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Brexanolone

Updated: April 12, 2019.

OVERVIEW

Introduction

Brexanolone is a unique, intravenously administered, neuroactive steroidal antidepressant used in the therapy of moderate-to-severe postpartum depression. In prelicensure clinical trials, brexanolone therapy was not associated with an increased rate of serum aminotransferase elevations, and it has not been linked to instances of clinically apparent acute liver injury.

Background

Brexanolone (brex an' oh lone) is allopregnanolone an active metabolite of progesterone which is found in high concentrations during pregnancy and falls precipitously at the time of delivery, shortly before the usual time of onset of postpartum depression. When given intravenously in doses that achieve plasma levels typical of pregnancy, brexanolone was found to be associated with marked improvement in depression symptoms, an effect that was sustained when the infusion was stopped. In vitro assays have shown that brexanolone also modulates synaptic and extra-synaptic GABA receptors, another possible mechanism of antidepressant activity. In two randomized controlled trials, a 60 hour intravenous infusion of brexanolone was found to be more effective than placebo in improving depression symptom scales and, in some instances, reversed the functional impairment that often accompanies severe postpartum depression. Brexanolone was approved in the United States in 2019 for use in treatment of moderate or severe postpartum depression. Brexanolone is available in solution in single use vials of 100 mg in 20 mL (5 mg/mL) under the brand name Zulresso. The recommended regimen starts with a dose of 30 mcg/kg/hour, which is gradually increased to a maintenance dose of 90 mcg/kg/hour which is decreased back 30 mcg/kg/hour before stopping, the total duration being 60 hours. Common, nonserious side effects include infusion site discomfort, sedation, headache, dizziness, dry mouth and flushing. Rare, potentially severe adverse events include loss of consciousness and suicidal thoughts or behaviors. The treatment requires continuous monitoring and is typically given in hospital which is often problematic for a new mother.

Hepatotoxicity

In premarketing studies, liver test abnormalities were uncommon in patients receiving brexanolone (<1%) and no more frequent than in placebo recipients. No instances of acute, clinically apparent liver injury attributed to brexanolone have been reported. However, general clinical experience with brexanolone has been limited.

Likelihood score: E (unlikely cause of clinically apparent liver injury).

Mechanism of Injury

The mechanism by which brexanolone might cause liver injury is not known. Brexanolone is metabolized largely via non-cytochrome P450 pathways, predominantly by keto-reduction, glucuronidation and sulfation. It has few significant drug-drug interactions. Concurrent use of other antidepressants may lead to excess sedation.

Drug Class: Antidepressant Agents

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Brexanolone – Zulresso®

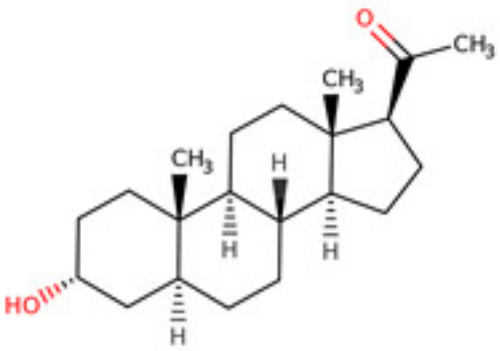
DRUG CLASS

Antidepressant Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NO.	MOLECULAR FORMULA	STRUCTURE
Brexanolone	516-54-1	C21-H34-O2	

ANNOTATED BIBLIOGRAPHY

References updated: 12 April 2019

Zimmerman HJ. Antidepressants. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 493-8.

(Expert review of hepatotoxicity published in 1999, before the availability of brexanolone).

Larrey D. Hepatotoxicity of psychotropic drugs and drugs of abuse. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 2nd ed. New York: Informa Healthcare USA, 2007, pp. 507-26.

(Review of hepatotoxicity of antidepressants published in 2007 before the availability of brexanolone).

O'Donnell JM, Bies RR, Shelton RC. Drug therapy of depression and anxiety disorders. In, Brunton LL, Hilal-Dandan R, Knollmann BC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 13th ed. New York: McGraw-Hill, 2018, pp. 267-78.

(Textbook of pharmacology and therapeutics).

Available at: https://www.accessdata.fda.gov/scripts/cder/daf/

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

(FDA Drug Approvals website that has product labels [package inserts], letters of approval and full FDA scientific review of the new drug application for safety and efficacy).

Voican CS, Corruble E, Naveau S, Perlemuter G. Antidepressant-induced liver injury: a review for clinicians. Am J Psychiatry 2014; 171: 404-15. PubMed PMID: 24362450.

(Review of the frequency and clinical features of drug induced liver injury due to antidepressants; several SSRIs are discussed [sertraline, paroxetine, fluoxetine, citalopram, fluvoxamine], but not brexanolone).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 20 cases were attributed to antidepressants including 5 to SSRIs [fluoxetine, escitalopram, sertraline], but none to brexanolone).

Kanes SJ, Colquhoun H, Doherty J, Raines S, Hoffmann E, Rubinow DR, Meltzer-Brody S. Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. Hum Psychopharmacol 2017; 32. PubMed PMID: 28370307.

(Among 4 women with severe postpartum depression treated with brexanolone infusions for 60 hours, all had rapid and striking improvements in depression symptom scores [improving by an average of 91%] and "there were no clinically important changes from baseline in…laboratory parameters").

Kanes S, Colquhoun H, Gunduz-Bruce H, Raines S, Arnold R, Schacterle A, Doherty J, et al. Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial. Lancet 2017; 390 (10093): 480-9. PubMed PMID: 28619476.

(Among 21 women with severe postpartum depression treated with brexanolone or placebo infusions for 60 hours, depression scores improvement and symptomatic remissions were greater with brexanolone and there were no serious adverse events or early discontinuations, overall adverse events being more frequent in the placebo group; no mention of ALT levels or hepatotoxicity).

Meltzer-Brody S, Colquhoun H, Riesenberg R, Epperson CN, Deligiannidis KM, Rubinow DR, Li H, et al. Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. Lancet 2018; 392 (10152): 1058-70. PubMed PMID: 30177236.

(Among 246 women with moderate-to-severe postpartum depression treated with 60 hour infusions of brexanolone or placebo in two randomized controlled trials, depression symptom scores improved more with brexanolone, while adverse event rates were similar in the two groups [50% in both] and ALT elevations occurred rarely [<1% vs 2%].

Frieder A, Fersh M, Hainline R, Deligiannidis KM. Pharmacotherapy of postpartum depression: current approaches and novel drug development. CNS Drugs 2019; 33: 265-82. PubMed PMID: 30790145.

(Review of the clinical features, epidemiology, pathogenesis and pharmacotherapy of postpartum depression including use of neuroactive steroids such as brexanolone; no mention of ALT elevations or hepatotoxicity).