Response to reviewers

I am extremely grateful to the three reviewers who have helped to improve this manuscript. The changes in the revised manuscript are in bold.

Reviewer #1: This review presents evidence for recognizing male female differences in schizophrenia. This issue is timely and important as effective prevention of schizophrenia may, in the future, be possible in a sex-specific manner. The review indicates that it is more difficult to accurately diagnose schizophrenia in women than it is to diagnose men. Women often do not exhibit the characteristic symptoms, drug doses usually need to be lower than doses recommended for men. Also, women are more vulnerable than men to adverse drug reactions. Moreover, women with schizophrenia are more often depressed than the men are and they suffer from a specific form of stigma (e.g., women with schizophrenia are widely considered incapable of being good mothers). The review ends with important recommendations for future studies on females with schizophrenia. The review is clearly written and based on sufficient references. I only noticed on three occasions the use of abbreviations which are not explained. They are as followed. Page 8, abbreviation IM needs to be spelled out and explained. Page 9, abbreviation QT needs to be spelled out Page 14, abbreviation CYP needs to be spelled out.

These abbreviations have now been omitted or explained.

Reviewer #2: The author has written a review article that addresses key issues in the lives of women who have schizophrenia. This is an important topic that has not been adequately studied. Highlighting the concerns of women with schizophrenia is an important task. Clinicians need to be properly informed on this

topic. Unfortunately, this manuscript falls short of its intended purpose.

While there are multiple specific issues to be addressed to improve the manuscript, the major limitation of the manuscript is that repeatedly recommendations are made based upon a conflation of association with causation.

This important point is now emphasized several times

For example, the author suggests that planning conception for women with schizophrenia such that births do not occur in the late winter or early spring would result in a lower risk of schizophrenia in their progeny. There is a slight increase in the prevalence of schizophrenia in those born in those months, but the author does not provide any data demonstrating that changing the time of the year for conception will decrease the incidence of schizophrenia.

This now emphasized

Even the author offers some literature to suggest that this issue may be related to Vitamin D levels. If so, regulating Vitamin D availability is more important than timing during the year.

I agree.

Another issue that is conflated is the prevention of relapse for someone who has schizophrenia is the same as prevention of onset of schizophrenia. Specifically, delaying the onset psychotic symptoms by increasing the dosage of an antipsychotic during a period of low estrogen does not mean that schizophrenia onset can be prevented by manipulating the onset of menarche or that "effective prevention of schizophrenia may, in the future, be possible in a sex-specific manner".

The sentence has been modified.

On several occasions in the manuscript, statements are made without supporting data being presented and they are also not adequately referenced.

This manuscript covers many areas, very many of which have been addressed in the literature from several different angles. It has been impossible to cite all the relevant literature. Many excellent articles have unfortunately been left uncited. I have added 8 more references.

For example, the author states "it is more difficult to accurately diagnose schizophrenia in women according to criteria than it is to diagnose men". Where is the supporting data for that statement?

This is, as now stated, from clinical experience.

Some discussion of this point followed in the manuscript, but when an assertion was made that certain conditions were more prevalent in women than men, the magnitude of the differences was not provided.

When the magnitude of difference is not stated, it is because it is impossible to quantify accurately, being dependent on very many often unknown variables. The main issue in many cases is not the size of the difference but the importance that the two sexes place on it.

Comments on specific statements follow:

1. On page 8 of the manuscript, a long list of issues that differ between genders is given. However, no additional information is given about any of them.

Not sure which list is being referred to. When there is no additional information stated, it is because the cited references provide the information better than I can.

2. On page 9, in the discussion of side effects, there is mention of the increased risk of side effects in women. What is the magnitude of the difference?

Because a side effect almost always is the end result of many factors, the magnitude of the difference changes from study to study.

Torsade de Pointes is specifically mentioned as being much more likely in women. However, is there any evidence that this has led to increased cardiovascular deaths in women?

There is not. This point has been added.

If not, could women be more susceptible but less vulnerable? That possibility is not considered.

This is certainly possible.

3. On page 9, the risk of embolic events is considered to be greater in women. While that potential may be present, what is the difference in prevalence of thromboembolic events in women with schizophrenia?

New references have been added pertaining to this issue.

4. On page 10, Table 1, side effects are listed, but the prevalence in men versus women is not given.

Prevalences are not given because many factors, besides being on medication, contribute to these outcomes:

genetics, adherence to prescribed drugs, type and dose of drug, menopausal status, smoking status, diet

The point I am making is that antipsychotic drugs negatively affect appearance in many ways and that appearance is more important to women than to men.

5. On page 11, it is stated that older women may be more susceptible than older men to tardive dyskinesia. What is the magnitude of the difference in susceptibility?

This is now discussed in some detail.

6. On page 11, there is a paragraph given to the discussion of the social, vocational, and avocational opportunities of women with schizophrenia. It is asserted that the housewife role is not realistic for most women with schizophrenia. However, no information is provided on the percentage of women with schizophrenia in various vocations or social relationships.

Vocational information varies with ups and downs of the labor market, regions of the world, cultural traditions and so on. I have had to rely on information from my own clinic.

7. On page 12, it is stated that those who suffer from schizophrenia are more often victims than perpetrators of violence. No data is given to support this assertion. What is the magnitude of the difference in being victim versus being a perpetrator?

There is now a fuller discussion of this issue.

8. On page 12, in the discussion of women with schizophrenia not being considered being capable of being good mothers, it would be helpful to provide information about ways of supporting women with schizophrenia who are mothers to be most effective.

This is addressed a little later in the paper.

9. On page 12, what is the incidence of women with schizophrenia attempting or being successful at suicide?

This issue is now more fully explored.

10. On page 13, in the Physical Health section, it is stated that "there is the probability of shared susceptibility genes between schizophrenia

and physical disease such as auto-immune diseases". This is in a paragraph on premature mortality associated with schizophrenia and suggests that the author is implying a role for auto-immune diseases and mortality with schizophrenia. If that has been established, then a reference on presentation of data should be offered.

This has not been established. Autoimmune diseases serves only as an example of shared genetics and can lead to death, though not usually directly.

11. On page 15, in Table 2, existential concerns are listed. No information is provided that these issues are different in women with schizophrenia in comparison to men with schizophrenia.

This is now addressed.

12. On page 15, in the Conclusions, a strong point is made about the differences in the X chromosome contributions to the genetic make-up of women. However, there is almost no mention of this in the remainder of the manuscript. I would have expected that this point would be made as a summary statement after considerable discussion in the rest of the manuscript.

This section is now called only "Future Directions". I have omitted the word 'conclusions'. Thank you for pointing this out.

Reviewer #3: This review focuses on clinical issues critical to women with schizophrenia. It is divided into eight main sections as follows: "effective prevention strategies for women", "early and accurate diagnosis", "guidance in navigating the complexities of the mental health system", "effective treatment and freedom from adverse effects", "access to social, vocational and avocational opportunities", "freedom from stigma", "self-harm and suicide", "maintenance of

physical, reproductive, and emotional health”. The author can look back on four decades of intensive research. In this review, she references her own work plus recent key papers from the PubMed database. The subject of the present work, i.e. the sex- and gender-related differences in schizophrenia, is of major relevance for both, clinicians and scientists. This comprehensive review is very well written and all descriptions and explanations bear witness of its high academic quality. The statements of the author are supported adequately by the cited literature.

Thank you.