

# Neuroactive steroids may induce prolonged antidepressant effects by altering brain states

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New research led by neuroscientists at Tufts University School of

Medicine suggests the prolonged antidepressant effects of allopregnanolone, a neuroactive steroid used therapeutically to treat postpartum depression, may involve the ability of the compound to modify communication in an area of the brain important for mood and emotion regulation.

Drawing in part on work Tufts neuroscientist Jamie Maguire did as a postdoctoral researcher identifying a role of brain-derived steroids as mood regulators in rodent models during and after pregnancy, Sage Therapeutics developed brexanolone, its proprietary formulation of a naturally produced neurosteroid called allopregnanolone. In clinical trials, one 60-hour intravenous infusion of brexanolone demonstrated a significant and clinically meaningful mean reduction in symptoms of [postpartum depression](#) within 60 hours that was maintained for up to 30 days. In March 2019, the drug became the first to receive FDA approval for the treatment of postpartum depression in adults.

In a study recently published online as a pre-proof in *Biological Psychiatry*, Maguire and researchers from Tufts and Sage examined the effect of a single treatment of allopregnanolone in mice to understand how the compound is able to induce long-lasting effects on mood in the treatment of postpartum depression.

"We were really struck by the persistent antidepressant effects of the medication in the [clinical trials](#), which long outlasted the treatment exposure. These prolonged effects were not well explained by the known mechanisms of action of these compounds," said Maguire, senior and corresponding author and a Kenneth and JoAnn G. Wellner Professor at Tufts School of Medicine. "Understanding the potential connection between allopregnanolone and network states in areas of the brain implicated in mood not only could identify the mechanisms mediating the prolonged antidepressant effects of this compound but also could shed light on the episodic nature of many mood disorders."

Oscillations occur when [brain cells](#) fire together in a specific rhythm or frequency and represent local and long-range communication in the brain. Specific frequencies of oscillations in the brain are associated with different behavioral states, like sleeping and waking. However, in neuropsychiatric disorders like depression and post-traumatic stress, oscillations can be disturbed in areas like the [basolateral amygdala](#), potentially leading to symptoms. In the current study, the researchers find long-term alterations in network states in the basolateral amygdala following [chronic stress](#), a major risk factor for psychiatric illnesses.

By recording brain oscillations in humans and rodents, the researchers found that the drug could change oscillations in the basolateral amygdala to mirror a healthier state. They also demonstrated that direct application of the drug in the basolateral amygdala can improve behavior in mice, suggesting that this area is critical in mediating the acute effects of the drug as well as the long-term changes in brain and behavioral states.

"Our results may provide an essential framework for understanding the role of oscillations and associated behavioral states," said Maguire, who is also a member of the neuroscience and MS in Pharmacology & Drug Development program faculty at Tufts Graduate School of Biomedical Sciences. "Although there may be many mechanisms involved in altering the brain's network state, if changing oscillations in the brain can lead to long lasting changes in behavior, this both adds to our understanding of the [brain](#) and may be a new strategy for [drug](#) therapies."

**More information:** Pantelis Antonoudiou et al, Allopregnanolone mediates affective switching through modulation of oscillatory states in the basolateral amygdala, *Biological Psychiatry* (2021). [DOI: 10.1016/j.biopsych.2021.07.017](https://doi.org/10.1016/j.biopsych.2021.07.017)

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