanzapine has disadvantages, including an increased risk of excessive weight gain, hyperlipidemia, and diabetes.

Risperidone is less likely to lead to weight gain and, thus, is safer for longer-term use. However, it tends to worsen insomnia and can cause intolerable sexual side effects. Furthermore, even at its very low dosing range (1 to 8 mg), patients may occasionally experience parkinsonian side effects. All of these drugs, but especially risperidone, are associated with an increased risk of hyperprolactinemia.

Quetiapine has the fewest side effects of the newer agents, but it is difficult to use because it requires a long dosage-adjustment period. The drug's dosage must be started at a comparatively low level (25 to 50 mg/d) and slowly titrated upward; sometimes, dosages as high as 1,000 mg/d are required for efficacy. This slow titration is difficult to accomplish on an outpatient basis because patients with schizophrenia tend to resist changes to their medication regimen.

Of the newer drugs, ziprasidone has the least propensity to increase appetite and result in unhealthy weight gain, but it does have important cardiovascular side effects, most notably QT prolongation. Tachycardia and postural hypotension may also occur from use of ziprasidone or other antipsychotic drugs, although these reactions are less clinically significant. Thus, the exact role of ziprasidone in the management of schizophrenia is yet to be determined.

The older anti-schizophrenia medications will induce extrapyramidal symptoms unless they are offset by the adjunctive use of anticholinergic drugs. Nevertheless, some patients can tolerate and will respond well to low doses of the older drugs. Although weight gain is still common, it is less severe than with the newer drugs. Should the woman not respond to these medications, a psychiatric consultant may suggest others, such as clozapine.

SEX DIFFERENCES

In my experience, it is somewhat easier to establish a therapeutic alliance with women than it is with men.⁶ It is usually easier to persuade women to try medication because they frequently experience somatic symptoms (such as headaches or insomnia) and mood problems (such as depression or anxiety) for which they are seeking relief. On the other hand, women are more likely to suffer adverse events from anti-schizophrenia drugs than men are. This is true for a number of reasons⁷:

- ◆ Women may be given doses calibrated to men's weight; these doses may be too high for many women.
- ◆ Antipsychotic drugs are lipophilic and stay for a long time in fatty tissue; women tend to have more fatty tissue than men do. Thus, the drugs remain in women's bodies longer and may accumulate over time. Accumulation is especially problematic with long-acting depot medications.
- ◆ Women are more likely than men are to be taking other medications, such as oral contraceptives, mood stabilizers, antidepressants, sedatives, anxiolytics, analgesics, anti-inflammatories, or antihistamines. Antipsychotic drugs may interact with these medications.

Adverse events in women can have serious consequences. For in-

stance, a drop in blood pressure in an elderly woman may cause a fall, hip fracture, and subsequent death. Other drug-induced adverse reactions that may be particularly problematic in women include:

- ◆ Passivity, which can increase tolerance of domestic abuse.
- ◆ Sedation, which can be a serious problem for women caring for young children.
- ◆ Weight gain, to which women are more prone than men are. (Additional weight is a major health risk for both sexes.)

Table 4. Treating schizophrenia

- ◆ Build therapeutic alliance
- ◆ Elicit family cooperation
- ◆ Begin antipsychotic medication, such as one of these:
 - Olanzapine
 - Ziprasidone
 - Risperidone
 - Quetiapine
- ◆ Minimize side effects and encourage exercise to combat any potential weight gain
- ◆ Provide comprehensive psychosocial treatment

MINIMIZING SIDE EFFECTS

Whenever possible, the medication regimen should be kept simple; for many patients, a once-a-day evening dose is best. Often, side effects can be minimized if the dose is started low and increased gradually until the therapeutic effect is attained. If side effects worsen, the doses can be spaced out; medication taken every two or three days may be sufficient to maintain a therapeutic effect.

All clinicians who treat patients with schizophrenia should inquire about their ability to function throughout the day. Somnolence in the morning can be averted by taking medication with supper instead of at bedtime. Encourage a healthy diet and regular exercise to help prevent weight

gain. It is also important to offer instructions on how to avoid postural hypotension.

BEYOND MEDICATION

Although antipsychotic drugs are important in the management of schizophrenia, equally crucial is comprehensive treatment.⁸ Beyond general health issues, clinicians will need to address situations related to self-esteem, safety, housing, income, family and relationships, education, skill building, and occupation. Relapse prevention is critical, as is suicide prevention. A multidisciplinary team of care providers, including the psychiatrist and primary care clinician, should work to ensure that all aspects of treatment are addressed.

SPECIAL ISSUES IN WOMEN

Women with schizophrenia have special care needs.⁹ Unfortunately, these women also tend to have poor medical coverage, and thus addressing their special needs can be difficult.

- ◆ Symptom fluctuations must be monitored during several menstrual cycles. Symptoms are generally worse when estrogen levels are low, so dose adjustments during the menstrual phases may be indicated.
- ◆ Medication should not be allowed to interfere with menstruation. Amenorrhea may result from drug-induced prolactin elevation. To reverse amenorrhea, lower the dose or change to another medication.
- ◆ Sex education should be provided, and the importance of contraception should be stressed. In fact, psycho-education to inform women with schizophrenia about the disease and its sequelae is recommended.
- ◆ Information on fetal health issues should be given to women who want to become pregnant. They should be advised against smoking, alcohol consumption, and

unregulated drug intake; encouraged to take folate and vitamin supplements; and counseled to make regular prenatal obstetric/gynecologic visits.

- ◆ Drug selection and dosing are particularly important during pregnancy and the postpartum period. Older antipsychotic drugs are generally safe for use during pregnancy; there is little experience with the newer ones. If possible, doses should be kept low during the first trimester, but they may need to be increased in the third trimester when blood volume expands. A 50% dose reduction is generally recommended one week before the expected delivery date to prevent interference with labor and to ensure that the newborn is not oversedated and does not suffer from drug withdrawal. Postpartum exacerbations of illness in women are extremely common; medication doses need to be relatively high during this period, and the patient requires close monitoring.
- ◆ Drug selection and dosing must continue to be monitored closely if the patient is adamant about breast-feeding. The older antipsychotic drugs have generally been considered safe for use during breast-feeding. However, these drugs cross into breast milk to a substantial degree. Also, in the past the women given these medications were counseled not to breast-feed, and thus it is not certain that they are in fact safe. The newer drugs (olanzapine, risperidone, and quetiapine) are also thought to be safe for use during breast-feeding, although there has not been much experience with them. Clozapine cannot safely be administered while a patient is pregnant or breast-feeding.
- ◆ However, the benefits of continued treatment probably outweigh the risks, and thus antipsychotic medications should not be with-

drawn while the patient is breast-feeding. Certain strategies can be used to help lower drug titers in breast milk. For example, mothers should be instructed to time nursing in order to avoid oversedating the infant; breast pumps may be useful. Also, increased

Table 5. Strategies that may help prevent schizophrenia in children

- ◆ Encourage fetal care (eg, avoid alcohol and inappropriate drugs; increase vitamin and folate intake) and regular obstetric/gynecologic visits
- ◆ If possible, avoid obstetric complications (eg, decrease antipsychotic dosages one week before the expected delivery date)
- ◆ Increase dosages during the postpartum period, as needed, since disease exacerbations are common during this time and may affect mother/child bonding
- ◆ Work closely with family, child protection workers, lawyers, and mental health providers to ensure maternal support and resources
- ◆ Perform a periodic parenting assessment; liaise with the children's school
- ◆ Make sure that ongoing treatment of the mother's illness is provided, as well as psychologic support and substance-abuse prevention for the children
- ◆ Help mother with socialization and assist her in providing children with a low-stress environment
- ◆ Help children with skill building

monitoring of the infant to ensure a healthy wake/sleep cycle and appropriate weight gain is recommended. The risk to the infant is greatest in the first weeks, when infant metabolism is immature, and lessens after the first month. Premature babies may be

at increased risk.

- ◆ Estrogen levels should be monitored as menopause approaches. Symptoms worsen as estrogen levels decrease, so drug doses tend to need an increase during this transition. The patient's bone mineral density, diet, and fitness habits should be assessed, and she should undergo mammography and Papanicolaou testing regularly. If appropriate, the clinician should offer hormone replacement therapy; it may ameliorate schizophrenic symptoms.

CAN WE PREVENT ADVERSE SEQUELAE?

Several interventions may be particularly helpful for women with schizophrenia who are or are considering becoming mothers (Table 5).¹⁰ Children of mothers who suffer from schizophrenia have a 1:10 statistical risk for schizophrenia themselves. There is hope that this risk can be reduced with early intervention for mothers—the provision of respite care for them and active ongoing treatment of their illness may help provide socialization opportunities, a low-stress environment, and skill development options for the children.

Too often, mothers with schizophrenia are not married, have incomes below the poverty level, and live in substandard housing. They may be isolated with no support system, substance abusers, and in abusive relationships. Child protection agencies may or may not need to be involved.

All clinicians who treat women with schizophrenia must be knowledgeable about parenting assessment practices, not only to ensure the safety of the children but also to intervene, when necessary, to support the mother. If the patient has given permission, the clinician should establish an active liaison with family lawyers and child protection workers, as well as interact with mental health workers and

family members.

Children of schizophrenic parents should be offered psychological support and substance-abuse counseling as they approach the hormonal changes of adolescence. These measures are critical as the children near the age of risk for schizophrenia onset.

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PRIMARY POINTS

Schizophrenia in Women

The diagnosis of schizophrenia is often made later in women than it is in men, sometimes as late as the perimenopausal years. In addition, diagnosis is more difficult in women because their emotional lability and ability to preserve function in the interpersonal sphere may suggest a mood disorder rather than schizophrenia.

Because they are more likely to have a long-standing relationship with the patient, primary care clinicians may be better able than psychiatrists or emergency room clinicians to convince a patient with schizophrenia that she needs treatment.

Newer antipsychotic medications used to treat schizophrenia include olanzapine, risperidone, quetiapine, and ziprasidone. Adverse reactions to these medications are more common in women than in men.

Reactions that may be especially problematic in women include weight gain and postural hypotension. Drug-induced hyperprolactinemia may result in amenorrhea. Passivity and sedation can interfere with a woman's ability to care for her children and for herself.

Hormonal fluctuations influence symptom severity. Drug efficacy should be monitored during several menstrual cycles because dosages may need to be adjusted during a cycle.

Older antipsychotic drugs are safe to use during pregnancy; there is little experience with the newer agents. The drugs are usually continued until the third trimester but should be reduced by 50% one week before the expected delivery date to prevent complications and protect the baby from oversedation. Higher doses may be necessary during the postpartum period. The drugs are considered safe during breast-feeding (with the exception of clozapine), although measures should be taken to minimize drug titers in breast milk.

Children of mothers with schizophrenia have a 1:10 chance of developing the disease. Early intervention, active ongoing treatment of the mothers, and psychological support for the children as they reach adolescence may help lower this risk.