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Psychosis in women: Consider midlife medical and psychological triggers

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Estrogen loss, other factors increase vulnerability for women after age 40

Dr. I, a 48-year-old university professor, is brought to the ER by her husband because she has developed an irrational fear of being chased by Nazis. The fears have become increasingly bizarre, her husband reports. She believes her Nazi persecutors are bandaging their arms and using wheelchairs to pretend to be disabled. When out with her husband, Dr. I points to people in wheelchairs, convinced they are after her, will kill her, and are incensed because she left Germany—her country of birth. Her husband brought her to the ER when she started to hear her persecutors addressing her in German at night.

Psychoses of unknown cause usually begin in late adolescence or early adulthood. Less frequently the onset occurs in later adulthood (age ≥40). Late-onset psychosis is much more prevalent in women than in men for reasons that are imperfectly understood.

When you are evaluating a midlife woman with first onset of psychosis, don't assume an illness of unknown cause (bipolar disorder or schizophrenia) until after you have done a comprehensive search for triggers of her psychotic symptoms. After age 40, women are more likely than men to develop psychosis because of gender-specific medical and psychological precipitants.

Predisposing factors for psychosis

Psychosis is an emergent quality of structural and chemical changes in the brain. As such, it can be expected to surface during:

- brain reorganization or transition (adolescence, se-

Box 1

Schizophrenia and bipolar psychosis in midlife women vs men

The incidence of schizophrenia in women age 40 to 60 is twice that of men of the same age, according to Riecher-Rossler et al.[a] They quote a yearly schizophrenia incidence after age 40 of 8.9 per 100,000 women vs 4.2 per 100,000 men. In their studies, a first hospital admission for schizophrenia occurred after age 40 in 10% of all male patients and in >20% of all female patients.

Although the prognosis in schizophrenia generally is reported as better in women than in men, it probably is worse in women who develop psychosis in later years.[b]

The perimenopausal years are a time of increased risk of bipolar psychosis for women,[c] especially those with a history of postpartum psychosis—which implicates hormones. Deterioration of pre-existing psychosis during perimenopause has been noted in women but does not occur in men of the same age.[d,e]

Initial onset, episode recurrence, increase in illness severity, development of treatment refractoriness, or decline in response to antipsychotic medication all have been observed to be more prevalent during midlife in women than in men.[f]

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nescence, brain trauma, stroke, starvation, inflammation, or brain tumor)

- change in brain chemistry (flux in gonadal, thyroid, or adrenal hormone levels; electrolyte imbalance; fever; exposure to chemical substances; immune response).

Psychological stress impacting the brain via stress hormones also can predispose a person to psychosis.

Because some individuals are more prone than others to develop psychosis during brain alteration, chemical and structural changes in the brain are assumed to interact with genetic propensities to influence gene expression. Once a psychotic event has occurred, it is thought to sensitize the brain so that subsequent events emerge more readily.[1]

Schizophrenia—though not the only illness in which psychosis plays a role—is a prototype for psychotic illness, and several reported sex differences in this disorder are worth noting.[2] The incidence of schizophrenia is approximately the same in both sexes, but women show a later age of onset—a paradox in that the brain develops at a faster pace in females and theoretically should reach the threshold for the first appearance of schizophrenia earlier. Women also require lower doses of antipsychotic medication to recover from an acute psychotic episode and to maintain remission, at least before menopause.[3,4] Both of these differences can be explained as an effect of estrogen on a) gene expression[5] and b) liver enzymes that metabolize antipsychotics.[6]

The estrogen hypothesis. Women show a tendency toward premenstrual and postpartum exacerbation of symptoms when estrogen levels are relatively low. These clinical observations, confirmed by some but not all studies, have led to the hypothesis that estrogens are neuroprotective[7] and also protect against psychosis.[8]

Estrogen withdrawal in specific brain cells may release a cascade of events that over time can increase the severity of psychotic and cognitive symptoms. The reason for suspecting such effects is based on what we know about estrogenic effects on neurotransmitter, cognitive, and stress-induction pathways, and—more fundamentally—on neuronal growth and atrophy.

According to the estrogen hypothesis, women are—to some degree—protected against schizophrenia by their relatively high gonadal estrogen production between puberty and menopause. Women lose this protection with the onset of perimenopausal estrogen fluctuation and decline, accounting for their second peak of illness onset after age 45.

Epidemiologic studies showing a second peak of schizophrenia onset in women (but not men) around the age of menopause support this hypothesis.[9,10] Longitudinal outcomes for schizophrenia—which are better in women than in men during late adoles-

Clinical Point

Estrogen withdrawal in specific brain cells may trigger a cascade of events that increase the severity of psychotic symptoms

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Estrogen loss, immune function, iron deficiency, thyroid function, and other factors may increase women's risk for psychotic illness

Table

Psychosis workup in midlife women: Consider these medical and psychiatric factors

Risk factor	Mechanisms of psychosis
Autoimmune disease and its treatment	Nearly 80% of autoimmune disease patients are women; corticosteroids have a well-documented history of triggering psychotic symptoms, and this is twice as likely in women as in men[a,b]
Psychiatric disorders	Consider posttraumatic stress disorder with psychotic symptoms, micropsychotic episodes in borderline personality disorder, and psychotic symptoms triggered by medications for depression and anxiety[c]
Thyroid dysfunction	1 in 8 prevalence of thyroid dysfunction in women increases with age; greatest risk with a family history of thyroid disease; either too little or too much thyroid hormone can manifest as psychosis and complicate diagnosis[d,e]
Self-induced starvation and diet aids	Weight-loss products, including those containing phenylpropanolamine or ephedrine; high doses of cough and cold medicines; methylphenidate; caffeine; and anabolic steroids[f]
Substance use and toxic substances	Association with psychosis is more common in men; in women, however, consider unsuspected addictions to home and office products—inhalants such as false eyelash and fingernail adhesives, fingernail hardeners, nail polish and polish remover, and aerosol cooking sprays[g-i]
Insomnia	Twice as likely in women as in men, especially during perimenopause (because of vasomotor symptoms) and after menopause; sleep deprivation also can contribute to postpartum psychosis and trigger psychosis at other times[j,k]
Iron deficiency	Heavy menstrual periods lead to low iron, which affects dopamine transmission and increases risk of psychotic states[l,m]

Source: For reference citations, see this article at CurrentPsychiatry.com

cence or early adulthood[11]—gradually even out after the first 15 years of illness, suggesting that women's advantage is lost at a time approximating menopause (***Box 1, page 65***).

The question, then, becomes: Is it only because of estrogen loss after age 40 that women become more prone to develop a psychotic illness? Other differences between the sexes that may play roles include immune function, low iron stores, sleep sufficiency, thyroid function, exposure to toxic substances (including therapeutic drugs), societal pressures to be slim while aging (***Table***), and the experience of stress.[12]

CASE CONTINUED

Exhausted and confused

Dr. I is a well-groomed, handsome woman, but she hardly speaks when interviewed, looking frightened and somewhat bewildered. She has never had a mental health problem, nor has anyone in her family. She agrees to stay in the hospital but is not sure why. She has slept no more than 1 or 2 hours in the last several days.

Her early history is unremarkable. She did well in school. After earning a PhD at the University of Leipzig, she and her husband immigrated to Canada. Both are university professors. They never decided not to have children, but children hadn't come. Her menstrual periods stopped 2 years before admission. The question about children is the only 1 that elicits emotion in Dr. I. When I ask about it, tears come to her eyes as she shakes her head.

Her husband reports that she has not been eating well and has, in the last year, started to drink more alcohol than usual—3 to 4 drinks of whiskey a night. She does not smoke cigarettes, and her health generally is good. She uses no medications. Her husband describes their marital relationship as very close, although it has become strained in recent weeks because of her unreasonable fears. He admits that their work is always stressful; competition is fierce, with more and more deadlines and less and less leisure time. The couple has few friends and no hobbies.

Late-onset psychosis symptoms

In late-onset psychosis (after age 45), men appear to suffer substantially milder symptoms and spend less time hospitalized than women.[13] Women with late-onset

schizophrenia have more severe positive symptoms than men and fewer negative symptoms.[14,15] Overall, patients with late-onset schizophrenia have a lower prevalence of looseness of associations and negative symptoms than those with earlier onset.[16,17]

In addition, individuals with schizophrenia who become ill in middle age have been reported to:

- show better neuropsychological performance (particularly in learning and abstraction/cognitive flexibility) than those with early onset
- possibly have larger thalamic volumes
- respond to lower antipsychotic doses.[18]

Auditory and visual hallucinations frequently are observed in patients with comorbid late-onset schizophrenia and auditory and visual impairment.[16] Palmer et al[18] reported no difference in family history of schizophrenia between early and late onset, but this is controversial. Convert et al[16] note that most studies reveal a lower lifetime risk of schizophrenia in first-degree relatives of patients with late-onset than early-onset schizophrenia.

CASE CONTINUED

Medical workup

Dr. I's physical exam is unremarkable. Her thyroid is not enlarged; there are no breast lumps. On mental status exam, her mood is flat. She is preoccupied with fears of the Nazis. Routine blood tests show slight anemia; fasting glucose levels are within normal range.

I give Dr. I zopiclone, 7.5 mg, to help her sleep. The next day she keeps to herself, eats very little, and appears disinterested in her surroundings. Nursing staff report that she often seems frightened. Dr. I asks to use the ward phone to call Germany but is told that she cannot make long distance calls from that phone. This seems to disturb her.

Differential diagnosis

Sensory impairment, substance abuse, and metabolic changes have been implicated in the appearance of psychosis in later life. More specific to women than men, however, are medical and psychiatric precipitants. These include autoimmune disease (and its treatment) and psychiatric disorders, as

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Psychosis in midlife women

Clinical Point

Compared with patients with earlier-onset schizophrenia, those who develop the illness in middle age respond to lower antipsychotic doses

Box 2

Gender-specific psychosis therapy: Estrogen studied for women

Researchers are investigating whether hormone replacement therapy (HRT) would be beneficial and safe in women with psychotic illness or women at risk.

Kulkarni et al[a,b] found that premenopausal women with schizophrenia who received adjunctive estradiol showed more rapid improvement in psychotic symptoms than women receiving antipsychotics alone. In a randomized, double-blind study, the same group[c] demonstrated that adjunctive transdermal estradiol significantly reduced positive symptoms and general psychopathologic symptoms.

Good et al[d] found statistically significant improvement of negative symptoms after a 6-month trial of estradiol and progesterone in 14 postmenopausal women with schizophrenia or schizoaffective disorder.

In case reports of HRT in postmenopausal women with schizophrenia:

- remission of first-rank psychotic symptoms was reported in a woman with first onset of schizophrenia during perimenopause who refused antipsychotic treatment and received transdermal estradiol and norethisterone acetate[e]
- a postmenopausal woman's psychotic symptoms improved on adjunctive estradiol.[f]

In a study of community-dwelling postmenopausal women with schizophrenia, Lindamer et al[g] compared 24 patients receiving HRT with 28 who had never received HRT. HRT users needed a relatively lower average daily dose of antipsychotic medication to achieve remission, especially of negative symptoms.

Source: For reference citations, see this article at CurrentPsychiatry.com

well as thyroid dysfunction, self-induced starvation (anorexia nervosa) and diet aids, substance use and abuse, insomnia, and iron deficiency (***Table, page 66***).

Autoimmune disease and treatment. Nearly 80% of patients with autoimmune disease are women, and these disorders (as well as their treatment) can manifest as psychosis. Corticosteroids have a well-documented history of triggering psychotic symptoms, which are twice as likely in women than in men. The incidence of severe psychosis while taking oral prednisone ranges from 1.6% to 50% and averages 5.7%. The average daily dose of corticosteroids for patients who develop psychosis is 59.5 mg/d.

Corticosteroid creams absorbed through skin as well as inhaled and intranasal corticosteroids in their more potent formulations can have systemic effects, including psychosis. Nonsteroidal anti-inflammatory drugs such as ibuprofen also can trigger psychosis.[19]

Psychiatric disorders. Posttraumatic stress disorder with psychotic symptoms may overlap with categories such as psychogenic psychoses, hysterical psychoses, nonaffective remitting psychoses, acute brief psychoses, reactive psychoses, acute and transient psychoses, and bouffées délirantes (in France, the name for transient psychotic reactions).[20] Consider these female-predominant conditions in the differential diagnosis, along with micropsychotic episodes in borderline personality disorder, in which the predominance of women is 3:1.

Medical treatment for depression and anxiety also can lead to psychotic symptoms through individual susceptibility to the action of specific drugs or through withdrawal effects.

Clinical assessment

Question all women presenting with psychosis about eating habits and diet pills, and check for hypokalemia and hypocalcemia to rule out starvation effects and reactions to stimulants. Also ask about inhalants, and examine for anemia and thyroid dysfunction. Consider all medications as having the potential to trigger psychotic symptoms.

A family history of illness is important, with a focus on autoimmune disorder and its treatment. A thorough psychiatric his-

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tory is crucial and needs to include assessment of sleep, mood, and relationships with attachment figures. Do not assume illnesses of unknown cause (bipolar disorder or schizophrenia) until after a comprehensive search for precipitants of psychotic symptoms.

CASE CONTINUED

Guilty feelings

To address her delusions, I start Dr. I on risperidone, 2 mg at bedtime. She goes home for the weekend, and her husband reports that she slept throughout the visit. When she returns, she spends a lot of time in bed but is more communicative.

When I ask Dr. I whether she has called Germany, she says she called her recently widowed father. Dr. I begins to cry when talking of her mother, and tells the nurse she feels guilty for not visiting for the last few years. When her mother died 6 months ago, Dr. I had not seen her in 4 years.

Her fears remit with risperidone, maintained at 2 mg/d, but Dr. I remains depressed and responds slowly to treatment with citalopram, 20 mg/d, and supportive therapy. Her final diagnosis is mood disorder with psychotic features.

Treatment

When treating women with late-onset psychosis, remove all potential triggers and address underlying illness. Cognitive therapy targeting specific symptoms is useful; antipsychotics probably will be necessary. Age-related physiologic changes make older persons more sensitive to the therapeutic and toxic effects of antipsychotics.

Estrogen therapy? Women suffering from schizophrenia show significantly lower estrogen levels than the general population of women, and they experience first-onset or recurrence of a psychotic episode significantly more often in low estrogen phases of the cycle. Estrogens have therefore been postulated to constitute a protective factor against psychosis, which means perimenopause is an at-risk period.[21] Although evidence is limited, preliminary studies have found beneficial effects from short-term, off-label use of estrogen therapy in women with psychotic illness (***Box 2, page 68***).

Because continuous use of estrogen plus progestin has been associated with an increased risk of adverse effects,[22] off-label use of selective estrogen receptor modulators (SERMs) also is being investigated in women with schizophrenia. SERMs act as tissue-specific estrogen agonists and antagonists because they can either inhibit or enhance estrogen-induced activation of estrogen response element-containing genes.[23]

Wong et al[24] used a crossover design to compare the SERM raloxifene with placebo as adjunctive treatment for 6 postmenopausal women with schizophrenia. Each woman received 8 weeks of raloxifene, 60 mg/d, and 8 weeks of placebo. Three began with placebo and 3 with raloxifene.

Verbal memory was measured weekly with the California Verbal Learning Test, using 5 memory trials, free and cued short-delay recall, and long-delay recall. At baseline, the participants had lower scores than older adults in the general population. Eight weeks of placebo improved scores somewhat, suggesting a practice effect. Eight weeks of raloxifene improved cognitive scores to a level similar to that of schizophrenia-free subjects. After 16 weeks, however, cognitive scores in the 2 groups were indistinguishable.

continued

Related Resources

- Women and psychosis: A guide for women and their families. Centre for Addiction and Mental Health. University of Toronto. www.camh.net/About_Addiction_Mental_Health/Mental_Health_Information/Women_Psychosis.
- Seeman MV. Women and psychosis. www.medscape.com/viewarticle/408912.
- Chattopadhyay S. Estrogen and schizophrenia: Any link? The Internet Journal of Mental Health. 2004;2(1). www.ispub.com/journal/the_internet_journal_of_mental_health.html.

Drug Brand Names

Citalopram • Celexa
Estradiol • Estrace, Estrofem, others
Estradiol transdermal • Estraderm , Climara, others
Methylphenidate • Concerta, Ritalin, others
Prednisone • Deltasone, Orasone, others
Raloxifene • Evista
Risperidone • Risperdal

Disclosure

Dr. Seeman reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

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Clinical Point

Short-term estrogen therapy is beneficial for women with psychotic illness but continuous use increases the risk of adverse effects

Clinical Point

Selective estrogen receptor modulators are being investigated as a treatment for women with schizophrenia

At present I do not recommend estrogen for women with late-onset schizophrenia because the risk is too high and raloxifene does not enter the brain sufficiently to be a valuable cognitive enhancer. Novel SERMs with more specific efficacy for improving cognitive function may prove useful in the future,[25] however, as may phytoestrogens. Adjunctive hormone modulation is a promising area of gender-specific treatment for serious mental illness.[26]

CASE CONCLUSION

Gradually improving

Dr. I's depression was triggered by her mother's death and regrets about not visiting and not being a mother. The content of her delusions was related to her guilt about not having returned to Germany; the delusions were probably triggered by depression, alcohol intake, her relative hypoestrogenic state, stress at work, lack of social supports, and dependence on her husband.

Over the next few years, Dr. I is maintained on a low dose of risperidone (reduced from 2 mg/d to 1 mg/d) and citalopram (reduced from 20 mg/d to 10 mg/d). She becomes increasingly engaged in supportive dynamic therapy, and her symptoms gradually improve.

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Bottom Line

Psychosis onset in midlife is mostly a female phenomenon because a perimenopausal estrogen decline increases women's susceptibility. Seek specific triggers such as medical illness or response to a drug before assuming an illness of unknown cause such as bipolar disorder or schizophrenia. Cognitive therapy targeting specific symptoms is useful; antipsychotics probably will be necessary.