Brexanolone (SAGE-547 injection) in post-partum depression: a randomised controlled trial

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Summary

Background Post-partum depression is a serious mood disorder in women that might be triggered by peripartum fluctuations in reproductive hormones. This phase 2 study investigated brexanolone (USAN; formerly SAGE-547 injection), an intravenous formulation of allopregnanolone, a positive allosteric modulator of γ-aminobutyric acid (GABA) receptors, for the treatment of post-partum depression.

Methods For this double-blind, randomised, placebo-controlled trial, we enrolled self-referred or physician-referred female inpatients (±6 months post partum) with severe post-partum depression (Hamilton Rating Scale for Depression [HAM-D] total score ≥26) in four hospitals in the USA. Eligible women were randomly assigned (1:1), via a computer-generated randomisation program, to receive either a single, continuous intravenous dose of brexanolone or placebo for 60 h. Patients and investigators were masked to treatment assignments. The primary efficacy endpoint was the change from baseline in the 17-item HAM-D total score at 60 h, assessed in all randomised patients who started infusion of study drug or placebo and who had a completed baseline HAM-D assessment and at least one post-baseline HAM-D assessment. Patients were followed up until day 30. This trial is registered with ClinicalTrials.gov, number NCT02614547.

Findings This trial was done between Dec 15, 2015 (first enrolment), and May 19, 2016 (final visit of the last enrolled patient). 21 women were randomly assigned to the brexanolone (n=10) and placebo (n=11) groups. At 60 h, mean reduction in HAM-D total score from baseline was 21·0 points (SE 2·9) in the brexanolone group compared with 8·8 points (SE 2·8) in the placebo group (difference –12·2, 95% CI –20·77 to –3·67; p=0·0075; effect size 1·2). No deaths, serious adverse events, or discontinuations because of adverse events were reported in either group. Four of ten patients in the brexanolone group had adverse events compared with eight of 11 in the placebo group. The most frequently reported adverse events in the brexanolone group were dizziness (two patients in the brexanolone group vs three patients in the placebo group) and somnolence (two vs none). Moderate treatment-emergent adverse events were reported in two patients in the brexanolone group (situs tachycardia, n=1; somnolence, n=1) and in two patients in the placebo group (infusion site pain, n=1; tension headache, n=1); one patient in the placebo group had a severe treatment-emergent adverse event (insomnia).

Interpretation In women with severe post-partum depression, infusion of brexanolone resulted in a significant and clinically meaningful reduction in HAM-D total score, compared with placebo. Our results support the rationale for targeting synaptic and extrasynaptic GABA_A receptors in the development of therapies for patients with post-partum depression. A pivotal clinical programme for the investigation of brexanolone in patients with post-partum depression is in progress.

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Introduction Post-partum depression is a serious mood disorder consistently observed in an estimated 10–20% of all mothers who give birth in high-income and low-income countries worldwide.1–4 Following delivery, post-partum depression is characterised by clinically significant depressive symptoms, often co-occurring with anxiety.1–4 Severe post-partum depression is defined as a major depressive episode in the post-partum period with marked impairment in functioning in both the International Classification of Diseases (ICD)-10 and Diagnostic and Statistical Manual of Mental Disorders (DSM)-5.5,6 Estimates of the point prevalence of severe post-partum depression generally range from 5% to 10% of all cases of post-partum depression, depending on the setting.7,8 Furthermore, post-partum depression is a leading cause of maternal mortality9,10 and, by affecting maternal functioning, poses serious risks to the emotional, cognitive, behavioural, and physical development of the infant and siblings.11–13 Findings from several studies implicate peripartum fluctuations in reproductive hormones (in particular, the major progesterone metabolite allopregnanolone) having pivotal pathophysiological roles in post-partum depression.14–22 Allopregnanolone, a potent positive allosteric modulator of synaptic and extrasynaptic GABA_A receptors,23,24 has been shown to have profound effects on
alterations in concentrations or ratios of serum neuroactive steroids during pregnancy and parturition, and showed depression-like and anxiety-like behaviours and abnormal maternal behaviours that were reversed by administration of allopregnanolone. These findings lend support to the hypothesis that changes in neuroactive steroid concentrations during pregnancy and post partum are capable of provoking affective dysregulation. Neuroactive steroids such as allopregnanolone might function as behavioural switches, suggesting a potentially important role in treatment of reproductive and endocrine-related mood disorders such as post-partum depression.

We searched PubMed (all indexed dates up to Feb 1, 2017) for clinical trials with the terms “allopregnanolone”, “neuroactive steroid”, “GABA, positive allosteric modulator”, and “postpartum depression”. This search retrieved no trials examining the neuroactive steroid or GABA,-receptor mechanism in post-partum depression. A previous report by several of this study’s investigators describes an open-label, exploratory study of brexanolone in four women with severe post-partum depression.

Added value of this study
To our knowledge, this study is the first randomised, double-blind, placebo-controlled trial of a therapeutic formulation of the neuroactive steroid allopregnanolone in patients with post-partum depression. The current standard of care for post-partum depression includes psychotherapy and pharmacological therapies. However, no pharmacological therapies are specifically indicated for the treatment of post-partum depression. Antidepressant medications used to treat depressive disorders outside of the perinatal period, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, are commonly used in post-partum depression. However, these therapies are not directly linked with existing hypotheses regarding the causes of post-partum depression, their onset of efficacy can be delayed by several weeks or months, and their overall remission rate in post-partum depression is low. In particular, rapid onset of action is desirable in severe post-partum depression to quickly mitigate the serious, negative effects of the disorder on the mother, infant, and family. Our study suggests the potential for the development of a GABA,,-positive allosteric modulator, such as the neuroactive steroid brexanolone, as a new mechanism for treatment of post-partum depression that is related to the underlying pathophysiology.

Implications of all the available data
Together with preclinical and clinical studies suggesting a role for neuroactive steroids and GABA, receptor regulation in the pathophysiology of post-partum depression, our findings support the rationale for further examining brexanolone in patients with post-partum depression. Several pivotal clinical trials are currently examining the efficacy and safety of brexanolone in post-partum depression.
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