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Do we need sex-oriented clinical practice guidelines for the treatment of schizophrenia?

Piyumi Fernando^a, Iris E.C. Sommer^b, and Alkomiet Hasan^{a,c}

Purpose of review

Clinical practice guidelines (CPGs) do not usually offer a sex-specific approach for the management of schizophrenia. With this narrative review, we aim to give an integrated and synthesized overview of the current state of knowledge regarding sex-specific aspects in schizophrenia and how this topic may be adapted in the development of CPGs.

Recent findings

Recent studies further suggest sex-specific differences in epidemiologic features, the course of illness, underlying pathomechanisms, response likelihood to antipsychotic medication and differences in tolerability. Beyond this, selective estrogen receptor modulators like raloxifene have shown beneficial effects on symptom severity and cognition in women with schizophrenia.

Summary

Sex-specific aspects can already be integrated in clinical guideline recommendations, especially with regard to efficacy and tolerability of antipsychotic treatment. Moreover, these aspects may be used for an individual risk-stratification. Recent studies provide evidence supporting the hypothesis of sex-specific modulation in schizophrenia and build the groundwork for sex-specific novel treatment options. However, there remains a clear need for additional studies focusing on women with schizophrenia to substantiate current findings.

Keywords

antipsychotics, evidence-based psychiatry, guidelines, schizophrenia, sex-specific differences

INTRODUCTION

Schizophrenia is among the most debilitating mental disorders, and though being rare in comparison to other diseases, is ranked by WHO as one of the top contributors to years lived with disability (YLDs) worldwide [1]. Extensive research has led to a better understanding of risk factors; however, the exact underlying pathomechanisms, especially with regard to sex-specific aspects, remain yet to be understood. Sex-related differences in schizophrenia are broad and encompass increased male prevalence rates [2], age of onset, treatment response, adverse-effects and course of illness. In women, worsening of symptoms is often seen after menopause [3[¶]]. Despite the available knowledge of sex-specific aspects (as detailed in this review), clinical practice guidelines (CPGs) do usually not entail sex-specific recommendations [4,5], possibly because women are underrepresented in clinical trials. Newer international CPGs recommend taking sex aspects into account when treating schizophrenia patients [6[¶]]. However, because of a lack of consistent evidence from clinical trials,

sex-specific guidelines do not exist to this date. In that regard, the European Medicines Agency decided to foster the development for separate guidelines for woman as a specific population in clinical trials [7]. Future guidelines of the World Federation of Societies of Biological Psychiatry will consider this sex-sensitive perspective [8] but in general this topic

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KEY POINTS

- The likelihood to have experienced a trauma is higher in female patients with schizophrenia.
- Female patients with schizophrenia are at-risk to be underdiagnosed, and thus, early sex-specific recognition programs should be implemented.
- Symptoms may differ between female and male patients with more affective symptoms in female patients and more negative symptoms in male patients.
- Female patients are more likely to respond to an antipsychotic and are more likely to develop substance-specific and sex-specific side-effects (e.g. motor side-effects, metabolic syndrome), thus, lower dosages and careful tapering of antipsychotics is needed.
- It may be useful to prolong injection intervals for depot-intervals if female patients develop substance-specific side-effects bearing in mind the off-label character of this strategy.
- Estrogen augmentation treatment can improve outcomes in female patients with schizophrenia with low natural estrogen. Female patients may need estrogen-replacement therapy during and after menopause to prevent clinical deterioration.

receives still little attention. In order to give a focused overview of this topic, we performed a qualitative literature search for this narrative review to identify interesting new studies regarding sex-specific differences in outcome dimensions in schizophrenia (see Table 1).

DIFFERENCES IN CLINICAL PRESENTATION AND COURSE OF ILLNESS

Increasing evidence suggests a significant sex-difference regarding the at-risk stage, clinical presentation and course of illness [9]. Although age of onset is significantly lower in men with a single age peak at around 21–25 years, women are considered to present with a bimodal age of onset, the first peak being between 25 and 30 years and the second during the perimenopausal or postmenopausal period [10–12]. However, new unpublished findings indicate that disease onset in women can occur at any age between 16 and 65 years resulting in a relative second peak at the menopause because of reduced incidence in male patients [in preparation, personal communication]. The age of onset most likely follows an individual pattern involving genetic and environmental factors. Genetic differences encompass the protective effects of estrogen on brain health and cognition as well as the postulated higher dopamine

activity in men [13]. Although men are more likely to present with a clear prodromal stage, early substance abuse and especially a high prevalence of cannabis abuse [14], women have more often suffered from heightened stress and traumatic events during the years preceding the onset [15,16]. Despite having a higher likelihood to experience trauma and despite the constant observation that trauma worsens psychosis, women have in general, better outcomes than men. With regard to the core symptom domains of schizophrenia, namely positive, negative, affective and cognitive symptoms [17], evidence is available suggesting a sex-related presentation of symptoms. Psychotic symptoms are reported to be pronounced in female patients [18], whereas men present with more negative symptoms, such as flat affect, reduced activity and social withdrawal [19,20]. Women are more likely to demonstrate more affective symptoms, such as depressive mood and anxiety [20,21]. Female patients with an early onset are more likely to develop less negative and more severe positive symptoms compared with those with a late onset [22]. Robust evidence is available indicating pronounced cognitive symptoms in men, whereas it remains elusive to which extend the higher drug abuse rates in men account for these differences. In more detail, women scored better in testing of cognitive functions, such as attention, memory, language, executive functions and emotion perception [17,21,23,24]. Although positive and negative symptoms are considered crucial in predicting outcomes, evidence gathered in past years indicate that cognitive impairments are associated with a higher burden of illness and impact patient outcome and recovery [25,26]. Some studies showed fewer hospitalization, longer remission periods and fewer relapses in women [17,27]. Better outcomes in female patients were reported in a 3-year longitudinal study including 17 384 patients showing that women had slightly better outcomes regarding remission rates. Although these results were consistent for Southern and Northern Europe, no significant difference was found in other regions, highlighting that cultural and socioeconomic background should also be considered when discussing sex-specific aspects [28]. A 14-year follow-up study extends these findings showing that, for example, homelessness and reduced family support is associated with a male sex [29]. However, other studies are available questioning these examples of sex-specific differences in outcomes [19].

EARLY DETECTION AND DIAGNOSIS IN MEN AND WOMEN

Although these findings and further research indicate a more positive outcome and less severe course

Table 1. Selective overview of recent studies dealing with sex-specific differences in schizophrenia with regard to several outcome domains

Study	Sample-size	Type of study	Main findings	Main limitations
Novick <i>et al.</i> [28]	16 380 participants in 37 countries	Prospective observational study (3 years)	Higher frequency of clinical remission (58 vs. 51.8%), functional remission (22.8 vs. 16.0%), and recovery (16.5 vs. 16.0%) at 3 years in women. More positive course of illness in females for all three outcomes was only seen in Southern Europe and Northern Europe. Findings with the pooled sample showed that blunted affect, social withdrawal, alcohol abuse, and self-neglect were more frequent in males than in females at 1-year and 2-year follow-ups.	This study was initially designed for the analysis of comparative cost and outcome rather than sexes and outcome. Outcome was analyzed between sexes and socioeconomic background. However, data on factors known to impact outcome like family history, estrogen levels and more importantly differences in antipsychotic treatment were not collected. Therefore, the results presented in this study might have lower conclusive value.
De Boer <i>et al.</i> [83 [■]]	9 RCTs, 561 participants	Systematic review and meta-analysis	Nine double-blind randomized study that compared raloxifene versus placebo in treatment of schizophrenia. De Boer <i>et al.</i> found moderate but significant effects of raloxifene on general PANNS scale, on negative and positive symptoms. Results were not dose-dependent nor treatment-dependent. No significantly positive effect of raloxifene on cognition was found.	As only few studies have been conducted testing the effect of raloxifene on cognition, the results shown in this study regarding cognition might be a lower conclusive value.
Eugene and Masiak [51]	4 studies, 72 participants	Modeling and simulation study	Pharmacometric analysis indicated that women require 10 mg/day and men 20 mg/day of olanzapin to reach 70% D2-receptor occupancy.	Though the results show conclusive value for sex difference, approximately 1/4 of included patients were bipolar ($n = 17$). The disease-specific effect of on D2 receptor binding was, probably because of small sample size, not taken into account. Thus, results have a lower conclusive value regarding gender-differences in schizophrenia.
Weiser <i>et al.</i> [84 [■]]	200 female participants	Randomized-controlled trial	The group that received estrogen patches over the course of 8-weeks presented statistically significant improvement in the primary clinical outcome measure compared with the placebo group. Interestingly, the effect of estradiol versus placebo was evident only in participants older than 38 years, whereas participants younger than 38 years did not show a significant benefit in comparison to those in the placebo group.	The study included a demographic subgroup. So results are not applicable to other demographic groups (men, older women). Eight weeks represent a short period, thus the results might be representative for short-term effect of estrogen, however, no conclusion can be made regarding long-term effects of estrogen. Furthermore dosage-dependence was not tested, neither was the menstrual cycle and natural fluctuations in blood levels of estradiol in women taken into account.
Plana-Ripoll <i>et al.</i> [39 [■]]	7 369 926 participants, 103 848 with schizophrenia	Cohort Study	In this register-based cohort study, data of 7 369 926 Danish people (among those 762 419 with mental disorders) was analyzed using following health metrics: mortality rate ratio (MRR) and life-years lost (LYL). MRR was higher among people with mental disorders compared to the general population. MRR and LYL in males with schizophrenia (LYL 12.06 years) were higher compared with females with schizophrenia (LYL 9.37 years).	Although the amount of analyzed data is extensive, results presented rely on the accuracy of the datasets used for analysis. Data on factors that possibly impact MRR and LLY estimates (e.g. remission and people with schizophrenia who were never in inpatient care or generally admitted in to a hospital) were not included in the analyzed data pool.

of illness for female patients [9], it is important to note that the diagnostic identification of schizophrenia in women is delayed [30]. The female form may start with severe affective symptoms, might feature self-harm, suicide attempts and lack severe negative symptoms [31,32]. This makes the likelihood of misdiagnosis in women higher (e.g. psychotic depression, bipolar disorder or borderline personality disorder). Misdiagnosis may lead to under-treatment, to incorrect treatment (e.g. antidepressants instead of antipsychotics) and increase the duration of untreated psychosis (DUP). Considering that DUP negatively influences course of illness, a delay in diagnosis may result in unfavorable disease outcomes in women. Such diagnostic pitfalls may be curtailed by the use of female-specific criteria for early detections and diagnosis. Moreover, clinicians must know about the difference in symptomatic presentation of women in order to improve the correct diagnostic classification according to ICD-10 or DSM-V.

MORTALITY

An increased risk for premature death with a reduced life expectancy of up to 25 years for schizophrenia patients has been confirmed by a tremendous amount of studies [33–38]. A recent study from the Danish Psychiatric Central Research Register including more than 7 million people [39^{***}] confirmed and extended these findings for the subgroup of patients with schizophrenia. Although this recent study confirmed significantly higher mortality rate ratios for schizophrenia in male patients than female patients, no significant differences in life expectancy were found [39^{***}]. However, separate meta-analyses suggest otherwise. Although one meta-analysis found a significant difference of life expectancy between the sexes, two other meta-analyses found no differences in mortality ratios [40–42].

PHARMACOKINETICS AND PHARMACODYNAMICS

Antipsychotics are absorbed, dispersed and metabolized differently between sexes [43]. Absorption depends partly on gastric emptying and gastrointestinal transit time, which are faster in men [44,45]. The distribution of antipsychotics depends on various factors, such as weight, gastric emptying and percentage of adipose tissue. Due to the lipophilic profile, most antipsychotics accumulate in adipose tissue increasing their half-life periods. Women are on average smaller in height and present with a higher body fat percentage, thus suggesting a difference in half-time period between the sexes [45]. This

should especially be taken into account with regard to intramuscular long-acting (depot) medication, as resorption of intramuscular injections is slower in women [46]. This may result in a need to prolong injection intervals in women in cases of an increase of side-effects bearing in mind the aspect of off-label use. Furthermore, renal clearance is higher in men, which accounts for a longer half-life time in women for urine-secreted drugs [47]. Bioavailability is also dependent of protein binding (e.g. glycoprotein), which could restrict passing the blood–brain barrier and thus, restrict the drugs from reaching the brain. Estrogen and progesterone have been shown to reduce levels of glycoprotein, suggesting better bioavailability in women [48]. Apart from sex-related differences mentioned above, female sex hormones affect the activity of the liver enzyme cytochrome P (CYP) [49]. Lower activity of CYP450 1A2, together with lower prevalence of tobacco consumption reduces the metabolism of, for example, olanzapine and clozapine in women [50]. One study using pharmacodynamics modelling established that women need approximately 10 mg olanzapine per day to achieve 70% dopamine striatal D2 receptor occupation, whereas the dose for men is 20 mg per day for the same D2 occupation level [51]. These results might be explained through evidence that the number of D2 receptors in the striatum is lower in women [52]. Indeed, the summary of product characteristics (SPC) for olanzapine mentions that lower dosages may be needed for women [53]. CYP2A4, an enzyme involved in the metabolism of, for example, haloperidole, risperidone and aripiprazole, is expressed at higher levels in women, which may indicate a need for a higher dosage of these antipsychotics in female patients, highlighting the need to consider sex-dependent effects on drug clearance [54].

ANTIPSYCHOTIC TREATMENT RESPONSE

Several studies have concluded that women generally have a higher response likelihood to neuroactive medication, including antipsychotics, in general, whereas men require higher doses for an equivalent therapeutic response [50,55–57]. Apart from pharmacodynamics, other factors may explain the higher response likelihood in women. Although some studies have indicated a better treatment compliance, more recent studies did not show significant difference in drug adherence between the sexes [58,59]. Interestingly, men tend to have higher relapse rates following antipsychotic treatment discontinuation compared with women [60,61]. With regard to the assumed second peak of onset in women, it should be noted

that antipsychotic response gradually declines after menopause, suggesting that an increase in dosage and/or estrogen replacement may be necessary [62,63]. As treatment response in schizophrenia decreases with the number of episodes [64], the delayed onset in women may be a protective factor regarding treatment nonresponse after relapse.

ADVERSE EFFECTS

Adverse effects play a pivotal role in treatment response, drug compliance, patient safety and overall quality of life [65]. Though evidence suggests that women require lower treatment doses and show better responses, they are twice as common to report adverse effects [66–68]. Although adverse effects also depend on personal tolerance, women are biologically more prone to develop specific adverse effects. For example, prolactin-increasing antipsychotics have a different impact on women. Adverse effects following an increase in prolactin have a high-impact on the well being of women with schizophrenia. First-generation antipsychotics and, for example, risperidone have an impressive effect on prolactin. High prolactin levels reduce estrogen production, leading to amenorrhea, infertility and hirsutism. Despite the situation that the relationship between antipsychotic treatment, prolactin increase and osteoporosis remains elusive [69], one could speculate that prolactin augments osteoporosis risk in women with schizophrenia [70]. It is established that women have a higher risk to develop hematological adverse effects or cardiac complications, such as torsade de points [71–74]. Antipsychotics, especially second generation antipsychotics, are associated with a higher risk for metabolic syndrome in patients with severe mental illness. In this regard, it should be noted that some studies indicate a higher susceptibility for women treated with antipsychotics to gain weight and to develop subsequent metabolic syndrome. However, on the other hand, some evidence also suggests that men with schizophrenia are more likely to accumulate metabolically more adverse visceral adipose tissue [79]. One adverse effect that receives little attention is venous thromboembolism (VTE). Despite a lack of a clear association, antipsychotics, in particular, clozapine, olanzapine and zuclopenthixole [75,76], may increase the risk for a VTE as part of a complex scenario [77,78]. Taking into account that other VTE risk factors, such as pregnancy, obesity [79], menopause, hormone replacement are more pronounced in or exclusive to women, one could assume that female antipsychotic users are at a higher risk to develop VTE

associated with an antipsychotic treatment than men [79,80].

HORMONE HYPOTHESIS AND RESULTING TREATMENT OPTIONS

The hypothalamic–pituitary–gonadal axis, affecting brain development and functioning, is involved in the pathophysiology of schizophrenia. It is postulated that the delayed onset and the second peak in women is because of the neuroprotective attributes of estrogen [81]. This hypothesis is supported by observations that symptoms worsen during low estradiol phases of the menstrual cycle. Lower estrogens hamper the protective effects on the central nervous system (including beneficial effects on dendritogenesis, synaptic plasticity and neural excitability) and may deteriorate the course of illness in women. Given the natural decrease in estrogen with menopause, it is discussed that hormone substitution should be offered in early postmenopausal women with schizophrenia, and possibly also in premenopausal women with low natural estrogens [62,82]. A recent meta-analysis showed that the selective estrogen receptor modulator (SERM) raloxifene was effective in reducing total, positive, negative and general symptom severity in women with schizophrenia [83]. A recently published randomized controlled trial conducted in 100 women with schizophrenia showed that an 8-week add-on treatment with 200- μ g estradiol patch was superior to placebo in improving positive and negative symptoms [84]. One could discuss that estrogen augmentation with transdermal patches (for postmenopausal women), or in combination with progesterone as in oral contraceptives (for premenopausal women) can be cost-effective alternatives to raloxifene. When no hormone substitution is provided to women with schizophrenia around menopause, lower estrogen levels will increase drug metabolism and higher dose of antipsychotics may be indicated [62]. Although a majority of studies have focused on estradiol, there is evidence also suggesting a neuroprotective component to progesterone and DHEA (precursor of testosterone and estrogen) [85]. A systematic review and meta-analysis indicated that the add-on use of estrogens and SERMs could be effective augmentation strategies for several symptom domains in women. However, potential side effects related to a long-term use of such compounds must be considered as a part of a balanced risk–benefit evaluation [86].

For premenopausal women with schizophrenia, fertility and wish for contraceptives is an important topic for clinical discussions. Women who do not wish to become pregnant need effective

contraceptives when sexually active. Additive benefit from contraceptives that increase estrogen levels may be expected and could be an extra reason to start contraceptives in these young women. Given the increased risk for thromboembolic events, the benefits of estrogen increase need to be weighed against the potential for the aforementioned VTE [87].

CONCLUSION

So, do we need sex-specific clinical practice guidelines for the treatment of schizophrenia? Extensive evidence is available suggesting relevant differences in the course and clinical presentation of schizophrenia, in the response to antipsychotics, in the likelihood to develop side-effects, in pharmacokinetics and pharmacodynamics and the pathophysiology between sexes. These findings would argue for a clear 'yes' to that question. However, in order to provide sex-related clinical guideline recommendations, more knowledge is needed regarding, for example, feasibility of women-specific early detection, dose titration of antipsychotic medication and benefits of contraceptives to improve estrogen signaling. As few randomized controlled trials are available stratifying outcomes regarding sex and as most of the major clinical trials do not include enough women to allow for an investigation of sex-specific differences in treatment response or required dosages, the development of sex-specific guidelines is a challenging process. On the other hand, from the available data, sex-specific evidence-based recommendation can be made using moderate-to low-levels of evidence. Most importantly, professionals involved in the diagnostics and treatment of patient with schizophrenia must be aware of the here described sex-specific aspects of schizophrenia (detailed in the key points).

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