Oestrogen — a new treatment approach for schizophrenia?

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ABSTRACT

- The oestrogen protection hypothesis proposes that oestrogen has a protective effect against onset of schizophrenia. In support of this:
  - Epidemiological studies have shown that young women are less likely to develop schizophrenia than men of the same age, and women are more likely to develop late-onset schizophrenia after menopause.
  - Clinical studies have shown higher psychotic symptoms in perimenopausal women, and women at the low oestrogen phase of the menstrual cycle.
  - Animal studies provide further evidence in support of the oestrogen protection hypothesis.
  - Three randomised double-blind placebo-controlled trials and an open-label study showed that adding oestradiol to women's usual antipsychotic medications was associated with significant abatement of schizophrenia symptoms.
  - A small study of men with schizophrenia who received oral oestradiol valerate also showed a significant abatement in psychotic symptoms.
- Although oestrogen appears to be a useful treatment for schizophrenia, further research is required to determine the correct dose and duration of use of oestradiol.
- New types of oestrogen compounds may provide a safer, non-feminising approach for the treatment of schizophrenia.

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One of the most compelling hypotheses to emerge in the understanding of the possible causes and potential new treatments for schizophrenia is the oestrogen protection hypothesis.[1,2] The hypothesis is described in two parts:

- In women, oestrogen "protects" women from developing severe schizophrenia at an early age.
- Fading oestrogen secretion at menopause in vulnerable women leads to relapse of schizophrenia symptoms or new, late-onset schizophrenia.

There are three main areas of support for the oestrogen protection hypothesis — epidemiological findings, clinical evidence and animal studies exploring the effects of oestrogens on key neurotransmitters that are implicated in producing psychotic symptoms. Randomised controlled trials are providing evidence for the use of oestradiol to ameliorate the symptoms of schizophrenia.

Epidemiological evidence

Epidemiological sex differences in schizophrenia have been reported for over a century. In 1910, Kraepelin described a later age of first admission for women with schizophrenia compared with men.[3] A review of over 50 studies showed the same sex difference in the age of admission and onset of the first episode of schizophrenia.[4] In a population-based sample of 232 first-episode schizophrenia presentations, there was a steep early increase in the age of schizophrenia onset in men between the ages of 15 and 25 years.[5] In women, the rates of onset were less steep and had a broader age of onset between the ages of 15 and 30 years plus a smaller, second peak between the ages of 45 to 50 years.[5] This pattern of sex differences has been replicated worldwide in population studies, such as the Danish Case Register.[6]

Clinical support

A clinical study has shown that perimenopausal women with schizophrenia required increased antipsychotic drug doses to maintain remission.[2] This study strongly suggested that due to the declining oestrogen levels during menopause and beyond, the "protective" or "antipsychotic" effect of oestrogen is diminished, leading to the patient requiring a greater dose of antipsychotic medication to treat symptoms of schizophrenia. A small study of 32 women found that psychotic symptoms were worse during the low-oestrogen phase of their menstrual cycles.[7] This suggests that higher circulating oestradiol levels provide an antipsychotic effect for women with schizophrenia.[8]

Animal studies

Many animal studies have demonstrated several neuroprotective effects of oestrogens. Dopamine and serotonin are key neurotransmitter systems involved in the formation of the main symptoms of schizophrenia, and oestrogen has a psychoprotective action that appears to be mediated by central dopaminergic and serotonergic mechanisms.[9] The effects of oestrogen are broadly classified into the slower, classical, intracellular "genomic" and the more rapid, direct, non-genomic actions.[10] Both the genomic and direct effects of oestrogen on the central nervous system are thought to contribute to oestrogen's antipsychotic properties.

Clinical trials of oestrogen in schizophrenia

Following these epidemiological, clinical, and animal study results, we conducted a series of clinical trials of oestradiol in women of child-bearing age with schizophrenia. Beginning with an open-label pilot study,[11] we found that women who received 2 mg oral oestradiol valerate made a significantly more rapid recovery from acute psychotic symptoms and reported improvement in their general health status compared with a matched control group who did not receive oestradiol ($P < 0.05$).

Subsequent to this, we conducted a dose-finding study for the optimal use of oestradiol in women with schizophrenia.[12] This was a three-arm, double-blind, placebo-controlled 28-day study, in which 12 women received 50 μg transdermal oestradiol plus standardised antipsychotic drug, 12 women received 100 μg transdermal oestradiol plus standardised antipsychotic drug, and 12 women received placebo plus standardised antipsychotic drug. All of the women had a diagnosis of schizophrenia according to the *Diagnostic and statistical manual of mental disorders*, fourth revision (DSM-IV). The group receiving adjunctive 100 μg oestradiol showed greatest improvement across the study compared with the other two groups using the well validated Positive And Negative Syndrome Scale (PANSS) rating system[13] ($P < 0.01$).

To extend our findings, we conducted a proof-of-concept study of 102 women with DSM-IV schizophrenia.[14] In this double-blind randomised controlled 28-day study, women received either an active 100 μg oestradiol skin patch treatment ($n = 56$) or an identical

placebo patch ($n = 46$). All patients received antipsychotic drug treatment according to a standardised protocol. Psychopathology was assessed by the PANSS. Serum levels of oestrogen, progesterone, prolactin, luteinising hormone, and follicle stimulating hormone were measured. Several cognitive tests was also administered. We found that patients who received the 100 μg oestradiol adjunct made a significantly better recovery in their total, positive, negative and general symptoms of schizophrenia than the patients who received standard antipsychotic medication only ($P < 0.01$). Women who received the oestradiol patch also showed significant improvement in cognition ($P < 0.01$).

We are currently undertaking a three-site replication and dose-finding study of 100 μg transdermal oestradiol adjunct compared with 200 μg transdermal oestradiol adjunct versus placebo adjunct in 180 women of child-bearing age with schizophrenia. Called ADEPT (A Definitive Estrogen Patch Trial), it is an 8-week trial with tighter control of the concurrent antipsychotic medication and comprehensive cognitive testing.

Results from our studies provide strong evidence for the oestrogen protection hypothesis. We found that the addition of transdermally delivered oestradiol was associated with significant abatement of psychotic symptoms in women with DSM-IV schizophrenia when compared with standardised antipsychotic drug treatment alone ($P < 0.01$). The impact of administering 100 μg of oestradiol transdermally, as indicated by its effect on the pituitary gland (measured by luteinising hormone assay), suggests that this dose and type of unconjugated oestrogen directly affects the hypothalamic–pituitary–gonadal axis, and appears to have an antipsychotic effect on the dopamine and serotonin systems.

A commonly asked question is whether the addition of oestrogen to antipsychotic treatment would be useful for men with schizophrenia. As the oestrogen protection hypothesis states that oestrogen is a potent neuroprotective agent, oestrogen should also have a protective effect on men with schizophrenia.

We tested the use of adjunctive oestradiol in a small sample of 11 men with schizophrenia.[15] We gave 2 mg oral oestradiol valerate as an adjunct to six men who were taking antipsychotic drugs. Five men received oral placebo plus their standard antipsychotic medication for 7 days. Our small study was only conducted for 7 days to avoid feminisation and other side effects in the men. The groups were matched for age, illness severity and duration. Oral, rather than transdermal, oestradiol was used to ensure treatment adherence in men with acute psychosis. Psychopathology was assessed using the standardised rating scales, PANSS and the Brief Psychiatric Rating Scale.[16] By Day 5, the oestradiol group showed significant abatement of psychotic symptoms compared with the placebo group and, by Day 7, the oestradiol group made further improvements. This study, although small in sample size and short in duration, raises the possibility that non-feminising oestrogen may provide useful treatment possibilities for men with schizophrenia.

Conclusion

The use of oestrogen as a potential treatment for schizophrenia opens up exciting new possibilities for both the preventive and acute treatment of schizophrenia in men and women. There is still considerable research to be done to determine the correct dose and duration of use of oestradiol, its safe use in women and men with schizophrenia with respect to the known side effects, and whether it may be used eventually as a standalone medication rather than as an adjunct.

We are currently conducting clinical trials of new types of oestrogen compounds — the selective oestrogen receptor modulators, or "brain oestrogens". This rapidly developing area of hormone treatments may be a potentially safer, non-feminising new approach for the treatment of schizophrenia and other mental illnesses in women and men. Studying the mechanisms by which oestrogen potentially ameliorates psychotic symptoms may also further our understanding of the aetiology of schizophrenia. We are, of course, mindful of the potential adverse effects of oestrogen treatments as highlighted by the Women's Health Initiative Study.[17] It is important to monitor patients' general health while using short-term oestradiol adjuncts.

We need new treatments, such as oestrogen, to help people with schizophrenia achieve symptom remission and significantly improve their quality of life.

Competing interests

None identified.

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