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Perspective

Impact of Neuro-steroid Dysregulation on Women's Mental Health and its Potential Treatment

Alison Klatz*

Department of Psychiatry, Ludwig Maximilian University of Munich, Munich, Germany

DESCRIPTION

Neuro-steroids are a class of endogenous or exogenous steroids that can modulate the activity of neurotransmitter receptors and other targets in the brain. They have a variety of effects on mood, cognition, memory, stress, anxiety, depression, epilepsy, and neuroprotection. Some of the most studied neurosteroids are allopregnanolone, pregnenolone, Dehydroepiandrosterone (DHEA), and their sulfated derivatives. These neurosteroids can be synthesized in the brain or in peripheral tissues and cross the blood-brain barrier. They can also be influenced by hormonal fluctuations during the menstrual cycle, pregnancy, menopause, and aging in women. Neurosteroid pharmaceuticals are synthetic analogs or derivatives of neurosteroids that are designed to mimic or enhance their effects in the brain. They may have advantages over conventional drugs that act on neurotransmitter receptors, such as better specificity, safety, tolerability, and efficacy. Some of the novel neurosteroid pharmaceuticals which are currently under development or clinical trials for various neurological and psychiatric disorders in women include Brexanolone which is a synthetic analog of allopregnanolone, an inhibitory neurosteroid that acts as a positive allosteric modulator of the GABA (Gamma-Aminobutyric Acid) is receptor. Brexanolone was approved by the FDA (Food and Drug Administration) in 2019 for the treatment of Postpartum Depression (PPD), a condition that affects about 15% of women after childbirth and is associated with low levels of allopregnanolone. Brexanolone is administered as a continuous intravenous infusion for 60 hours and has shown rapid and sustained antidepressant effects in clinical trials. Brexanolone is also being investigated for the treatment of other mood disorders, such as Major Depressive Disorder (MDD) and bipolar disorder. SAGE-217 is another synthetic analog of allopregnanolone that has similar effects on the GABA a receptor as brexanolone. However, unlike brexanolone, SAGE-217 can be taken orally and has a longer half-life. SAGE-217 has shown potential results in phase 2 and 3 clinical trials for the treatment of PPD4, MDD5, insomnia6, and essential tremor. SAGE-217 is expected to be submitted for FDA approval for PPD and MDD in 2022. Ganaxolone is a synthetic analog of allopregnanolone that has been developed for the treatment of epilepsy, a neurological disorder characterized by recurrent seizures. Ganaxolone has anticonvulsant and neuroprotective effects by enhancing GABA a receptor function and reducing glutamate excitotoxicity. Ganaxolone has been tested in various forms of epilepsy, such as refractory focal epilepsy, status epilepticus, tuberous sclerosis complex, CDKL5 (Cyclin-Dependent Kinase-Like 5) deficiency disorder, and PCDH19 (Protocadherin 19) -related epilepsy. Ganaxolone has received orphan drug designation from the FDA for some of these indications and is currently in phase 3 clinical trials. Prasterone, also known as DHEA, is an excitatory neurosteroid that acts as a precursor for other sex hormones, such as estrogen and testosterone. Prasterone also has direct effects on several neurotransmitter receptors, such as NMDA (N-Methyl-D-Aspartate), sigma-1, and estrogen receptors. Prasterone levels decline with age and are associated with cognitive impairment, mood disorders, sexual dysfunction, and osteoporosis in women. Prasterone has been used as a dietary supplement for anti-aging purposes, but its efficacy and safety are controversial. Prasterone has also been developed as a pharmaceutical product for specific indications in women, such as vulvovaginal atrophy, systemic lupus erythematosus, and adrenal insufficiency. Prasterone has received FDA approval for some of these conditions under the brand names Intrarosa and Zynquista. TS-121 is a synthetic analog of DHEA sulfate, an excitatory neurosteroid that acts as a partial agonist of the sigma-1 receptor. Sigma-1 receptors are involved in various cellular processes, such as calcium signaling, protein folding, and mitochondrial function, and modulate the activity of several neurotransmitter systems, such as glutamate, dopamine, serotonin, and acetylcholine. Sigma-1 receptors are implicated in the pathophysiology of several neurological and psychiatric disorders, such as depression, anxiety, addiction, pain, stroke, and neurodegeneration. TS-121 has been developed to activate sigma-1 receptors and produce antidepressant, anxiolytic, analgesic, and neuroprotective effects.

Correspondence to: Alison Klatz, Department of Psychiatry, Ludwig Maximilian University of Munich, Munich, Germany, E-mail: kla@mun.com

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CONCLUSION

Novel neurosteroid pharmaceuticals are emerging as a potential class of drugs for the treatment of various neurological and psychiatric disorders in women. These drugs target the neurosteroid system, which is involved in the regulation of mood, cognition, memory, stress, anxiety, depression, epilepsy, and neuroprotection. These drugs may offer advantages over conventional drugs by being more specific, safe, tolerable, and effective. However, more research is needed to determine the optimal doses, formulations, modes of administration, safety profiles, and long-term effects of these drugs. Moreover, individual variations in neurosteroid metabolism, response, and interactions with other hormones should be taken into account when prescribing these drugs to women. Novel neurosteroid pharmaceuticals represent a new frontier in the field of neuroscience and pharmacology and may have significant implications for the health and well-being of women.