



## ALLOPREGNENALONE FOR MOOD, BRAIN, AND HPA AXIS SUPPORT

Allopregnanolone is a progesterone metabolite known for its anxiolytic, antidepressant, neuroprotective, and neurogenic effects. This metabolite is a positive modulator of GABA action on the GABAA receptor, the main inhibitory neurotransmitter in the brain, which usually can improve mood, calm anxiety, and support sleep.

When progesterone is supplemented via the oral route a large proportion is metabolized by the liver to allopregnanolone. While oral progesterone is not typically effective to raise salivary levels of progesterone or to counter the proliferative effects of estrogen supplementation on the endometrium, it can be an effective treatment for anxiety, depression and sleep issues in some women.

Low allopregnanolone levels have been associated with major depression, anxiety disorders, premenstrual dysphoric disorder (PMDD), and Alzheimer's disease. Low levels of allopregnanolone during pregnancy have been associated with depression and a recent study found that infusion of allopregnanolone can rapidly treat postpartum depression (PPD). This led to the 2019 FDA approval of Brexanolone, a synthetic form of allopregnanolone, to treat PPD. Allopregnanolone is also being studied as a potential therapy for Alzheimer's Disease. Murine research has shown that allopregnanolone can increase generation of new brain cells, reduce formation of beta-amyloid plaques, and improve cognitive function; human trials are underway.

Allopregnanolone targets one of the common underlying factors involved in disorders like depression, anxiety and insomnia – dysregulated response to stress. Findings from rat research suggest that allopregnanolone may help regulate HPA axis reactivity. Pretreatment of rats with allopregnanolone can decrease the stress-induced release of cortisol and ACTH. In humans, allopregnanolone levels increase in response to stimulation by CRH or ACTH, which may be a mechanism to help protect the brain during stress and to help restore a calm state.

Note that certain women may have paradoxical reactions to allopregnanolone exposure due to differences in the subunit on the GABA receptor called alpha-4. When too much  $\alpha$ -4 is produced, the receptor's capacity to use GABA is blunted, and this can cause increased anxiety and worsened mood for some. Up to 8% of women exposed to allopregnanolone paradoxically experience significant negative mood symptoms, so be sure to pay close attention to patient response to oral progesterone therapy.

Because of its calming and mood-lifting effects, oral progesterone supplementation can be a great consideration for treating anxiety, depression and insomnia. A typical starting dose is between 100 and 200mg orally at night. Oral progesterone can be used concurrently with physiological doses of topical progesterone without causing excessively high salivary levels. The best way to achieve safe therapeutic dosing of bioidentical hormones is by testing hormone levels in saliva before initiating treatment and repeating testing 8 to 12 weeks into therapy.

### References

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