Hormone Replacement Therapy in Adult Women As a Treatment Adjunct for Psychosis: A Literature Review

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Introduction

- The prevalence of psychosis is estimated to be between 1.5 and 3% of the population worldwide. Schizophrenia (~1%) is associated with shorter life expectancy, increased suicide risk, unemployment, costly psychiatric care, and is one of the top 10 causes of long-term disability. The mainstay therapeutic options are antipsychotic medications, which carry a number of potential adverse effects and tend to have lower efficacy for negative and cognitive symptoms.[1]
- Psychotic disorders exhibit variations in the age of onset, incidence, and presentation between men and women, with a more severe presentation typically appearing in men.[1,2] Women tend to have fewer negative symptoms, a more favorable response to medications, fewer hospitalizations, less brain abnormalities, and less overall disability.[1,3] These trends, along with estrogen's effects on mood, cognition, and behaviors, have led to the exploration of estrogen as a potential adjunct therapy for psychotic disorders.[1,2]

The "Estrogen Hypothesis"

- Studies have shown the estrogen offers neuroprotective effects against insults such as inflammation, ischemia, excitotoxicity, oxidative stress, neuronal cell death by way of reparative processes, neurogenesis, and synaptic plasticity.[1,3] Clinical and epidemiological studies have shown that estradiol, a form of estrogen, protects against the development and severity of psychosis, and that lower estrogen levels in women are associated with "greater psychosis spectrum behaviors".[1,3,4] This protection is posited to occur through estrogen's stimulatory activity on striatal and cortical dopamine pathways, genomic and non-genomic effects, epigenetic mechanisms, the aforementioned neural plasticity, and its modulation of serotonergic, glutamatergic, and cholinergic pathways.[1,4,5] Consequently, psychosis in women often follows a bimodal distribution, with peak age-at-onset occurring in early adulthood (~5 years later than in men) and again in midlife (after age 40). These peaks are associated with greater symptom severity, the latter of which coincides with the changes in ovarian hormones during the "perimenopausal transition" and subsequent dysregulations in mesolimbic dopamine systems.[2,3,4,6,7] Early puberty has been associated with later onset of psychotic disorders (with later menarche being associated with earlier onset), and pregnancy, characterized by elevated plasma estrogen levels, is associated with reduced relapse rates of psychotic episodes.[2,5,6,7] In many women with schizophrenia, hyperprolactinemia, gonadal dysfunction, or estrogen deficiency are frequently observed, even those naive to antipsychotics.[6]

The "Estrogen Hypothesis", cont'd

- Additionally, episodes of psychosis in women occur more often when estrogen levels are low (aka "estrogen withdrawal"), such as during the first stage of menses, after abrupt discontinuation of oral contraception or estrogen replacement, post-abortion, postpartum, and after menopause.[2,3,5,6] Moreover, estrogen enhances dopamine receptor sensitivity, so when estrogen levels are lower, antipsychotics may be less effective, requiring a higher dose.[2,3,7,8]

Hormone Replacement Therapy with Estrogen

- The current literature supports the idea that estrogen treatment alone or in combination with antipsychotics can not only help reduce positive and negative symptoms in both men and women, but it has also been shown to decrease the required dose of antipsychotic medication.[1,3,7,9] Kulkarni et al demonstrated reduced positive symptoms and total PANSS scores in 183 premenopausal women with 8 weeks of 17β-estradiol (100 or 200 ug) and haloperidol compared to haloperidol alone, with the largest effects in the groups receiving 200 ug.[9] This was, however, not replicated by Bergemann et al who treated 46 hypoestrogenic women with schizophrenia with combo 17β-estradiol-progestin and an antipsychotic medication, finding no significant difference in relapse events, antipsychotic doses, or tolerance levels.[10] Lindamer et al looked at postmenopausal women with schizophrenia both with and without hormone replacement therapy (HRT) and found that those taking HRT had fewer negative (but not positive) symptoms.[11] Other studies with conjugated estrogen have shown mixed but promising results involving improved PANSS scores in positive and negative symptoms.[1]

Selective Estrogen Receptor Modulators

- Raloxifene, a selective estrogen receptor modulator (SERM) has been investigated as an adjunct with antipsychotics in a number of clinical trials. The results thereof suggest that SERMs may offer safer treatment by way of lower effective antipsychotic doses and decreased long-term side-effect burden (i.e. lack of feminization in male patients), and lower risk of breast cancers. SERMs specifically have been found to decrease cognitive deficits in addition to both positive and negative symptoms in schizophrenia, even when psychotic symptoms are refractory to other treatments. Additionally, studies have revealed that Raloxifene can improve occupational and social functioning as well as learning abilities in both men and women.[1,3,8,12] A randomized controlled trial by Huerta-Ramos et al, however, showed no improved cognitive function in 68 postmenopausal women on Raloxifene and an antipsychotic.[13]

Discussion

- Increased incidence of breast, ovarian, and endometrial cancers, as well as strokes, myocardial infarctions, and thromboembolisms (DVTs and PE) are associated with long term unopposed estrogen use. The USPSTF recommends against estrogen and combined estrogen-progestin (D grade) for the prevention of chronic conditions in postmenopausal women.[14,15,16] These risks are especially concerning when one factors in the already increased metabolic and cardiovascular risks associated with psychotic disorders and antipsychotic use. SERMs, therefore, may be a more favorable option due to their pro-estrogen effect on the brain and bones, and anti-estrogen effect in the uterus and breasts.[8,12]
- Further research is needed to help us better determine estrogen's efficacy and safety as an adjunct treatment for psychosis, and should focus on the following areas: a) Estrogen's impact on cognitive symptoms of schizophrenia, as studies have mixed results. b) Estrogen's interactions with monoamine pathways outside of dopamine may yield additional treatment modalities. c) The role of progesterone and progestin containing HRT options.[16] d) The effects of prolactin on psychosis: Hyperprolactinemia is observed in patients with psychosis (on or off antipsychotics), however, some studies postulate that prolactin stimulates dopamine secretion, while others have shown an inverse relationship with treatment response.[8] e) A closer look at estrogen use in men with schizophrenia, as studies suggest men with schizophrenia have decreased estrogen levels.[8] f) Estrogen use in other disorders with psychotic features such as major depression and bipolar disorder. g) The positive effects of estrogen on functional cerebral asymmetries (FCAs), which are known to be affected in psychotic disorders, which have shown promise.[17]

Conclusions

- The neuroprotective effects of estrogen are now widely accepted, with such effects explaining later onset of psychosis in women with a bimodal distribution, lower burden of illness during periods of higher estrogen levels, and attenuated symptom severity.[1-7] The current literature surrounding the use of estrogen HRT as an adjunct for treatment of psychotic disorders is promising, albeit with mixed outcomes.[1,3,9-11] Additionally, the risks associated with long term estrogen use (cancer, MI, and blood clots) must be given due consideration, with SERMs posited as being a safer alternative.[12,13] Although more research is required, it is not unreasonable to consider how future treatment recommendations may involve antipsychotic dose adjustments that coincide with the monthly estrogen fluctuations in in premenopausal women, higher doses in postmenopausal women, and tailored use of estrogenic OCPs in women with psychotic disorders.

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