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Ganaxolone for management of seizures associated with CDKL5 deficiency disorder

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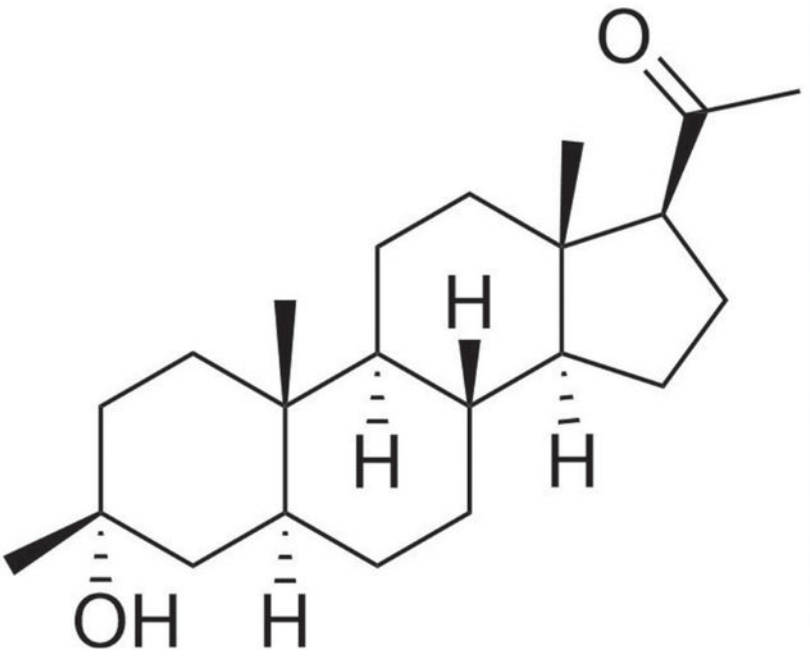

STRUCTURE: Ganaxolone is a 3β-methylated synthetic analog of the natural neurosteroid allopregnanolone, a metabolite of progesterone. It is also called 3α-hydroxy-3β-methyl-5α-pregnan-20-one and has a molecular formula $C_{22}H_{36}O_2$, with a molecular weight of 332.5 g/mol. The 3β-methyl substitution prevents rapid metabolism and thus increases its stability (terminal half-life: 34 h). Ganaxolone is a white crystalline powder that is insoluble in water but soluble in organic solvents.

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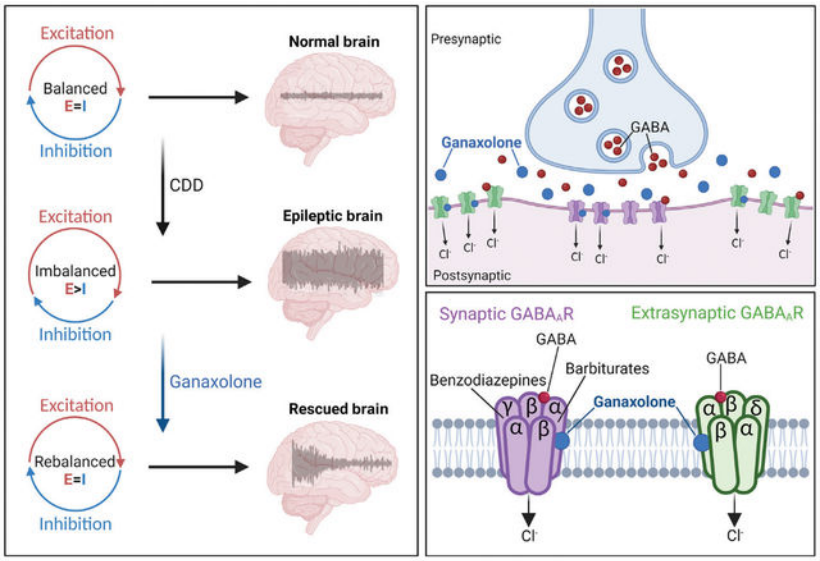
Declaration of interests

The authors declare no conflict of interest.



MECHANISM OF ACTION: γ-Aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system. Its principal role is to lower neuronal excitability, mainly via acting on the GABA receptor A subtype ($GABA_AR$), a ligand-gated ion channel receptor. Upon activation by GABA released from the presynaptic neurons, $GABA_AR$ on the postsynaptic cell selectively allows the influx of negatively charged ions (mainly chloride anion, Cl^-) into the neurons, resulting in decreased neuronal excitability. $GABA_AR$ has long been implicated in neurological conditions, including seizures; it is the primary target for a number of antiseizure drugs (ASDs). Ganaxolone is a small molecule that has been identified as a positive allosteric modulator for $GABA_AR$ and demonstrated to significantly reduce the frequency of major motor seizures associated with the cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder (CDD) in clinical trials. The mechanism of action of ganaxolone in the management of seizures is not fully understood; however, its antiseizure action is likely attributed to its potentiation of $GABA_AR$ activation. Ganaxolone is able to augment the activities of both synaptic $GABA_AR$ (containing α, β, and γ subunits) and extrasynaptic $GABA_AR$ (containing α, β, and δ subunits) through a binding site distinct from benzodiazepines or barbiturates (binding sites on $GABA_AR$ are indicated). By contrast, these two groups of conventional ASDs only act on the synaptic $GABA_AR$. Ganaxolone's capability of activating $GABA_AR$ on both synaptic and extrasynaptic sites leads to enhanced and persistent suppression of neuronal excitability during seizures. This unique feature differentiates ganaxolone from other GABA-potentiating ASDs, such as benzodiazepines or barbiturates.

Acknowledgments

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Literature

1. Lattanzi S et al. (2021) Ganaxolone treatment for epilepsy patients: from pharmacology to place in therapy. Expert. Rev. Neurother. 21, 1317–1332 [PubMed: 33724128]

2. Knight EMP et al. (2022) Safety and efficacy of ganaxolone in patients with CDKL5 deficiency disorder: results from the double-blind phase of a randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 21, 417–427 [PubMed: 35429480]

3. Saporito MS et al. (2019) Intravenously administered ganaxolone blocks diazepam-resistant lithium-pilocarpine–induced status epilepticus in rats: comparison with allopregnanolone. J. Pharmacol. Exp. Ther. 368, 326–337 [PubMed: 30552296]

4. Yawno T et al. (2017) Ganaxolone: a new treatment for neonatal seizures. Front. Cell. Neurosci. 11, 246 [PubMed: 28878622]

5. Noebels JL et al. (2012) Jasper's Basic Mechanisms of the Epilepsies. (4th edn), National Center for Biotechnology Information

6. Galanopoulou A (2008) GABAA receptors in normal development and seizures: friends or foes? Curr. Neuropharmacol. 6, 1–20 [PubMed: 19305785]

7. Chuang S et al. (2018) Genetic and molecular regulation of extrasynaptic GABA-A receptors in the brain: therapeutic insights for epilepsy. J. Pharmacol. Exp. Ther. 364, 180–197 [PubMed: 29142081]

8. Greenfield LJJ (2013) Molecular mechanisms of antiseizure drug activity at GABAA receptors. Seizure 22, 589–600 [PubMed: 23683707]

9. Jakimiec M et al. (2020) CDKL5 deficiency disorder-a complex epileptic encephalopathy. Brain Sci. 10, 107 [PubMed: 32079229]

10. Sills GJ and Rogawski MA (2020) Mechanisms of action of currently used antiseizure drugs. Neuropharmacology 168, 107966 [PubMed: 32120063]

NAME:

Ganaxolone; commercially available under the brand name ZTALMY.

DRUG CLASS:

First-in-class positive allosteric modulator that targets both synaptic and extrasynaptic GABA A receptor ($GABA_AR$).

CLINICAL USE:

Indicated for the treatment of seizures associated with CDKL5 CDD in patients 2 years of age and older. Ganaxolone is administered as an oral suspension three times daily. CDD is a rare genetic disorder (one in 40 000–60 000 newborns) characterized by infantile-onset epilepsy and severe neurodevelopmental delay. It is caused by mutations in the CDKL5 gene, which encodes a protein essential for normal brain functions. Seizures in CDD patients are usually severe and difficult to control.

DEVELOPED BY:

Originally developed by CoCensys Inc. and acquired by Purdue Pharma in 1999. Marinus Pharmaceuticals acquired the compound from Purdue Pharma in 2004.

ADVERSE EFFECTS:

Somnolence, pyrexia, salivary hypersecretion, and seasonal allergy. Avoid concomitant use with strong or moderate CYP3A4 inducers as they will decrease ganaxolone exposure.

TIMELINE:

2018–2021, Phase 3 trials, NCT03572933

March 18, 2022, FDA approval for ZTALMY® (ganaxolone).

2023–2024, Phase 3 trials, NCT05249556