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Commentary

Estrogen – A key neurosteroid in the understanding and treatment of mental illness in women☆

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ABSTRACT

The commentary is an invited brief about my contribution to Psychiatry Research. My work has built on the "estrogen hypothesis", as stated by Hafner, Riecher-Rossler and Seeman in the 1990's. This hypothesis was that estrogen provides 'protection' against the early onset of severe schizophrenia in women, and with decreasing brain estrogens at the menopause, mental ill health worsens in women. In this paper, results from clinical trials conducted over many decades, that involved administering exogenous estrogen in different types and doses, show an overall positive impact - with improved symptoms of schizophrenia in women. This led to the conduct of further successful clinical trials of gonadal hormone treatment in women with PMDD and menopausal depression, plus understanding more about depression caused by hormone contraceptives. The role of estrogens in stress vulnerability is reflected in the sex-dependent reaction to childhood trauma, which has led to our new work in the neurobiological effects of early life trauma in women.

As a junior doctor training in Psychiatry, the most significant experience I had was caring for patients in the "Chronic Women's Ward". In this setting, I was greatly influenced by the women's stories and the dreadful conditions of the old ward. One of my patients said, "It's my hormones Doc – that's what caused it all." Her words stayed with me as I reviewed histories that included women with psychosis long after childbirth, perimenopausal psychosis and stories of early life trauma.

This experience made me determined to explore the connection between gonadal hormone fluctuations and psychosis. I also wanted to improve the ward conditions for women who needed inpatient psychiatric care and to understand the role of trauma in the development of mental illness in women. I began to advocate for women's mental health to be a separate area of research and clinical service provision. My career in women's mental health, began with research into women and schizophrenia, but later expanded into clinical research of women with other mental health issues.

Picking up on the clinical clues about menopause related psychosis and postnatal illness, I began to explore the relationship between gonadal hormones and schizophrenia. In the early 1990's, key articles appeared on gender differences in schizophrenia. Pioneer researchers in this field included Mary Seeman, Anita Reicher-Rossler, Heinz Hafner and Jill Goldstein. In an important edition of Schizophrenia Bulletin in 1990, Goldstein (Goldstein and Tsuang, 1990) wrote: "The last 10 years of schizophrenia research have indicated a renewed interest in understanding gender differences in schizophrenia…Gender differences in schizophrenia have been found in the areas of premorbid history, symptomatology, brain morphology, brain functioning, neurochemistry, family transmission, course, and treatment response."

Researchers Hafner, Reicher-Rossler and Seeman developed the 'Estrogen Hypothesis – in which they postulated that (endogenous) estrogen postponed the early onset of severe symptoms of schizophrenia (Häfner et al., 1998; Seeman and Lang, 1990). This "estrogen hypothesis" was derived from epidemiological, clinical, and animal studies. Building on the "estrogen hypothesis", we conducted a series of clinical trials over many decades, administering exogenous estrogen with the overall impact of improving symptoms of schizophrenia in women

The first estradiol treatment trial for women with schizophrenia was an open label pilot study (Kulkarni et al., 1996). Eleven women of childbearing age diagnosed with schizophrenia were given 20 micrograms (mcg) oral ethinyl estradiol as an adjunct to antipsychotic medication for eight weeks, compared to a similar group who received antipsychotics. The group receiving estrogen made a significantly better recovery from acute psychotic symptoms. Following the open label pilot study, we conducted a double-blind placebo-controlled study of

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adjunctive transdermal 50mcg and 100mcg estradiol in women with schizophrenia (Kulkarni et al., 2001). This was followed by further clinical trials utilising 100mcg or 200mcg transdermal estradiol patches (Kulkarni et al., 2008, 2015). Our findings consistently showed that adjunctive estradiol treatment improved psychosis symptoms in women, especially 100mcg transdermal estradiol. We conducted a small study in men with schizophrenia and found that adjunctive estradiol also improved psychotic symptoms in men (Kulkarni et al., 1999). It is important to note that estradiol can cross the blood brain barrier and hence impact neurotransmitters and circuits, but not conjugated estrogens that are commonly used in treating menopause symptoms.

In more recent times, the possible mechanisms of estrogen action in improving psychosis symptoms have been explored. Estrogens increase dopamine sensitivity of dopamine D2/D3 receptors in the ventral tegmental area (VTA) (Brand et al., 2021; Vandegrift et al., 2017), that reduces psychotic symptoms. Estrogens also inhibit COMT gene transcription, which regulates dopamine activity (Dean et al., 2020).

In the early 2000's, concerns about the safe use of estrogens were raised - although these have been minimised by subsequent studies. At this stage, Selective Estrogen Receptor Modulators (SERMs) were being developed to treat osteoporosis in menopausal women. SERMs have an estrogenic effect in the brain and bone but do not impact estrogen receptors in gonadal, uterine or breast tissue. Hence, SERMs appeared to be useful as potential 'brain estrogens' and we conducted the first ever study in women with schizophrenia (Kulkarni, 2010). Subsequent trials with newer SERMs revealed utility in the adjunctive treatment of psychosis. Kulkarni et al. (2016), which opened another avenue for the development of adjunctive estrogen treatment. The concept of using estrogen in the treatment of schizophrenia that underpinned my clinical trials and treatments in clinical practice was further ratified in an independent replication study by Weiser et al. (2019).

Over the years, my research has expanded to include gonadal hormone treatment in women with PMDD (Robertson et al 2021) and menopausal depression (Kulkarni et al., 2018) plus consideration of depression caused by hormone contraceptives (Mu and Kulkarni, 2022). There is a growing body of research showing that changing levels of estradiol in the brain may directly modify dorsal and ventral emotional regulation nodes and circuits, with behavioural and emotional outcomes. Varying estradiol levels may have a significant impact on depression, emotional reactivity, and associated cognitive mechanisms in vulnerable women (Frey et al., 2010; Newhouse and Albert, 2015).

The role of estrogens in stress vulnerability is also reflected in the sex-dependent reaction to childhood trauma (Pruessner et al., 2019) Childhood trauma thus seems to amplify the typical sex-specific expression of symptoms, possibly mediated by estrogens effects on the HPA-axis (Handa and Weiser, 2014). We have undertaken new work in the neurobiology effects of early life trauma in women and development of new treatments for complex PTSD and Borderline Personality Disorder (Kulkarni et al., 2018) plus advocating for safer, better wards for women needing inpatient care.

Women's mental health has been largely neglected as a special area in Psychiatry. In particular, more neurobiological research is urgently needed to enable half the population to receive tailored treatments in modern, respectful surroundings. Using a 'biopsychosocial' approach in both research and clinical practice in women's mental health seems to be a better way forward. I hope future generations of researchers will carry on with research that continues to be informed by women with lived experience of mental ill health - who are desperately seeking new, safe and effective treatments to improve their outcomes and overall quality of life.

Declaration of Competing Interest

I have no conflict of interest to declare for this Commentary piece

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