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### **Pathogenesis in menstrual cycle-linked CNS disorders.**

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That 3alpha-hydroxy-5alpha/beta-pregnane steroids (GABA steroids) have modulatory effects on the GABA-A receptor is well known. In behavioral studies in animals high exogenous dosages give concentrations not usually reached in the brain under physiological conditions. Animal and human studies show that GABA-A receptor-positive modulators like barbiturates, benzodiazepines, alcohol, and allopregnanolone have a bimodal effect. In pharmacological concentrations they are CNS depressants, anesthetic, antiepileptic, and anxiolytic. In low dosages and concentrations, reached endogenously, they can induce adverse emotional reactions in up to 20% of individuals. GABA steroids can also induce tolerance to themselves and similar substances, and rebound occurs at withdrawal. Menstrual cycle-linked disorders can be understood by the concept that they are caused by the action of endogenously produced GABA-steroids through three mechanisms: (a) direct action, (b) tolerance induction, and (c) withdrawal effect. Examples of symptoms and disorders caused by the direct action of GABA steroids are sedation, memory and learning disturbance, clumsiness, increased appetite, worsening of petit mal epilepsy, negative mood as tension, irritability and depression during hormone treatments, and the premenstrual dysphoric disorder (PMDD). A continuous exposure to GABA steroids causes tolerance, and women with PMDD are less sensitive to GABA-A modulators. A malfunctioning GABA-A receptor system is related to stress sensitivity, concentration difficulties, loss of impulse control, irritability, anxiety, and depression. An example of withdrawal effect is "catamenial epilepsy," when seizures increase during menstruation after the withdrawal of GABA steroids. Similar phenomena occur at stress since the adrenals produce GABA steroids during stress.