



Review

Schizophrenia Psychosis in Women

Mary V. Seeman

Department of Psychiatry, University of Toronto, 260 Heath St. West, Toronto, ON M5P 3L6, Canada;
mary.seeman@utoronto.ca

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Abstract: A first step towards personalized medicine is to consider whether, for some disorders, the safest and most effective treatment of women needs to differ from standard guideline recommendations developed on the basis of clinical trials conducted, for the most part, in men. A second step is to consider how women's reproductive stages—pre-pubertal years, menstrual phases, pregnancy trimesters, lactation and postpartum periods, menopausal and postmenopausal/aging status—affect the optimal choice of treatment. This review focuses on these two steps in the treatment of psychosis, specifically schizophrenia. It discusses genetics, precursors and symptoms of schizophrenia, reproductive and associated ethical issues, antipsychotic drug response and adverse effects, substance abuse, victimization and perpetration of violence, and issues of immigration and of co-morbidity. The conclusions, while often based on clinical experience and theoretical considerations rather than strictly on the evidence of randomized controlled trials, are that clinical recommendations need to consider clinical and role differences that exist between men and women and make appropriate correction for age and reproductive status.

Keywords: women; schizophrenia; prevention; staged treatment; symptoms; response

1. Introduction

The term 'psychosis' describes a mental state during which a person is awake but experiencing periodic distortions of internal and external reality. The main symptoms of such a state are delusions (false convictions of reality) and hallucinations (visual and auditory and somatic perceptions or sensations that are internally generated). These symptoms occur in the context of several psychiatric illnesses, notably schizophrenia and delusional disorders, but are also seen (less often) in the course of affective and anxiety disorders. They also occur in many non-psychiatric disorders, whether endocrine, metabolic, or neurologic. Psychosis can be a transitory, time-limited response to a trauma, a toxin or a fever or it can be a recurring phenomenon, as it is in schizophrenia.

The lifetime prevalence of psychotic disorders in a given population is approximately 3%: 0.9% schizophrenia, 0.2% delusional disorder, 0.2% bipolar I disorder, 0.4% major depressive disorder, 0.4% substance-induced disorder, and 0.2% psychotic disorders due to a general medical condition [1]. This latter grouping includes genetic disease such as Wilson's disease, neurologic disease such as Parkinson's or Alzheimer's disease, autoimmune disease such as systemic lupus erythematosus, endocrine disease such as hyper or hypothyroidism, and vascular disease such as stroke, brain tumors, and brain injury.

The aim of this review is to focus clinicians' interest on the psychotic manifestations of schizophrenia as they are expressed in women, distinguishing women's experience with this illness from that of men.

The method used to collect information for this review was subjective. I first prepared a list of factors that I had noticed, in my now 60 years of treating schizophrenia, as showing significant difference between men and women. This list was based on clinical experience but also on the psychiatric literature, both classical and current. Having pre-determined which subtopics I wanted to

highlight, I searched my own past writings plus recent (mainly published in the last ten years) relevant papers from around the world. When there were several recent studies pertaining to the same issue, I selected the one with the most clinically relevant results. Many excellent articles have unfortunately had to be omitted in order to keep this review to a manageable length.

2. Differences in Schizophrenia between Men and Women

Differences in incidence or expression or treatment response between men and women experiencing schizophrenia (Table 1) have been explained in multiple ways [2]: by differences in male/female genetics, varying hormone levels, dissimilarities in physiology, pharmacodynamics, metabolics, immune factors, exposures to trauma, toxins, as well as by comorbidities, social roles, social perceptions, and cultural pressures. In general, illness prognosis has been found to be superior in women than in men, at least at younger ages [3]. Suicide and incarceration are less frequent in women; women are hospitalized involuntarily less often than men, and they are more often partnered and living with family and less often homeless. Medication doses are, on average, lower in women than in men and women are less stigmatized, less feared, and less likely to be perceived as dangerous [3]. Women's social networks tend to be larger [4]. All this may vary, however, depending on geography and culture. World Health Organization data on 16,380 individuals [5] show that, in most regions studied, women with schizophrenia had higher rates of symptom remission and clinical recovery than men. They also had a later onset age, a lower symptom severity and prevalence of substance abuse, and a higher likelihood of living with a spouse/partner or of living independently. Nevertheless, while this was the pattern in Northern and Southern Europe, it was not true for Central and Eastern Europe nor for Latin America, East Asia, North Africa, or the Middle East, where different patterns emerged in different regions. The authors of this study point out that regional variations underscore the importance of psychosocial and cultural factors in mediating the link between sex and outcome in schizophrenia. Importantly, they note that it is in countries where inferior social status is accorded to women that the expected female advantage in schizophrenia outcome is diluted. At the same time, it is equally important to appreciate that individuals of different cultural backgrounds and traditions often interpret the same symptom differently, sometimes perceiving it as pathological and sometimes not [6]. Descriptions of sex differences can, thus, arise from interactions among a wide variety of facts, perceptions, and interpretations.

Table 1. The Diagnostic and Statistical Manual of Mental Disorders (DSM)5 criteria for schizophrenia.

1. Two or more of the following for at least a one-month period of time; at least one of them must be one of the first three listed. Delusions Hallucinations Disorganized speech Grossly disorganized or catatonic behavior Negative symptoms, such as diminished emotional expression
2. Impairment in one of the major areas of functioning (work, interpersonal relations, or self-care) for a significant period of time since the onset of symptoms.
3. At least some signs of the disorder must last for a continuous period of 6 months.
4. Schizoaffective disorder and bipolar or depressive disorder with psychotic features, effects of a substance or another medical condition have been ruled out before a diagnosis of schizophrenia is made.

2.1. Genetics and Sex Difference

It is currently thought that mutations involved in the development of schizophrenia are probably ones located on genes associated with synaptic signaling and brain circuitry. Some of these genes are sex-biased, a term that includes genes that are expressed exclusively in one sex as well as those that are expressed in both sexes, but at a higher level in one than in the other [7]. Such sex-biased genes, seen much more often in the brain than in any other organ, underpin sexual dimorphism. Some sex-biased genes, as might be expected, are located on sex chromosomes. Many, however, are on autosomal

chromosomes, and in approximately one third of these, expression is influenced by sex hormones. The other two thirds impact one sex more than the other through modifications of chromatin modeling [8]. In the brain, Mayne et al. have found the most striking sexually dimorphic gene expression to result from sex chromosome genes, which, in their hands, constituted 65% of sex-biased genes found in the amygdala and 78% in the frontal cortex. By contrast, 91% of sex-biased genes in the nucleus accumbens, 95% in the anterior cingulate cortex, 91% in the dorsolateral prefrontal cortex, 60% in the cerebellum, and 89% in the hippocampus were autosomal genes. Each brain region was unique in its proportion of sex-biased genes [8].

The available literature on sex differences in schizophrenia focuses either on the influence of sex hormones on genes or on epigenetic changes in DNA methylation, histone modifications, and non-coding RNA [9], changes determined by environmental exposure. It must not be forgotten, however, that other, as yet unknown, mechanisms may also be at play [2].

2.2. Premorbid Differences between Women and Men

Currently, there is no consensus as to the definition of a 'start' to schizophrenia, which makes concepts such as premorbidity or age of onset inexact. The old definition of 'start' meant the onset of delusions or hallucinations (e.g., psychotic features), but many investigators today believe that delusions and hallucinations are not necessarily the core symptoms of schizophrenia but, rather, epiphenomena of prior brain disturbance [10].

Staying with the old definition of 'start' or in other words, with the emergence of psychotic symptoms, girls show less social and academic impairment premorbidly than boys do [11]. Girls who are diagnosed with schizophrenia have generally had a history of fewer birth complications than boys, less head trauma, closer relations within the family, larger friendship circles, and better school grades. Both sexes do, however, show considerable premorbid psychopathology (autistic traits, learning disorders, depression, social anxiety, obsessions, phobias, eating disorders, substance abuse) before the emergence of frank psychosis. In girls, this usually takes the form of depression, anxiety, and eating disorder. Boys, in contrast, are more likely to show earlier autistic and attention deficit disorders, conduct disorders, and substance abuse. During the at-risk mental state that precedes the emergence of psychotic symptoms, girls reportedly describe unusual fears and worries, whereas boys are more likely to report social withdrawal and difficulties with thinking [12].

2.3. Trauma as a Precursor to Psychosis

A vital unanswered question is whether childhood trauma, physical or psychological, can lead to psychosis, and whether this potential risk factor affects one sex more than another. Current thinking is that girls and boys are, indeed, differently affected by circumstances such as childhood maltreatment [13]. Clarifying this issue would represent a large leap forward in the field of prevention [14,15].

2.4. Gender Aspects of Onset Age

The clinical emergence of psychotic symptoms usually takes place in late adolescence or early adulthood. The average onset is 2–4 years later in young women than it is in young men, as demonstrated by Heinz Häfner et al. [16,17].

Explanations for this well (but not universally) accepted female lag range from maturational discrepancies between the two sexes, social support differences, male preferential exposure to substances of abuse and brain trauma, an accumulation of premorbid difficulties in males, and a possible neuroprotection conferred by female pubertal hormones [18]. There is a surge of estrogens during puberty in girls and estrogens are known to be neuroprotective in all species studied [19]; in humans, estrogen protects against neurodevelopmental and neurodegenerative diseases such as schizophrenia [20].

The onset of psychotic features may be instigated by a variety of different factors, as recently suggested by results of a study from Australia [21]. The investigators found that individual-based

factors, such as cannabis use, predicted onset age in males, whereas social factors, such as immigration, were more likely to trigger schizophrenia in females. The fact that, as outlined in the next section, the symptoms of schizophrenia in women frequently do not conform to a typical male pattern of presentation may partially explain why female onset is reported as delayed [22]. Both sex-specific triggers and diagnostic challenges such as this need further investigation.

In contrast to schizophrenia symptoms that begin in early adulthood, among individuals in whom symptoms start late (over age 40), women are significantly over-represented [23]. Women constitute approximately 80% of first onset patients who are over age 60. This has been attributed to the dramatic endocrine changes of menopause, the relative longevity of women, and the stresses of the caretaking roles often assumed by aging women [24].

2.5. Gender-Associated Symptoms in Schizophrenia

Gender-specific symptoms (depression and anorexia/bulimia in women; attention deficits and substance abuse in men) have been reported in patients during the at-risk for psychosis stage that often precedes schizophrenia [25,26]. Comparing men and women during the early years of illness (the first five years), Comacchio et al. [27] found that men show more negative symptoms and that women more frequently than men report comorbid depression.

Over the schizophrenia life span, there is general agreement that delusions and hallucinations are more often endorsed by women than by men, whereas negative symptoms (listlessness, lack of ambition and volition, social withdrawal, emotional blandness) and cognitive defects (memory and attention problems) are more often endorsed by men [28]. Affective symptoms (depression and hypomania) are more commonly seen in women, which is why the diagnosis of schizoaffective disorder is more prevalent in women than in men [29], though not all epidemiological studies agree on this.

Because of disagreement in the literature and the fact, alluded to earlier, that sex differences in this illness vary with culture and geography and age, among other variables, it is difficult to state with certainty which differences between men and women will withstand the test of time and societal change. Replication in different settings will help with the ability of clinicians to translate these findings into illness management guidelines.

3. Hormone-Related Periodicity in Women

Many women with schizophrenia experience fluctuations in their psychotic symptoms related to the menstrual stage, with symptom severity increasing premenstrually [24,30,31].

Because many older drug treatments for schizophrenia raised prolactin levels and consequently lowered the likelihood of conception, and also because many care providers mistakenly believed that women with this illness did not engage in sexual activity, psychiatrists did not usually offer contraceptive advice. This is still true even though newer medications raise prolactin to a much lesser extent, and women with schizophrenia do get pregnant [32], often not intending to. Contraceptive advice and referral thus become important aspects of the care of women with schizophrenia [33].

In my practice, despite the fact that serum concentrations of most antipsychotics significantly fall by the third trimester because of the increased volume of distribution [34], women with schizophrenia usually remained free of psychotic symptoms during pregnancy [35]. This may have been due to the extra medical attention they received during their pregnancy. When compared to pregnant women in the general population, however, women with this illness suffer a higher prevalence of pregnancy-related complications [36,37] and their pregnancy can present important ethical challenges [38,39].

For instance, women with schizophrenia sometimes deny their pregnancy or harbor other delusions that lead them to take risks with respect to the health and welfare of their fetus. This can take the form of continuing to smoke cigarettes and use alcohol and street drugs when pregnant or of not adhering to prenatal medical prescriptions. Many clinicians have asked whether it is legal, in those instances, to declare a woman incompetent and involuntarily commit her to hospital for the sake of the

health of the fetus. The answer hinges in large part on whether or not a fetus is legally considered a person, opinions differing on this question in different jurisdictions.

A frequently encountered dilemma arises when women who are acutely psychotic whilst pregnant or breastfeeding refuse antipsychotic medication because they do not want to harm their fetus or neonate. Their concern is legitimate, which makes it difficult to declare them incompetent and treat them against their will to prevent mental health deterioration [40].

Other ethical dilemmas are decisions about abortion and post-abortion sterilization made by women whose decision-making capacities are clouded by severe delusions. If a woman is judged incompetent, can a surrogate make these personal decisions on her behalf? What, in the case of abortion, are the rights, if any, of the baby's father [40]?

When child welfare agencies obtain evidence that a woman with schizophrenia poses a danger to her child, they have a legal duty to remove the child from the mother's care. Physicians also have the legal responsibility to report women who pose such danger to child welfare authorities. These decisions often need to be made during the postpartum period when many women suffer psychotic relapse, a state that does not necessarily reflect future parenting ability. Such actions are always difficult to take, especially because a mother's current state may or may not predict her future parenting ability, while giving up a child, even temporarily, leaves lingering negative effects on both mother and child.

Immediately postpartum is the time when decisions about parenting fitness are often made, and it is also a time when women with psychosis are at their most vulnerable [41]—when they show more severe psychotic symptoms than they otherwise would. This has been attributed to the abrupt fall in estrogen levels after delivery, but it also depends on the quality and availability of effective assistance and social support, the degree of the mother's sleep deprivation, and the accessibility of psychiatric care. Immunological and thyroid dysfunction may further contribute to postpartum psychosis [42]. A major clinical problem is that postpartum women with schizophrenia who have stopped antipsychotic medication during pregnancy may fail to resume it after the baby's birth, at a time they need it most. Many do not want to take sedating medications that makes them less alert to the baby's needs [43]. They may erroneously think that not taking medications shows child welfare workers that they are now well and can take care of their baby.

The postpartum period is a difficult period for women with psychotic illness. Taking the infant into temporary care may often be necessary but child welfare and mental health agencies need to coordinate their approaches and attempt to reunite mother and infant as soon as it is safe to do so.

Whether women on antipsychotic medication should or should not breastfeed has been yet another controversial issue in the management of women with schizophrenia. Best practice depends on several factors, including the specifics of the drugs to be taken and their doses. Breast milk is important for the baby's health, but not when it contains drugs that may potentially harm the baby's developing brain. The issue of downstream effects of antipsychotic drugs on a child's neurodevelopment has not yet been resolved [44].

Adoption decisions sometimes have to be made when a woman with schizophrenia is unable to care for her child. These are never easy. The mother's family may formally or informally adopt the child, and such an arrangement can have both positive and negative consequences [45]. Currently, because of the rise in open adoptions, mothers may be able to keep in touch with their offspring whoever the adoptive parents are, but there is no literature yet as to outcomes for a mother with psychosis and her child in the context of non-family adoptions.

Domestic abuse is a too frequent and recurring problem for women with schizophrenia, perhaps because these women sometimes enter into relationships with abusive and substance abusing men [46]. Abuse appears to be aggravated during pregnancy [47,48].

Self-harm can also surface during pregnancy in this population of women [49]. Women with severe mental illness are at increased risk of suicide in the perinatal period, and these suicides are often preceded by instances of self-harm. In one study of 420 women with serious mental illness, 103 (24.5%) had a record of suicidal ideation and 33 (7.9%) reported instances of self-harm during a pregnancy [49].

Losing custody of children [50] or experiencing parenting difficulties [51] are high on the list of concerns of women with schizophrenia. These are areas where appropriate intervention can be of great assistance. Respite care appears clinically effective, as does engaging family and support networks to help vulnerable mothers. For the patient, adherence to a therapeutic regimen is critical because parenting is stressful. Public health nurses, peer support workers, family therapists, and parenting groups are all helpful. Close linkage with child welfare services and the provision of an emergency number that mothers can call whenever they feel burdened prevent crises for both mother and child [52–55].

After pregnancy and giving birth, the next significant hormonal transition in a woman's life is menopause. During menopause, estradiol levels in women abruptly decline to reach a level below that of men. It is generally agreed that estrogens exert protective effects on the central nervous system [56], so that estrogen loss at menopause renders specific cells in the brain vulnerable to deleterious gene expression and to environmental stress [57,58].

In women with schizophrenia, menopause ushers in a period of increasing severity of psychotic symptoms and a worsening response to antipsychotic medication [59–62]. This is complicated by the concomitant emergence of menopausal symptoms (hot flashes, vaginal and urinary symptoms, insomnia, mood changes), worsening bone, joint, metabolic and heart health, and adverse effects of increasing doses of antipsychotic drugs (increased because effectiveness is waning) plus the psychosocial accompaniments of this time of life—aging parents, children leaving home, dwindling employment or romantic opportunities, foreshortened future. Much can be done to support women through this transition and through the period of aging that follows. Mental health professionals can facilitate referrals to appropriate health specialists, inform patients about the necessity for osteoporosis and cancer screening, adjust antipsychotic doses for both effect and tolerability, refer for cognitive therapy targeting insomnia and anxiety, treat depression, and offer family intervention and other forms of psychosocial counseling. Hormonal replacement therapy is now considered safe for the first five years after menopause onset [59].

Estradiol and the selective estrogen receptor modulator, raloxifene, have been used as augmentation therapy for women with schizophrenia (and sometimes men), lessening symptom severity and, therefore, potentially leading to reduced doses of antipsychotic medication and fewer adverse effects [63,64]. The effectiveness of estrogen has been attributed to its many neuroprotective actions [58,65], one of which is its anti-inflammatory effect. Çakici et al., in a recent meta-analysis, [66] found that four categories of anti-inflammatory agents are effective in the reduction of psychotic symptoms— aspirin, estrogens, minocycline, and *N*-acetylcysteine.

The neuroprotective actions of estrogens and their effectiveness as adjunctive treatments for psychosis have been demonstrated in randomized trials by a variety of research groups. Evidence for their value is persuasive, as is the evidence for worsening psychosis during time periods in women's lives when estrogen levels abruptly fall—postpartum and menopause. The effectiveness of other interventions discussed in this section are based on clinical evidence alone.

4. Antipsychotic Drug Response in Women

There are theoretical reasons why, throughout reproductive life, women's effective doses of antipsychotics might need to be lower than guidelines recommend for men. The presence of estrogen at dopamine receptor sites in the brain helps to block the transmission of dopamine and the emergence of psychotic symptoms. Estrogen also regulates the activity of specific cytochrome P450 CYP enzymes that metabolize antipsychotic drugs, thus potentially increasing the levels of those metabolized by CYP1A2, e.g., clozapine and olanzapine [67].

Because there are so many variables that impinge on antipsychotic response, it is difficult to provide guidance that applies to all women. What is evident, however, is that, after menopause, many women need to increase their antipsychotic dose. Other reproductive stages (late luteal menstrual phases, pregnancy, the postpartum period) in women's lives require special prescribing considerations

as well [68–70]. Recently, sex-specific treatments for psychoses and other central nervous disorders have been proposed [71,72].

Side Effects

Compared to men, women's greater susceptibility to adverse effects of drugs may be explained both by the idiosyncracies of the female immune system [73] and by the fact that female pharmacokinetics differ from men's while dosing guidelines are generally derived from drug trials where participants are mostly men [74].

One of the best examples of sex differences in response to antipsychotic drugs is the drug effect on the QTc (rate corrected QT interval on the electrocardiogram). The QTc is an index of ventricular repolarization after the blockade of cardiac potassium channels by drugs such as antipsychotics. It is inherently longer in women than in men and, if overly long, can lead to a serious cardiac condition called Torsades de Pointes [75].

Hypercoagulability states leading to venous thromboembolism, pulmonary embolism, and cerebrovascular events such as stroke are further adverse effects of antipsychotic medication that are more commonly seen in women than in men. This may perhaps be explained by women's use of hormonal contraceptives and hormone replacement therapies [76].

Women also suffer more than men from the hyperprolactinemia induced by antipsychotics, an effect that can lead to sexual dysfunction, hirsutism, amenorrhea, galactorrhea, and increased risk of osteoporosis and subsequent bone fractures. For instance, in a study of 199 patients hospitalized for schizophrenia in China, low bone mineral density scores were seen in 56% of the males but in 76% of the females [77].

The effect of antipsychotic drugs on one's outward appearance has received little attention in psychiatry. Prior to treatment, the body image of persons with serious mental illness is already reported to be poor [78], perhaps because of socio-economic disadvantage and the negative symptoms of schizophrenia, which, together, undermine the ability and motivation for hygiene and grooming [79]. Added to this are antipsychotic side effects such as weight gain, tremor and tics, shuffling gait, frequent blinking, salivation, rashes, and gingivitis, all of which augment perceived unattractiveness and poor self-concept. One's outward appearance leads to real life consequences in the form of diminished opportunities and social stigma [80]. There is much that health professionals can do to help improve a patient's appearance. Doses can be adjusted, adjunctive drugs added, and exercise encouraged. Referrals can be made to dentists, dermatologists, and ophthalmologists [81–84]. The hypothesis that such interventions improve quality of life in this population needs to be investigated.

Because of individual differences in human pharmacokinetics and individual differences in antipsychotic drugs, it is difficult to state categorically that women as a group metabolize these drugs significantly differently than men and that the side effects they experience differ, on average, from those of men. However, there is sufficient evidence to recommend that clinicians pay attention to individual characteristics when they prescribe antipsychotic medication.

5. Impact of Substance Abuse

Men in the general population, and also men with schizophrenia, are more likely to use substances than women, but the use gap is narrowing and adverse medical, psychiatric, and functional consequences of street drugs and alcohol are often reported to be more severe in women than in men [85]. Infrequently mentioned substances of abuse, such as diet pills and laxatives, are specific to women [86]. Pregnancy is a time of special concern because of potential effects of substances not only on the mother but also on the fetus [87]. Many biological, psychological, and social sex differences with respect to the metabolism of alcohol and drugs have been reported, but reports do not all agree. On the whole, however, women appear to suffer greater functional impairment than men from overuse of substances; prevention is indicated and treatment needs to start early and continue over time.

Psychiatric comorbidity such as depression and anxiety have been identified as especially important targets for intervention in women to prevent or decrease the use of substances [85].

Differences in male/female habits such as substance abuse are not fixed but change over time and circumstance. Reactions also change depending on drug and dose and confounding variables. The take away lesson for clinicians is that substance use in women, especially during pregnancy, needs to be prevented because there is ample evidence of its potential for harm.

6. Victimization and Violence

This review was written during the COVID-19 pandemic, a period of worldwide psychological and economic stress and family isolation that has drawn public attention to the serious problem of intimate partner violence perpetrated against women [88]. The problem is significant among psychiatric patients and their partners, reaching a yearly prevalence in this population of between 16% and 92% depending on the definition one uses of victimization [89]. Women with schizophrenia are reported targets of violence, not only at home, but also on the street, and even in institutions such as hospitals and prisons. Because of social isolation, passivity, cognitive defects, psychotic symptoms, substance abuse, homelessness, and poverty, they are vulnerable to prostitution and sex-trafficking [90,91]. As a result, they suffer shame and guilt, increased severity of psychotic symptoms, and an increased risk of sexually transmitted disease, unwanted pregnancy, and multiple abortions.

It is commonly assumed that violence in the context of schizophrenia is a male problem, which is exacerbated by substance abuse. Violence, like victimization, has been defined in many different ways (physical aggression, verbal aggression, hostility, criminal aggression) [92]. Some studies suggest that violence in women with schizophrenia has been underestimated and that women engage more often than men in certain forms of violence, notably verbal aggression [93]. The underestimation may stem from the fact that the violence committed by women, compared to that of men, is relatively unlikely to result in serious physical injury. It may also receive comparably less attention because women are more likely than men to limit their aggression to family members and spare strangers. Women may also react to different triggers to violence than men, threats to their young serving as an example of an important trigger for women [94].

The evidence for male/female difference in victimization and perpetration of violence in the context of schizophrenia is only beginning to accumulate. For violence prevention in both sexes to be effective, potential gender differences need to be better understood.

7. Non-Psychiatric Comorbidities

Some comorbidities associated with schizophrenia are specific to women, for instance, Turner's syndrome [95] or polycystic ovaries [96]. Some are very much more common in women than in men, for instance, eating disorders, thyroid disease, autoimmune disorders, and fertility disorders [97–100].

Epilepsy is associated with schizophrenia and some forms of epilepsy such as idiopathic generalized epilepsy and photosensitive epilepsy are more common in women than in men. Catamenial epilepsy is a neuroendocrine condition in which seizures emerge in a cluster around specific times of the menstrual cycle, most often around the perimenstrual or periovulatory period [101]. Breast cancer is more common in women with schizophrenia than in women in the general population [102]. This is important because antipsychotic medication that causes weight gain and hyperprolactinemia has been considered as a potential risk factor, but there are many non-treatment aspects of schizophrenia in women that increase the risk of breast cancer—low parity, low prevalence of breast feeding, high consumption of caffeine and cigarettes, and obesity. Sleep difficulties are another common feature in schizophrenia, more common in women than in men [103]. Sexual dysfunction in schizophrenia, attributable to antipsychotic drugs and the resultant hyperprolactinemia, is most often considered a uniquely male problem, but it affects females as well [104,105].

Important for health providers is the fact that psychotic episodes can be triggered or exacerbated by drugs used to treat commonly occurring comorbidities. Examples are corticosteroids for autoimmune disease [106] and agents used to treat infertility [107,108].

Although a recent study suggests that, in the context of schizophrenia, women are altogether more at risk of physical comorbidity than men [109], this gender discrepancy is far from being established.

8. Immigration

The rate of psychosis is known to be high among migrant communities, more so for some ethnic groups than others [110,111]. The observation has been made in at least some migrant groups that women are less vulnerable than men to the psychotogenic effects of immigration [112]. Finding explanations for the gender gap in relation to immigration may shed light on the more general (and relative) protection from psychosis seen in women during their reproductive years. The potential reasons why immigration appears to lead to increased risk of psychosis are not yet understood. This is an important novel area of research.

9. Schizophrenia Treatment Guidelines

Given the undisputed differences between men and women with schizophrenia, e.g., symptom response to hormonal changes, antipsychotic exposure risk to fetuses and infants, women's relative vulnerability to physical injury when victimized, and the many other not necessarily universal differences described in this review, I searched recent schizophrenia treatment guidelines of English-speaking countries [113–118] to see how these differences were being addressed. All the guidelines dealing with psychopharmacology mention pregnancy and breast-feeding. None mention potential maternal-fetal conflicts and ethical dilemmas with regard to pregnancy and parenting. The later guidelines mention gender differences related to certain pharmacological agents but the focus is on the drug rather than on the woman. The best guidelines with respect to personalized medicine are those from Australia and New Zealand [114]. These have separate sections for Special Populations, e.g., Indigenous groups and women. In the women section, several of the issues mentioned here are broached. Disappointingly, although the guidelines from Australia and New Zealand were out earliest, neither Britain, Canada, India, nor the U.S. subsequently adopted the Special Population format, which allows quick access to important clinical issues potentially affecting all women.

10. Concluding Remarks

This brief overview of the literature on women and schizophrenia points out how much remains unknown and how much more research is required in order to identify the specific needs of women with schizophrenia as distinct from those of men. Although these needs change over the course of a woman's life, in general, women have somewhat different symptoms, different comorbidities, and different social roles, especially where those roles impinge on parenthood and care giving. Issues pertaining to violence, victimization, and stigma also markedly differ. The changes that take place in women over hormonal transitions, and that often require distinctive treatment, are of growing interest to psychiatrists. A critical issue is mental health care during pregnancy and neuroprotection of the fetus and neonate. This field requires continuing research in biological, psychological, social, and cultural aspects of gender differences and the impact of such differences on the development and maintenance of schizophrenia defects, on the progress of illness once schizophrenia begins, on treatment response, and on downstream effects on offspring. Studying gender differences constitutes a first step towards individualized treatment, a goal that needs emphasis in international schizophrenia treatment guidelines.

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