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## Towards better care for women with schizophrenia-spectrum disorders

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Women with a schizophrenia-spectrum disorder (SSD) have a better clinical profile than do men at the start of their illness but progress to the same state within the first few years of living with SSD. There are benefits to be gained across different areas in the care currently offered to women with psychosis. An important point for improvement is the early detection of female-specific signs of a first episode of psychosis, to shorten the duration of untreated psychosis, with prompt access to early intervention services. Special attention should be paid to sexual health, and to any history of childhood trauma. Antipsychotics require dosing and prescription tailored to the female physiology that consider hormonal life phases such as menopause. Switching to prolactin-sparing medications can benefit both mental and somatic health. Finally, hormone replacement therapy should be considered for postmenopausal women. By providing female-specific care, women with schizophrenia-spectrum disorders will have optimal chances to fare well.

### Introduction

It has long been known that the onset of schizophrenia differs in women compared with men. Men usually have the first episode of psychosis around the age of 20 years, but in women a first episode can present at middle or even older age.<sup>1</sup> This later onset enables many women to complete education, start a relationship, and even build a family before the first episode of psychosis. In addition, comorbid substance misuse is less frequent in women with schizophrenia and cognitive and negative symptoms tend to be milder than in men.<sup>2,3</sup> By comparison, affective symptoms are often an integral part of the clinical picture in women,<sup>4</sup> and are probably the reason why women are more frequently diagnosed with schizoaffective disorder or other non-schizophrenia diagnoses than are men.<sup>5</sup> It is therefore more appropriate to use the term schizophrenia-spectrum disorders (SSD; ie, psychosis not otherwise specified, schizophrenia, schizophreniform disorder, and schizoaffective disorder).

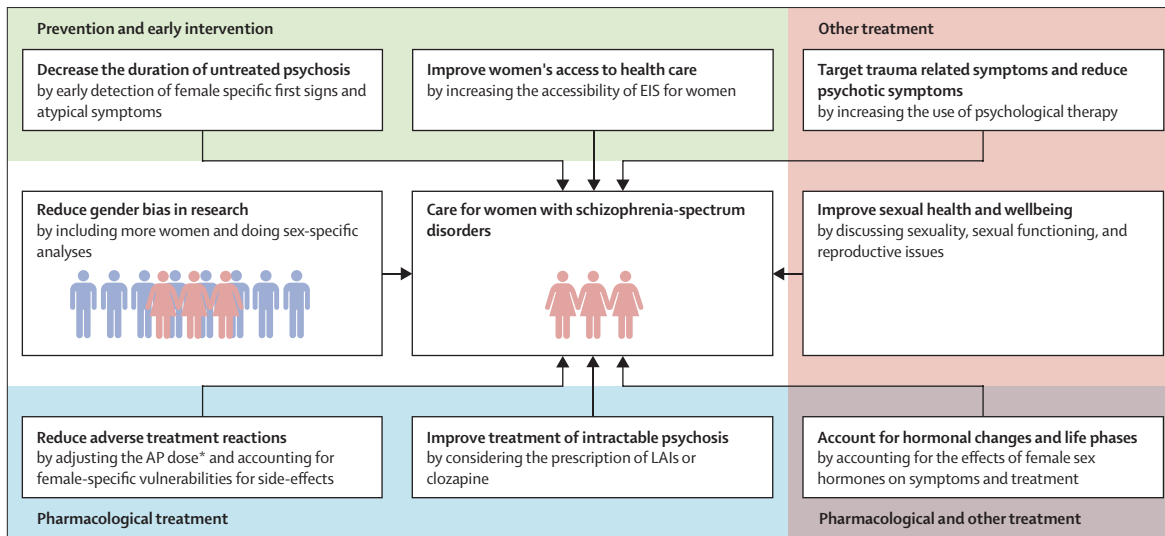
Because of this later onset, women are often thought to show a milder course of SSD over their lifetime. Unfortunately, the evidence suggests otherwise. A meta-analysis of 50 studies found largely similar recovery rates in women (12·9%) and men (12·1%).<sup>6</sup> A nationwide registry study in Finland including 7142 women and 9006 men with schizophrenia or schizoaffective disorder found that in the first 10 years after the diagnosis, 69·5% of both genders needed at least one psychiatric re-hospitalisation, with slightly more hospitalisations for women.<sup>7</sup> Ayesa-Ariola and colleagues<sup>8</sup> found similar functional outcomes for men (n=114) and women (n=94) 10 years after a first episode of psychosis. Women had more favourable premorbid and baseline characteristics than did men, which were associated with better outcomes during the first 3 years, but their outcomes were similar to those of men after an average period of 10 years.<sup>8</sup> In Ethiopia, a cohort study followed up 358 patients with SSD and found no differences in functioning or recovery between men and women with SSD after 10–13 years follow-up.<sup>9</sup> Dama and colleagues<sup>3</sup>

even found that the advantage that women have in global functioning that was present in the first year after diagnosis had already disappeared after 2 years of treatment.

These sobering findings challenge the view that SSD takes a milder course in women. Despite their later onset, women with SSD seem to lose their advantage in global functioning over the first years of illness. We propose that this might be due to suboptimal care, which follows insufficient understanding and awareness of how women with SSD are differently affected and have a different need for care compared with men.

Less effective diagnosis and treatment in women result from underrepresentation of women in trials. Historically, women have been excluded from phase I drug trials for reasons of safety (ie, risk for pregnancy). Even now, women are still underrepresented in clinical trials across all medical disciplines, including mental health,<sup>10–12</sup> which means that conclusions on drug efficacy and safety profiles are based on a population of predominantly male participants. Moreover, studies often apply an age limit of around 45 years for SSD diagnosis, resulting in the exclusion of women who often receive a diagnosis later in life.<sup>4</sup> Menopause is precisely when the course of SSD in women becomes worse, so the exclusion of women older than 45 years disproportionately affects those with poor functioning. In addition, most studies do not include sex-specific analyses. From 768 trials on ClinicalTrials.gov on the treatment of depression,<sup>13</sup> 89% reported the inclusion of both men and women, but less than 1% analysed their results by sex. Even when sex-specific analyses were intended or done, the female subgroup was mostly underpowered,<sup>10,12</sup> which hinders any reliable conclusions for women.

The underrepresentation of women is an important disadvantage, because some treatments—eg, augmentation with immune modulators—could be especially promising for women, who more often have an atopic constitution and are at higher risk of autoimmune disorders, such as auto-immune encephalitis.<sup>14,15</sup> Similarly,



**Figure:** Focus points to facilitate better care for women with schizophrenia-spectrum disorders

AP=antipsychotic medications. EIS=early intervention services. LAIs=Long-acting antipsychotics. \*Before menopause, doses can be lowered for all common antipsychotics except for lurasidone and quetiapine.

augmentation with antidepressants or mood stabilisers could be more effective in women than men with SSD, given women's more prominent affective symptoms. These biases show that care for women is less evidence-based than that for men.<sup>16</sup> Owing to these structural shortcomings, there is much to be done when it comes to care for women with SSD. We describe the main objectives that need to be pursued across various areas to achieve better care for women with SSD (figure).

### Duration of untreated psychosis

Duration of untreated psychosis is an important determinant of outcome.<sup>17</sup> In a well known case simulation experiment, psychiatrists received a written case description of a patient with symptoms of emerging psychosis that could be interpreted as schizophrenia. Case descriptions were identical, apart from the patient's pronoun being described either as he or she. A diagnosis of schizophrenia was given significantly less often to the female than to the male case.<sup>18</sup> Therefore, even with identical symptoms, there is a tendency to diagnose schizophrenia in men more readily than in women.

Given that symptoms are usually gender diverse, it is even more challenging to recognise a first psychotic episode in women. This could be a result of the representativeness heuristic, which involves judgments about the probability of a hypothesis based on how much the present case resembles the prototypical case.<sup>19</sup> Although common symptoms of SSD reported by both women and men are similar to standard norms (ie, delusions, disorganised behaviour, and hallucinations), women are more likely than men to report atypical first signs, such as trouble with focus and attention,<sup>20</sup> and prominent affective symptoms,<sup>7</sup> while remaining sociable and rarely exhibiting overt apathy or

other gross negative symptoms.<sup>21</sup> Emerging psychosis in women might initially be classified under borderline personality disorder, anxiety, post-traumatic stress disorder (PTSD), or depression that is sometimes specified as psychotic.<sup>22</sup>

In addition, women are often described as being more in tune with their feelings and are perceived as being more in control of their symptoms.<sup>23</sup> Women more often prioritise the needs of family members at the expense of their own health, even when they are in need of specialised help.<sup>24</sup> Women's access to health services can furthermore be limited by stigma, contempt, and fear of retaliation.<sup>24</sup>

All these factors culminate in longer duration of untreated psychosis in women than in men. The Danish national schizophrenia project reported a duration of untreated psychosis of 6.6 years for women, compared with 2.5 years for men.<sup>25</sup> Duration of untreated psychosis correlated with severity of depressive symptoms in women, but not in men,<sup>26</sup> supporting the hypothesis that women are more likely to be misdiagnosed as having depression instead of psychosis because of their prominent affective symptoms, which affirms the insufficient awareness of how SSD differently affects women. Although women do receive a diagnosis at an early stage, this is often not an SSD diagnosis, which delays appropriate treatment. This diagnostic delay was shown in a recent Finnish cohort study,<sup>7</sup> in which a gap of 4 years was observed between the last admission to hospital for a non-SSD psychiatric disorder and the first admission for SSD in women, but not in men.

### Access to early intervention services

A meta-analysis including 2176 patients showed that those who received specialised care in early intervention

services during their first episode of psychosis scored significantly better on all 13 outcomes analysed than did those treated in a regular setting.<sup>27</sup> Early intervention teams typically focus on adolescent boys and young men. The maximum age of admittance, which is usually 26 years, prevents many women from being included, because more than 50% of them will be too old to be offered care in these services at the time of their diagnosis.<sup>7</sup> Lappin and colleagues<sup>28</sup> showed that at diagnosis of SSD, 58% of men and 71% of women were too old to meet Australian early intervention service entry criteria, and 21% of men and 34% of women were too old to match the British early intervention services criteria, thus showing a substantial disadvantage for women in both countries. Sometimes even women who have a first episode of psychosis before the age of 26 years are not invited for specialist early intervention services, because they do not match the typical profile of other service users,<sup>29</sup> for example, by being better educated, having a partner, or not having comorbid illicit drug use.

### Need and preference for psychological therapy

Traumatic events during childhood are an important risk factor for most psychiatric disorders, including SSD. In women with SSD, childhood sexual and emotional abuse are more common than in men with such diagnoses.<sup>30,31</sup> Severe childhood physical and sexual abuse are associated with the onset of psychosis in women, but not in men.<sup>32</sup> Furthermore, a history of childhood trauma significantly affects the age of onset specifically in women,<sup>31,33</sup> and patients with childhood trauma achieve lower rates of positive and negative symptom remission at 12–14 months after diagnosis, than do those without such trauma.<sup>30</sup> Associations between childhood trauma and psychotic and depressive symptoms and poorer functionality are repeatedly found specifically in women with SSD,<sup>34,35</sup> indicating that these women could benefit from early identification and treatment of childhood trauma. In fact, trauma-focused therapy can have long-term positive effects on symptoms of PTSD, depression, and psychosis in people with severe psychotic disorders.<sup>36</sup> Of note, there is a large gender bias in treatment preference, with women opting for psychological therapy substantially more often than men, which makes them good candidates for this type of intervention.<sup>37</sup> However, implementation of psychological treatment in psychosis remains low in routine clinical services as only a third of all patients with schizophrenia receive at least one session of psychotherapy.<sup>38</sup>

### Sexual health and wellbeing

Sexual health and wellbeing is a crucial, yet understudied area in women with SSD.<sup>39</sup> Although individuals with SSD have similar sexual desires and needs as individuals without psychosis,<sup>40</sup> they experience low sexual satisfaction, impaired libido, and high rates of sexual dysfunction.<sup>41</sup> The prevalence of sexual dysfunction in

SSD is similar in men and women (ranging from 25–85% in women and 33–85% in men), with a loss of libido slightly more common in women (31–100% in women vs 26–94% in men).<sup>41</sup> However, women with SSD are at high risk for adverse sexual health outcomes, including more unintended pregnancies, more induced abortions, and lower use of contraception than women without SSD.<sup>42</sup> Furthermore, women with SSD more often become victims of sexual violence than do unaffected women.<sup>43</sup> These crucial vulnerabilities are exacerbated by several factors related to different levels of care. Sexual dysfunction is a difficult topic to discuss for patients of both sexes,<sup>42</sup> yet women in particular might not feel comfortable to discuss their sexual problems or need for contraception.<sup>44</sup>

The ability to engage in intimate relationships is another important pillar of sexual health.<sup>42,45</sup> Although women with SSD might more often be partnered or married than men with these disorders, they often have problems in maintaining a healthy and stable relationship, leading to deterioration after the onset of SSD.<sup>45</sup> Childhood trauma is also associated with a higher risk for experiencing adverse sexual health outcomes, including low sexual satisfaction and a higher risk of intimate partner violence.<sup>42</sup>

Presence or absence of a desire for pregnancy is an important topic to address with women as part of psychosis care. Antenatally and postnatally, women with SSD face problems with stigma, fears about loss of child custody, little focus on the mother, and an unmet need for information and education.<sup>46</sup> A recent Finnish study showed that the risk for psychosocial and somatic complications during and after pregnancy is substantially higher in women with SSD than in women without a psychotic disorder, with an odds ratio's between 1.3 and 2.0.<sup>47</sup> Mothers with SSD are often single parents, and postpartum home visits and parenting support are frequently required. In women who want to avoid pregnancy, it is essential to discuss effective use of contraceptives as part of a care plan, because unplanned rapid repeat pregnancies are significantly more prevalent in women with psychotic disorders.<sup>48</sup>

### Sex-specific antipsychotic treatment

The female body differs from the male body in many aspects that affect pharmacodynamics and pharmacokinetics.<sup>49</sup> These differences result in higher serum concentrations for most antipsychotic drugs in women, especially before menopause.<sup>50,51</sup> In addition, dopamine receptor occupancy is considerably higher in women than in men, even when antipsychotic drug serum concentrations are similar.<sup>52</sup> Yet, national guidelines and summaries of product characteristics for antipsychotic prescription generally do not have female-specific dosing recommendations.<sup>53</sup> As a consequence, many women with SSD are overmedicated,<sup>50,51</sup> with a higher

prevalence of side-effects.<sup>54</sup> Optimal antipsychotic management in women with SSD needs to consider their life stage and social and hormonal circumstances. In previous work, we made a series of recommendations about adapting pharmacotherapy to these different life stages.<sup>49</sup> Of note, in women with SSD who are also being treated for depression, sex differences in the pharmacokinetics of antidepressants should also be considered.<sup>55</sup>

### Improving treatment of intractable psychosis

For patients who do not reach remission after two different antipsychotic drugs, clozapine is the drug of choice, unless specific contraindications (eg, neutropenia) are present. A recent study among 2266 patients with treatment-resistant SSD in south London (UK), showed that women are less often offered clozapine than are men (odds ratio 0.66; 95% CI 0.44–0.97), independently from gender differences in clinical factors such as aggression, neutropenia, or somatic comorbidity.<sup>56</sup> This finding shows that a delay in prescribing clozapine could prevent women from reaching remission.<sup>56</sup> However, there are risks and consequences associated with the decision to prescribe clozapine, because clozapine largely increases the risk for metabolic and cardiovascular side-effects and type 2 diabetes,<sup>57</sup> to which women are already more vulnerable, especially in the postmenopausal phase of life.<sup>49</sup> Moreover, women often find the risk of weight increase more difficult to accept than men do.<sup>58</sup> We therefore advocate a thorough evaluation of the potential risks and benefits of clozapine use, that should be tailored to the individual patient.

Another important difference in treatment relates to the use of long-acting antipsychotics (LAI). Although LAI are not associated with better response than oral antipsychotics, they do improve treatment adherence and reduce relapse risk.<sup>59</sup> The use of LAI after the first episode of psychosis can reduce re-hospitalisation by 20–60%.<sup>60</sup> Yet, several studies have shown that women are less often prescribed LAI,<sup>7,61</sup> even though they are not more adherent to oral antipsychotics than men.<sup>62,63</sup> It should be noted that women are at a greater risk of being overmedicated with LAIs because of the increased accumulation of these drugs in adipose tissue, and therefore LAIs should be prescribed at female-specific doses and intervals.<sup>49</sup> The under-prescription of both clozapine and LAI in women with SSD negatively affects their outcomes, and awareness of these issues in clinical services is an important step to improving outcomes for these women.<sup>56,62</sup>

### Hormonal changes

Oestrogens largely account for the later age of onset and the higher efficacy and lower tolerability of antipsychotics in women than in men with SSD.<sup>64</sup> For optimal care, it is therefore important to consider the different hormonal

phases that a woman goes through during her life, which might cause hormonal fluctuations important for illness management (eg, pregnancy, giving birth, lactation, menopause).<sup>65</sup> Oestrogens regulate dopamine neurotransmission,<sup>66</sup> and augment the efficacy of antipsychotics.<sup>67</sup> Endogenous and exogenous (contraceptives) oestrogens also strongly affect concentrations of drugs, including antipsychotics, in serum.<sup>49,68</sup> Therefore, dose adjustments are required when such hormonal changes occur.<sup>64,69</sup> Menopause is a particularly important period during which permanent hormonal changes take place and adjustments of antipsychotic doses are needed, something that is not yet common practice.<sup>4</sup>

A meta-analysis has shown the beneficial effects of hormonal replacement therapy with raloxifene (a selective oestrogen receptor modulator) on both cognitive dysfunction and symptom severity in postmenopausal women with SSD.<sup>70</sup> The adjuvant raloxifene can also ameliorate the efficacy of antipsychotics, thereby improving treatment efficacy.<sup>71</sup> As a result, women on this drug might need a lower dose of antipsychotics and thus be protected against antipsychotic side-effects.

### Iatrogenic prolactin increases

Typical antipsychotics and several atypical antipsychotics (ie, risperidone, amisulpride, and paliperidone) are notorious for inducing high prolactin serum concentrations,<sup>49</sup> which can lead to hypo-oestrogenic states in women and worsen the symptoms of SSD.<sup>64</sup> Hyperprolactinaemia and secondary hypogonadism cause side-effects such as hirsutism, painful breast tension, sexual dysfunction, polycystic ovary syndrome, and osteoporosis, and increase the risk of breast cancer.<sup>72–74</sup> This increased risk is especially worrisome because genetic similarities have been shown between breast cancer and schizophrenia phenotypes,<sup>75</sup> and women with SSD are less inclined to visit breast cancer screening facilities and less often follow treatment guidelines, which results in increased mortality (odds ratio 1.55; 95% CI 1.32–1.82).<sup>76</sup> Taken together, the mental and somatic health of women with SSD can be improved substantially when hormonal dysregulation can be prevented.

### Towards female-specific care

The paucity of well-powered sex-specific analyses in drug trials prevents full understanding of how we can best treat women with SSD. Delayed diagnosis, restricted access to early intervention services, overmedication with antipsychotics, lower prescription rates of clozapine and LAI, iatrogenic hyperprolactinaemia, induction of secondary hypo-oestrogenic state, and failure to adjust medication dose after menopause and consider hormone replacement therapy are amongst the many factors that prevent women from having a more benign clinical course.

Most of these factors can be improved rather easily. To do so, the adage that women with SSD do better should

be changed to one that says that women with SSD can do better, provided that care is optimal and that their sex and hormonal status are taken into account. This change in approach requires better knowledge of therapeutic strategies for women with SSD of all ages, for both psychotherapy and pharmacotherapy. Future studies should be well powered to enable sex and gender analyses a priori, for example by including enough female participants to enable a sex-specific subanalysis. Specific augmentation studies (eg, with immune modulation, antidepressants, or trauma-focused therapy) in women with SSD are dearly needed. Optimal care for women with SSD starts with early and accurate detection of psychotic symptoms in women of all ages, especially those with affective presentation in whom diagnoses of SSD are easily missed. Early intervention programmes should be made available to older individuals and to women independently of their education status or illicit drug use comorbidities. As an alternative, centres with large catchment areas could consider creating early intervention groups specifically for women. Women with a history of childhood trauma might benefit from psychotherapy, which can be trauma focused or not. Sexual health and wellbeing is an important topic to be discussed with both genders, but effective contraception and perinatal care are of particular importance to female wellbeing. Antipsychotics clearly require dosing and prescription tailored to female-specific life phases, which should be mentioned in the summary of product characteristics and national guidelines.

Antipsychotics that raise prolactin serum concentrations deprive women of their natural oestrogen production and are therefore not the drugs of first choice for women. Menopause is accompanied by a similar large decline in oestrogen concentrations. Hormone replacement therapy after menopause can restore the protective effects of oestrogens and improve symptoms and cognition for older women. In conclusion, women do not have an easier course of schizophrenia, and if we can provide female-specific care, women with SSD will have optimal chances to fare well.

#### Contributors

BAB and IES wrote the first draft of the manuscript. All authors edited and approved the final version.

#### Declaration of interests

PD reports speaker's fees from Lundbeck, outside the submitted work. BAB, JNdB, and IES declare no competing interests.

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