

Advances in pharmacotherapy for postpartum depression: a structured review of standard-of-care antidepressants and novel neuroactive steroid antidepressants

Yardana Kaufman, Sara V. Carlini and Kristina M. Deligiannidis 

Ther Adv Psychopharmacol

2022, Vol. 12: 1–12

DOI: 10.1177/
20451253211065859

© The Author(s), 2022.
Article reuse guidelines:
[sagepub.com/journals-](https://sagepub.com/journals-permissions)
[permissions](https://sagepub.com/journals-permissions)

Abstract: Postpartum depression is one of the most common morbidities of childbearing, yet it is underdiagnosed and undertreated with negative consequences for mother and offspring. Despite the widespread use of standard-of-care antidepressants as the mainstay of treatment for postpartum depression, there is limited evidence on their safety and efficacy due to their slow onset of action and suboptimal outcomes. The emergence of gamma-aminobutyric acidergic neuroactive steroids may offer faster response and remission times and improved patient outcomes. This article reviews the evidence base for the efficacy of standard-of-care antidepressants, hormonal therapeutics including progestins and estradiol, and gamma-aminobutyric acidergic neuroactive steroids in the treatment of postpartum depression, as well as the safety of infant exposure to these agents during lactation.

Keywords: antidepressant, brexanolone, estradiol, ganaxolone, lactation, neuroactive steroids, pharmacotherapy, postpartum depression, progestin, treatment, zuranolone

Received: 24 May 2021; revised manuscript accepted: 23 November 2021.

Introduction

Postpartum depression (PPD) is one of the most common morbidities of childbearing, bearing a significant mental and public health concern. The Centers for Disease Control and Prevention (CDC) recently estimated the overall prevalence of PPD in the United States to be 13%, with a range of 9.7–23.5% by state.¹ Among women with PPD, 11.5% develop symptoms antenatally, 66.5% develop symptoms within 6 weeks of parturition, and 22% develop symptoms within 12 months of delivery.² PPD symptom onset occurs most often within the first few months of childbirth.³

The American Psychiatric Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)* categorizes PPD as unipolar major depression along with the specifier 'with peripartum onset' when the episode begins during gestation or within 4 weeks following childbirth.⁴ Despite this limited time frame, many experts define the postpartum period as the

first year after delivery.^{5,6} Women with PPD may present with excessive worry about their baby and feelings of being inadequate caregivers. A recent study categorized perinatal depression into five distinct subtypes (severe anxious depression, moderate anxious depression, anxious anhedonia, pure anhedonia, and resolved depression) based on differences in symptom quality and time of onset.⁷

Despite the high occurrence of PPD, it is underdiagnosed and undertreated. Of women with PPD, only 30.8% are identified in clinical settings, 15.8% receive treatment, 6.3% receive adequate treatment and 3.2% achieve remission.⁸ Untreated PPD can have short- and long-term harmful consequences for mother and offspring, including decreased maternal functioning,⁹ maternal-infant bonding difficulties,¹⁰ lactation failure¹¹ and impaired cognitive,¹² behavioral¹³ and emotional¹⁴ development of the child. Tragically, untreated PPD is the greatest risk factor for maternal

Correspondence to:
Kristina M. Deligiannidis
Women's Behavioral
Health, Zucker Hillside
Hospital, Northwell
Health, 75-59 263rd Street,
Glen Oaks, NY, USA

Departments of Psychiatry
and Obstetrics &
Gynecology, Donald and
Barbara Zucker School
of Medicine at Hofstra/
Northwell, Hempstead,
NY, USA

The Feinstein Institutes
for Medical Research,
Manhasset, NY, USA
Kdeligian1@northwell.edu

Yardana Kaufman
Sara V. Carlini
Perinatal Psychiatry
Center, Zucker Hillside
Hospital, Northwell
Health, Glen Oaks, NY,
USA

suicide,¹⁵ which is the leading cause of direct maternal mortality in the first postpartum year.¹⁶

Therapeutic interventions for PPD include evidence-based psychotherapeutic, pharmacotherapeutic, neuromodulation, and hormonal treatments. An APA taskforce recommends either psychotherapy or antidepressants as first-line treatment for mild-to-moderate PPD.¹⁷ Evidence-based psychotherapies for PPD including cognitive behavioral therapy and interpersonal psychotherapy^{18,19} should also be considered as an adjuvant to antidepressants in moderate-to-severe PPD and in cases where women are reluctant to take antidepressants.

Despite the widespread use of standard-of-care antidepressants as the mainstay of treatment for PPD, there is limited evidence on their efficacy and safety, and treatment outcomes remain sub-optimal due to their slow onset of action. Treatment with emerging gamma-aminobutyric acid (GABA)ergic neuroactive steroids (NAS), including brexanolone [US Food and Drug Administration (FDA) approved in PPD], zuranolone (investigational) or ganaxolone (investigational), may offer faster response and remission times and improved patient outcomes. This article reviews the evidence base for the efficacy of standard-of-care antidepressants, hormonal therapeutics including progestins and estradiol, and GABAergic NAS in the treatment of women with PPD, as well as the safety of infant exposure to these agents during lactation.

Method for the literature review

An electronic literature search was conducted in April 2021 limited to published English language manuscripts using Scopus, Web of Science, PubMed, Embase and Cochrane. We identified articles using the following key terms in various combinations: postpartum, postnatal, puerperal, depression, antidepressant, selective serotonin reuptake inhibitor (SSRI), serotonin and norepinephrine reuptake inhibitor (SNRI), noradrenergic and specific serotonergic antidepressant (NaSSA), tricyclic or tetracyclic antidepressant (TCA), monoamine oxidase inhibitor (MAOI) and the name of each antidepressant.

Search terms

Postpartum OR post partum or postnatal or postnatal or perinatal or peri natal or puerp* or

Postpartum Period OR 'postpartum care' OR Postnatal Depression OR Post-Partum Depression OR Postpartum Depression OR Post-Natal Depression OR Post Natal Depression OR Puerperal Disorder* or 'Postnatal Care'[Mesh] OR 'Depression, Postpartum'[Mesh] OR 'Postpartum Period'[Mesh] or intrapartum or intra partum or antepartum or ante partum

AND. Antidepressive Agents [tw] OR Antidepressive Agents[pa] or Serotonin Uptake Inhibitors [PA] OR Serotonin Uptake Inhibitors [tw] or 'Serotonin Uptake Inhibitors'[Mesh] OR SSRIs OR serotonin reuptake inhibitors or SSRIs serotonin-norepinephrine reuptake inhibitors or 'Serotonin and Noradrenaline Reuptake Inhibitors' [Pharmacological Action] OR 'Serotonin and Noradrenaline Reuptake Inhibitors'[Mesh] or SRNIs OR 'serotonin reuptake inhibitors' or 'Antidepressive Agents'[Mesh] OR Brexanolone OR MAOIs OR NASSAs OR TCAs or antidepress* or antidepress* or MAOI* or monoamine oxidase inhibit* or ((serotonin or norepinephrine or noradrenaline or nor epinephrine or nor adrenaline or neurotransmitt* or dopamine*) and (uptake or reuptake or re-uptake)) or noradrenerg* or antiadrenergic or anti adrenergic or SSRI* or SNRI* or TCA* or tricyclic* or tetracyclic* or heterocyclic* or psychotropic* or the name of each antidepressant.

We managed records obtained from the search in Covidence. Inclusion criteria were randomized controlled trials (RCTs) of women with PPD treated with antidepressants, progestin, estradiol or GABAergic NAS during the first year after childbirth, as well as systematic reviews and meta-analyses that included these RCTs or observational studies related to PPD treatment with the aforementioned agents. One of three review authors (YK) inspected abstracts resulting from the search and assessed them for inclusion based on the defined criteria. We excluded studies focused on PPD prevention and PPD treatment with only complementary, alternative, integrative, neuromodulatory, and psychotherapy treatments. Additional RCTs, systematic reviews and meta-analyses were identified by reviewing bibliographies of articles identified within the search.

Search results

The electronic literature search yielded 292 articles after 79 duplicates were removed. This review included the following RCTs from the search: 10 related to PPD treatment with standard-of-care

Table 1. Antidepressant randomized clinical trials for the treatment of postpartum depression.

Study	Intervention	Trial length	Sample size
Appleby <i>et al.</i> ²⁸	Fluoxetine, placebo, with each group added to either 1 or 6 counseling sessions	12 week	87
Misri <i>et al.</i> ²⁷	Paroxetine alone, paroxetine plus cognitive behavioral therapy	12 week	35
Wisner <i>et al.</i> ²⁶	Sertraline, nortriptyline	8-week comparative with 16-week continuation phase	109
Yonkers <i>et al.</i> ²⁵	Paroxetine, placebo	8 week	70
Sharp <i>et al.</i> ²⁴	Various antidepressants (mostly selective serotonin reuptake inhibitors), supportive counseling	18 week	254
Bloch <i>et al.</i> ²³	Sertraline, placebo, with each group added to brief psychodynamic therapy	8 week	40
Hantsoo <i>et al.</i> ²²	Sertraline, placebo	6 week	38
Chibanda <i>et al.</i> ²⁹	Amitriptyline, group problem-solving therapy	6 week	58
Milgrom <i>et al.</i> ²¹	Sertraline, specialized cognitive behavioral therapy program	12 week	45
O'Hara <i>et al.</i> ²⁰	Sertraline-case management, interpersonal psychotherapy, placebo-case management	12 week	162

antidepressants^{20–29} (Table 1), two related to PPD treatment with estradiol^{30,31} (Table 2), two related to PPD treatment with brexanolone,^{32,33} and one related to PPD treatment with zuranolone³⁴ (Table 3). The following additional trials were identified from the bibliographic reviews: one related to estradiol³⁵ and two related to progestin PPD treatment^{36,37} (Table 2). This review also included the following systematic reviews and meta-analyses from the literature search: three related to PPD treatment with antidepressants,^{38–40} two related to PPD treatment with brexanolone^{41,42} and two related to antidepressant use during lactation.^{43,44} The following additional systematic reviews and meta-analyses that did not result from the search were also identified by reviewing bibliographies of articles identified within the literature search: two related to PPD treatment with estradiol and progestins,^{45,46} three related to antidepressant use with lactation,^{47–49} and two related to the use of progestin during lactation.^{50,51}

Evidence for standard-of-care antidepressants for PPD

Antidepressants are indicated for moderate-to-severe PPD, with SSRIs typically considered as first-line therapy based on the perceived good

tolerability. However, the current evidence on antidepressant efficacy for PPD treatment is limited by small number and sample size of RCTs and the absence of long-term follow-up. In addition, the existing studies are heterogeneous in design with few using a placebo control vs an active comparator such as similar antidepressant or psychotherapy. Ten RCTs evaluated the use of antidepressants (mostly sertraline, fluoxetine, paroxetine and citalopram) for PPD treatment.^{20–29} All of these RCTs used a specific antidepressant except one which employed a variety of antidepressants (mostly SSRIs).²⁴ Two RCTs used the TCAs amitriptyline²⁹ and nortriptyline.²⁶ The remaining RCTs used SSRIs: sertraline,^{20–23,26} paroxetine^{25,27} and fluoxetine.²⁸ No RCTs have evaluated the use of SNRIs, bupropion, mirtazapine, trazodone, nefazodone, MAOIs or TCAs (except nortriptyline and amitriptyline) for PPD treatment.

While several RCTs support antidepressant efficacy in PPD treatment, results have been mixed.

A meta-analysis of three RCTs^{22,23,25} comparing SSRIs with placebo found that women who received SSRIs were more likely to show symptom response (52.2% *versus* 36.5%) or remission

Table 2. Randomized clinical trials of hormonal-based therapeutics for the treatment of postpartum depression.

Study	Intervention	Trial length	Sample size
Gregoire <i>et al.</i> ³¹	Transdermal estradiol, placebo	6 month	61
Lawrie <i>et al.</i> ³⁶	Norethisterone enanthate injection, placebo	6 week	180
Wisner <i>et al.</i> ³⁰	Transdermal estradiol, sertraline, placebo	8 week	85
Singata-Madliki <i>et al.</i> ³⁷	Depot medroxyprogesterone acetate injection, intrauterine device	3 month	242
Li <i>et al.</i> ³⁵	Transdermal estradiol, placebo	6 week	14

Table 3. Randomized clinical trials of GABAergic antidepressants for the treatment of postpartum depression.

Study	Intervention	Trial length	Sample size
Kanes <i>et al.</i> ³³	Brexanolone, placebo	60 hours, plus observational follow-up	21
Meltzer-Brody <i>et al.</i> ³²	Brexanolone, placebo	60 hours, plus observational follow-up	246
Deligiannidis <i>et al.</i> ³⁴	Zuranolone, placebo	14 days, plus observational follow-up	153

(46.0% *versus* 25.7%) at follow-up.⁴⁰ A systematic review of six RCTs^{23–28} concluded that SSRIs, nortriptyline and psychotherapy are efficacious for short-term PPD treatment, but there is insufficient evidence to demonstrate clear superiority of one over the other.³⁸ Another systematic review of the same studies concluded that evidence is insufficient to support the efficacy of antidepressants for PPD treatment,⁵² but the authors acknowledged that their findings may be explained by methodological limitations including low recruitment rates. Despite limited and inconsistent data, there is a consensus supporting antidepressant use in PPD treatment.

Evidence for estradiol and progestins as treatments for PPD

Current evidence on the use of estradiol is limited by the small number and size of RCTs and mixed results. A small double-blind RCT of transdermal estradiol (TE) in women with severe PPD showed greater and faster symptom improvement compared with those who received placebo, though these results may be confounded by the inclusion of women who were simultaneously treated with antidepressants.³¹ Another small double-blind RCT found that women who received TE exhibited non-significantly higher response and remission rates compared with those who received placebo patch, although this study was limited by under-recruitment and loss to follow-up.³⁵ One

large trial comparing TE with placebo did not show significant differences between groups for response or remission rates, though this study was underpowered as it was stopped early due to estradiol serum concentrations not reaching the expected levels.³⁰ Additional data from large RCTs is needed before estrogen may be recommended to treat PPD.

Fewer data exist on synthetic progesterone treatment. Two RCTs showed that women with PPD treated with the synthetic progestogens including intramuscular injections of norethisterone enanthate³⁶ and depot medroxyprogesterone acetate³⁷ experienced increased depressive symptoms compared with those receiving placebo³⁶ or with an intrauterine device.³⁷ A Cochrane systematic review concluded that synthetic progestogens should be used cautiously in postpartum women⁴⁵ when used for contraception, and are not recommended to treat PPD.

Development of GABAergic neuroactive steroids as novel, fast-acting antidepressants for PPD

Definition and mechanism of action

NAS are naturally occurring steroids and their metabolites that are synthesized from cholesterol. Neurosteroids (NS) refer specifically to those NAS

and their metabolites synthesized in the central nervous system (CNS).^{53,54} The NAS pregnenolone, progesterone, and deoxycorticosterone are pregnane steroid precursors.^{54,55} Allopregnanolone (3 α , 5 α -tetrahydroprogesterone), pregnanolone (3 α , 5 β -tetrahydroprogesterone), and tetrahydrodeoxycorticosterone are pregnane steroid metabolites.

Many NAS are positive allosteric modulators (PAMs) of the inhibitory GABA receptors (R), the ligand-gated and membrane-bound pentameric ion channels that allow or prevent passage of negatively-charged chloride ions into the postsynaptic membrane.^{56–58} Synaptic GABA_ARs contribute to low-affinity phasic inhibition, and extrasynaptic GABA_ARs contribute to high affinity tonic inhibition; these differences in function are accounted for by the particular subunits composing the receptor in addition to its location.^{59,60} GABA_ARs can bind barbiturates, benzodiazepines, general anesthetics, alcohol, and NAS in accordance with their subunit arrangement, composition, and location.⁶¹ Benzodiazepines interact with the abundant γ subunit types,⁶² particularly at α/γ interfaces,⁶³ but the presence of specific receptor subunits can render GABA_ARs unable to bind certain benzodiazepines.⁶⁴ NAS appear to bind primarily to the transmembrane α -subunit of GABA_ARs, with the $\alpha 2$ subunit potentially implicated in the anxiolytic effects of NAS,⁶⁵ although δ subunits play a large role in the overall sensitization of the receptor to NAS.⁶⁶ The homomeric $\rho 1$ GABA_ARs, currently understood to be largely insensitive to benzodiazepines and barbiturates, bind NAS.⁶⁷ As such, the complex pharmacology of GABA_ARs can only be understood in terms of its entire composition: binding properties arise from the interface of multiple subunits in addition to the composition of a specific subunit.⁶⁸ For these reasons, NAS studied as PPD pharmacotherapies should not be mistakenly assumed to be equivalent in mechanism or side effect profile to these other GABA_AR-binding psychoactive substances.

GABA_A R complexes in the brain are located in specific regions, circuits, and cells.⁶⁹ Therefore, in addition to subunit composition and phosphorylation, local steroid metabolism also contributes to the selectivity of the interactions between GABA_ARs and NAS.⁷⁰ The binding of NAS to GABA_ARs typically potentiates both synaptic and extrasynaptic receptors and results in increased GABA_A R surface expression.^{71,72} Both tonic and phasic GABAergic neurotransmission are modulated by

NAS, leading to changes in the excitatory–inhibitory balance of those specific networks.⁷³ NAS are critical in the regulation of the hypothalamic–pituitary–adrenal (HPA) axis during acute and chronic stress as well as nonstress conditions.^{74,75} One pathway that is important to the pathophysiology of PPD involves the hypothalamic paraventricular nucleus (PVN), an area of the brain involved in the neuroendocrine and autonomic response to stress; NAS affect the duration of stress-induced modulation of GABAergic transmission in the PVN.⁷⁶ In addition to integral action in the HPA axis, NAS have been shown to have anti-inflammatory and neurotrophic effects within the CNS.^{77,78} Multiple neuropsychiatric illnesses may involve the action of NAS,^{79–82} including PPD.^{83,84} Well-established research suggests that PPD involves a differential response of the stress steroid system as well as a differential (epi)genetic risk in serotonergic and GABAergic signaling which act as moderators or mediators between changes in the reproductive steroid system and clinical symptomatology.⁸⁵ Consequently, synthetic NAS and their analogs became a target of research as possible therapeutics.

Evidence for brexanolone as a treatment for PPD

Brexanolone (ZULRESSO) is the first FDA approved medication indicated for unipolar PPD. A soluble, intravenous preparation of synthetic allopregnanolone, brexanolone is a potent, selective, PAM of extrasynaptic and synaptic GABA_ARs.⁸⁶ It is administered as a 60-hour peripheral intravenous (IV) infusion through a programmable peristaltic infusion pump. The initial dosage is 30 $\mu\text{g}/\text{kg}/\text{hour}$ from hour 0 to 4, which is then increased to 60 $\mu\text{g}/\text{kg}/\text{hour}$ from hour 4 to 24, then increased again to 90 $\mu\text{g}/\text{kg}/\text{hour}$ from hour 24 to 52. At this time, a reduction in dosage to 60 $\mu\text{g}/\text{kg}/\text{hour}$ may be considered for women who do not tolerate 90 $\mu\text{g}/\text{kg}/\text{hour}$. During hour 52–56, the dosage is reduced to or continued at 60 $\mu\text{g}/\text{kg}/\text{hour}$, then reduced to 30 $\mu\text{g}/\text{kg}/\text{hour}$ during hour 56–60 hours, and finally the infusion is terminated at hour 60. The 60-hour infusion generally requires the preparation of five infusion bags with additional bags needed for women ≥ 90 kg.

Brexanolone has demonstrated rapid reduction of PPD symptoms in open-label⁸⁷ and placebo-controlled RCTs.^{32,33} The placebo-controlled trials were conducted in healthy women aged 18–45

who were within 6 months postpartum and had an onset of a major depressive episode no earlier than third trimester and no later than 4 weeks following delivery. Participants had moderate to severe depression as rated by the 17-item Hamilton Rating Scale for Depression (HAM-D₁₇)⁸⁸ total score ≥ 26 or 20–25 at study entry. Women entering the study were either antidepressant-free or were on a stable dose of a traditional antidepressant.

Subjects were randomized to receive placebo or brexanolone IV 90 $\mu\text{g}/\text{kg}/\text{hour}$ or 60 $\mu\text{g}/\text{kg}/\text{hour}$ for 60 hours. The primary outcome measure was the least-squares mean change in HAM-D₁₇ total score from baseline to hour 60. Safety, tolerability and depression severity were assessed through day 30. Across a range of disease severities, at hour 60, there were significantly larger mean reductions from baseline in HAM-D total scores with brexanolone IV 90 $\mu\text{g}/\text{kg}/\text{hour}$ (-17.0 ; $p < 0.001$) and brexanolone IV 60 $\mu\text{g}/\text{kg}/\text{hour}$ (-19.1 ; $p < 0.001$) *versus* placebo (-12.8). Significant differences from placebo were observed at hour 24 (both dose groups $p = 0.001$) and maintained through day 30 ($p \leq 0.021$).³² Post hoc analyses showed that depression remission (defined as HAM-D₁₇ total score ≤ 7) and response (defined as $\geq 50\%$ reduction in HAM-D₁₇ total score from baseline) rates were 50% *versus* 25% (brexanolone *versus* placebo) and 75% *versus* 55% (brexanolone *versus* placebo) at hour 60, respectively.

The most common adverse events reported in clinical trials with incidence $\geq 5\%$ and at least twice the rate of placebo were sedation/somnolence, dry mouth, loss of consciousness, and flushing/hot flush. Adverse events involving sedation and somnolence necessitated dose interruption or reduction in 5% of brexanolone-treated patients compared with 0% of placebo-treated patients. Four percent of the brexanolone-treated patients compared with 0% of the placebo-treated patients were reported to have loss of consciousness or altered state of consciousness during the infusion, with time to full recovery ranging from 15 to 60 minutes.³² Based on these adverse event reports, brexanolone is currently a Schedule IV medication with a black box warning for excessive sedation and sudden loss of consciousness. Infusion should be halted for any signs or symptoms of excessive sedation; it may be restarted after symptoms resolve with or without a dose reduction as clinically appropriate. In

the event of hypoxia or loss of consciousness, infusion should be stopped permanently.

Brexanolone is currently available only through a restricted risk evaluation and mitigation strategy (REMS) program to reduce the risk of serious adverse events. The REMS program ensures that brexanolone is administered in a medically supervised setting capable of providing monitoring, such as continuous pulse oximetry and assessment of sedation during awake periods, throughout the IV infusion, that health care settings and pharmacies involved in providing infusions are properly certified, that patients are informed of the risk for excessive sedation and sudden loss of consciousness and the necessity of monitoring for such symptoms during the infusion, and that patients are enrolled in a registry to monitor adverse events.

The terminal half-life of brexanolone is approximately 9 hours and it is extensively metabolized by non-CYP pathways including keto-reduction, glucuronidation and sulfation.⁸⁶ Brexanolone should not be used in patients with a hypersensitivity to allopregnanolone or other NAS and in patients with end stage renal disease with an estimated glomerular filtration rate (eGFR) $< 15 \text{ mL}/\text{minute}/1.73 \text{ m}^2$. As brexanolone is a GABA PAM, concurrent CNS depressants including benzodiazepines, opioids and alcohol should be used with caution. In placebo-controlled studies, a higher percentage of brexanolone-treated patients who used concomitant antidepressants reported sedation-related events.³²

Other neuroactive steroids in development for the treatment of PPD

Zuranolone is an oral, potent, selective extrasynaptic and synaptic GABA_AR PAM currently in clinical trials.^{89,90} A recent double-blind, placebo-controlled phase 3 trial randomized 153 participants to a 14 day course of zuranolone 30 mg or placebo.³⁴ Participants were then followed for 4 weeks. Participants receiving zuranolone had a significant reduction in least-squares mean HAM-D₁₇ total score *versus* those receiving placebo (-17.8 *versus* -13.6 , $p = 0.003$). In addition to efficacy for the primary endpoint of total score, significant differences in efficacy of zuranolone were observed at Day 3 ($p = 0.026$) and were sustained through Day 45 ($p = 0.003$). HAM-D₁₇ response (72% *versus* 48%, $p = 0.005$) and remission rates (45% *versus* 23%, $p = 0.012$) were significantly greater in the zuranolone group at Day 15, and

these significant differences were maintained through Day 45 (response $p=0.022$; remission $p=0.010$), 4 weeks after zuranolone cessation. The most common adverse events ($\geq 5\%$) reported in the zuranolone group were sedation, headache, somnolence, dizziness, upper respiratory tract infection, and diarrhea. One participant receiving zuranolone reported a transient confusional state with sedation on Day 3, which resolved within hours. Neither the active nor placebo group reported syncope or loss of consciousness. There is an ongoing randomized, double-blind placebo-controlled trial of oral zuranolone evaluating its efficacy in severe unipolar PPD (NCT04442503).

Ganaxolone, the 3β -methylated synthetic analog of allopregnanolone, is also in development for the treatment of unipolar PPD. Ganaxolone, like allopregnanolone, is an extrasynaptic and synaptic GABA_AR PAM, but it differs significantly in its lack of affinity for estrogen or progesterone receptors.⁹¹ Trials of ganaxolone have included both IV and oral formulations (NCT03460756; NCT03228394); however, published results are not yet available.

Safety of antidepressant pharmacotherapy use during lactation

The evidence on the safety of infant exposure to antidepressants during lactation largely consists of small observational studies. A variety of lactation safety indices have been used in the literature to estimate the amount of a drug transferred into breast milk. A systematic review comparing antidepressant excretion ratios into breast milk, derived from dividing the antidepressant concentration in breast milk by that in the maternal serum, found the highest ratios for venlafaxine, mianserin and escitalopram and the lowest ratios for reboxetine, trazodone and amoxapine.⁴⁷ The infant serum level of a drug is a more direct and accurate measure of infant exposure. In a pooled meta-analysis of 57 studies, the use of nortriptyline, paroxetine and sertraline during breastfeeding produced undetectable serum levels in more than 200 newborns, while fluoxetine, citalopram and the metabolite of venlafaxine, O-desmethylvenlafaxine, resulted in measurable but usually low levels in some infants.⁴⁸ This analysis indicated that while all antidepressants were detected in breast milk, they were not always spotted in infant serum.

The degree to which the concentration of medication found in breast milk and infant plasma

influences its lactation safety profile remains uncertain. Among SSRIs, while there is more data supporting the safety of sertraline⁴⁴ and paroxetine during lactation, a systematic review found that risk of infant exposure to this class through breast milk appears to be low.⁴³ In addition, while less breastfeeding safety data exists for SNRIs, the available data indicates that venlafaxine, desvenlafaxine and duloxetine are compatible with lactation.⁴³ Furthermore, TCAs may be used while breastfeeding since the infant exposure is low and serious side effects have not been observed, except doxepin.⁹² Nortriptyline is generally the preferred TCA for use with lactation due to its favorable safety profile.⁹² MAOIs are generally not used in breastfed infants given their potential adverse effects as insufficient data are available about their safety during lactation. Insufficient data are available regarding the safety of mirtazapine,⁴⁹ bupropion and serotonin modulators (trazodone, nefazodone and vilazodone) in breastfed infants. Nonspecific adverse effects to monitor for in nursing babies exposed to standard-of care antidepressants include sedation, sleep disturbance, irritability, and poor feeding.⁹³

Limited data indicate maternal use of transdermal estradiol up to a dose of 200 μg daily during lactation does not increase estradiol or estrone serum concentrations in breastfed infants or negatively impact infant growth;⁹⁴ however, it has been associated with an increased risk of impaired lactation.⁹⁵ Recent systematic reviews found that maternal use of progestin-only contraceptives does not adversely affect breast milk composition, lactation duration or the growth and development of breastfed infants.^{50,51}

For brexanolone, the maximum relative infant dose during infusion is between 1% and 2% of the maternal weight adjusted dosage.⁸⁶ A relative infant dose of $<10\%$ is considered acceptable in a healthy postnatal infant;⁹³ however, this parameter does not translate directly into bioavailability in the infant.

No studies of zuranolone or ganaxolone use during lactation resulted from our structured literature search.

Conclusion

There are a growing number of antidepressant pharmacotherapy studies in PPD. The recent novel therapeutic development of GABAergic NAS for

the treatment of PPD is a significant and exciting era in the field of PPD and other fields where NAS are under investigation, including post-traumatic stress disorder,⁹⁶ major depressive disorder⁹⁷ without peripartum onset, traumatic brain injury⁹⁸ and epilepsy.⁹⁹ When selecting an antidepressant, the clinician should consider factors including breastfeeding status, psychiatric diagnoses, current and past symptom severity, suicidal risk, past psychiatric history, prior and current psychiatric treatment efficacy and tolerability, medical comorbidities, family psychiatric history, patient treatment preference and ability to comply with the recommended treatment plan. Regarding use in lactation, the clinician must weigh the risks of infant drug exposure through breast milk with the risk of untreated maternal PPD. While limited high-quality data exist on antidepressant use during lactation, there is a consensus that the overwhelming benefits of treating PPD with antidepressants during lactation in most cases outweigh the low risks of antidepressant use while breastfeeding healthy, full-term infants. In addition, despite the varying levels of antidepressants found in breast milk and infant serum, the choice of antidepressant for a lactating woman should be based on her prior treatment history and potential adverse effects on the mother and infant.

Ideally, future novel PPD therapeutics should be fast-acting and offer shorter treatment duration. These properties will not only limit adverse events for the mother and her child, but also increase treatment adherence. Given the heterogeneous phenotypic presentation of PPD, future work should focus on determining which pharmacotherapeutic interventions, as well as other non-pharmacotherapeutic interventions not reviewed here, may preferentially benefit women with differing clinical presentations, thus personalizing care for the mother–infant dyad.

Acknowledgements

We acknowledge Janice Lester, MLS, the Reference and Education Librarian at the Health Science Library of Long Island Jewish Medical Center at Northwell Health for her assistance with the literature review search.

Author contributions

Yardana Kaufman: conceptualization, methodology, investigation, writing-original draft, writing-review and editing.

Sara V. Carlini: investigation, writing-original draft, writing-review and editing.

Kristina M. Deligiannidis: conceptualization, methodology, investigation, writing-original draft, writing-review and editing; supervision, funding acquisition.


Conflict of interest statement

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr Deligiannidis serves as a consultant to Sage Therapeutics, Inc, and Brie Biosciences, and reports grants awarded to Zucker Hillside Hospital/Feinstein Institutes for Medical Research during the conduct of the brexanolone injection and zuranolone clinical trials. Dr Deligiannidis received grants from the National Institutes of Health (NIH) and Vorso Corporation and royalties from an NIH employee invention outside of the submitted work. Drs Kaufman and Carlini have no conflicts of interest to declare.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: NIH grant (1R01MH120313) supported Dr Deligiannidis's time spent on writing and publication of this article.

ORCID iD

Kristina M. Deligiannidis  <https://orcid.org/0000-0001-7439-2236>

References

1. Bauman BL, Ko JY, Cox S, *et al.* Vital signs: postpartum depressive symptoms and provider discussions about perinatal depression – United States, 2018. *MMWR Morb Mort Wkly Rep* 2020; 69: 575–581.
2. Stowe ZN, Hostetter AL and Newport DJ. The onset of postpartum depression: implications for clinical screening in obstetrical and primary care. *Am J Obstet Gynecol* 2005; 192: 522–526.
3. Gavin NI, Gaynes BN, Lohr KN, *et al.* Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol* 2005; 106: 1071–1083.
4. APA. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, TX: American Psychiatric Association, 2013.
5. Gaynes BN, Gavin N, Meltzer-Brody S, *et al.* Perinatal depression: prevalence, screening

- accuracy, and screening outcomes. *Evid Rep Technol Assess (Summ)* 2005; 119: 1–8.
6. Stuart-Parrigon K and Stuart S. Perinatal depression: an update and overview. *Curr Psychiatry Rep* 2014; 16: 468.
 7. Putnam KT, Wilcox M, Robertson-Blackmore E, *et al.* Clinical phenotypes of perinatal depression and time of symptom onset: analysis of data from an international consortium. *Lancet Psychiatry* 2017; 4: 477–485.
 8. Cox EQ, Sowa NA, Meltzer-Brody SE, *et al.* The perinatal depression treatment cascade: baby steps toward improving outcomes. *J Clin Psychiatry* 2016; 77: 1189–1200.
 9. Field T. Postpartum depression effects on early interactions, parenting, and safety practices: a review. *Infant Behav Dev* 2010; 33: 1–6.
 10. Perry DF, Ettinger AK, Mendelson T, *et al.* Prenatal depression predicts postpartum maternal attachment in low-income Latina mothers with infants. *Infant Behav Dev* 2011; 34: 339–350.
 11. Dennis CL and McQueen K. The relationship between infant-feeding outcomes and postpartum depression: a qualitative systematic review. *Pediatrics* 2009; 123: e736–51.
 12. Tuovinen S, Lahti-Pulkkinen M, Girchenko P, *et al.* Maternal depressive symptoms during and after pregnancy and child developmental milestones. *Depress Anxiety* 2018; 35: 732–741.
 13. Leis JA, Heron J, Stuart EA, *et al.* Associations between maternal mental health and child emotional and behavioral problems: does prenatal mental health matter. *J Abnorm Child Psychol* 2014; 42: 161–171.
 14. Pearson RM, Evans J, Kounali D, *et al.* Maternal depression during pregnancy and the postnatal period risks and possible mechanisms for offspring depression at age 18 years. *JAMA Psychiatry* 2013; 70: 1312–1319.
 15. Lindahl V, Pearson JL and Colpe L. Prevalence of suicidality during pregnancy and the postpartum. *Arch Womens Ment Health* 2005; 8: 77–87.
 16. Knight MBK, Tuffnell D, Shakespeare J, *et al.* Saving Lives, improving mothers' care – lessons learned to inform maternity care from the UK and Ireland confidential enquiries into maternal deaths and morbidity 2016–18. Oxford: National Perinatal Epidemiology Unit, University of Oxford, 2020.
 17. Yonkers KA, Wisner KL, Stewart DE, *et al.* The management of depression during pregnancy: a report from the American Psychiatric Association and the American College of Obstetricians and Gynecologists. *General Hospital Psychiatry* 2009; 31: 403–413.
 18. Claridge AM. Efficacy of systemically oriented psychotherapies in the treatment of perinatal depression: a meta-analysis. *Arch Womens Ment Health* 2014; 17: 3–15.
 19. Sockol LE. A systematic review of the efficacy of cognitive behavioral therapy for treating and preventing perinatal depression. *J Affect Disord* 2015; 177: 7–21.
 20. O'Hara MW, Pearlstein T, Stuart S, *et al.* A placebo controlled treatment trial of sertraline and interpersonal psychotherapy for postpartum depression. *J Affect Disord* 2019; 245: 524–532.
 21. Milgrom J, Gemmill AW, Ericksen J, *et al.* Treatment of postnatal depression with cognitive behavioural therapy, sertraline and combination therapy: a randomised controlled trial. *Aust NZ J Psychiatry* 2015; 49: 236–245.
 22. Hantsoo L, Ward-O'Brien D, Czarkowski KA, *et al.* A randomized, placebo-controlled, double-blind trial of sertraline for postpartum depression. *Psychopharmacology* 2014; 231: 939–948.
 23. Bloch M, Meiboom H, Lorberblatt M, *et al.* The effect of sertraline add-on to brief dynamic psychotherapy for the treatment of postpartum depression: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2012; 73: 235–241.
 24. Sharp DJ, Chew-Graham CA, Tylee A, *et al.* A pragmatic randomised controlled trial to compare antidepressants with a community-based psychosocial intervention for the treatment of women with postnatal depression: the RESPOND trial. *Health Technol Assess* 2010; 14: iii–ivix.
 25. Yonkers KA, Lin H, Howell HB, *et al.* Pharmacologic treatment of postpartum women with new-onset major depressive disorder: a randomized controlled trial with paroxetine. *J Clin Psychiatry* 2008; 69: 659–665.
 26. Wisner KL, Hanusa BH, Perel JM, *et al.* Postpartum depression: a randomized trial of sertraline versus nortriptyline. *J Clin Psychopharmacol* 2006; 26: 353–360.
 27. Misri S, Reebye P, Corral M, *et al.* The use of paroxetine and cognitive-behavioral therapy in postpartum depression and anxiety: a randomized controlled trial. *J Clin Psychiatry* 2004; 65: 1236–1241.
 28. Appleby L, Warner R, Whitton A, *et al.* A controlled study of fluoxetine and cognitive-behavioural

- counselling in the treatment of postnatal depression. *Br Med J* 1997; 314: 932–936.
29. Chibanda D, Shetty AK, Tshimanga M, *et al.* Group problem-solving therapy for postnatal depression among HIV-positive and HIV-negative mothers in Zimbabwe. *J Int Assoc Provid AIDS Care* 2014; 13: 335–341.
 30. Wisner KL, Sit DKY, Moses-Kolko EL, *et al.* Transdermal estradiol treatment for postpartum depression: a pilot, randomized trial. *J Clin Psychopharmacol* 2015; 35: 389–395.
 31. Gregoire AJP, Kumar R, Everitt B, *et al.* Transdermal oestrogen for treatment of severe postnatal depression. *Lancet* 1996; 347: 930–933.
 32. Meltzer-Brody S, Colquhoun H, Riesenber R, *et al.* Brexanolone injection in post-partum depression: two multicentre, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet* 2018; 392: 1058–1070.
 33. Kaner S, Colquhoun H, Gunduz-Bruce H, *et al.* Brexanolone (SAGE-547 injection) in postpartum depression: a randomised controlled trial. *Lancet* 2017; 390: 480–489.
 34. Deligiannidis KM, Meltzer-Brody S, Gunduz-Bruce H, *et al.* Effect of zuranolone vs placebo in postpartum depression: a randomized clinical trial. *JAMA Psychiatry* 2021; 78: 951–959.
 35. Li HJ, Martinez PE, Li X, *et al.* Transdermal estradiol for postpartum depression: results from a pilot randomized, double-blind, placebo-controlled study. *Arch Womens Ment Health* 2020; 23: 401–412.
 36. Lawrie TA, Hofmeyr GJ, De Jager M, *et al.* A double-blind randomised placebo controlled trial of postnatal norethisterone enanthate: the effect on postnatal depression and serum hormones. *Br J Obstet Gynaecol* 1998; 105: 1082–1090.
 37. Singata-Madliki M, Hofmeyr GJ and Lawrie TA. The effect of depot medroxyprogesterone acetate on postnatal depression: a randomised controlled trial. *J Fam Plann Reprod Health Care* 2016; 42: 171–176.
 38. De Crescenzo F, Perelli F, Armando M, *et al.* Selective serotonin reuptake inhibitors (SSRIs) for post-partum depression (PPD): a systematic review of randomized clinical trials. *J Affect Disord* 2014; 152–154: 39–44.
 39. McDonagh MS, Matthews A, Phillip C, *et al.* Depression drug treatment outcomes in pregnancy and the postpartum period: a systematic review and meta-analysis. *Obstet Gynecol* 2014; 124: 526–534.
 40. Molyneaux E, Howard LM, McGeown HR, *et al.* Antidepressant treatment for postnatal depression. *Cochrane Database Syst Rev* 2014; 11: CD002018.
 41. Cooper MC, Kilvert HS, Hodgkins P, *et al.* Using matching-adjusted indirect comparisons and network meta-analyses to compare efficacy of brexanolone injection with selective serotonin reuptake inhibitors for treating postpartum depression. *CNS Drugs* 2019; 33: 1039–1052.
 42. Zheng W, Cai DB, Zheng W, *et al.* Brexanolone for postpartum depression: a meta-analysis of randomized controlled studies. *Psychiatry Res* 2019; 279: 83–89.
 43. Orsolini L and Bellantuono C. Serotonin reuptake inhibitors and breastfeeding: a systematic review. *Hum Psychopharmacol* 2015; 30: 4–20.
 44. Pinheiro E, Bogen DL, Hoxha D, *et al.* Sertraline and breastfeeding: review and meta-analysis. *Arch Womens Ment Health* 2015; 18: 139–146.
 45. Dennis CL, Ross LE and Herxheimer A. Oestrogens and progestins for preventing and treating postpartum depression. *Cochrane Database Syst Rev* 2008; 2008: CD001690.
 46. Lawrie TA, Herxheimer A and Dalton K. Oestrogens and progestogens for preventing and treating postnatal depression. *Cochrane Database Syst Rev* 2000; 2: CD001690.
 47. Schoretsanitis G, Westin AA, Stingl JC, *et al.* Antidepressant transfer into amniotic fluid, umbilical cord blood & breast milk: a systematic review & combined analysis. *Prog Neuropsychopharmacol Biol Psychiatry* 2021; 107: 110228.
 48. Weissman AM, Levy BT, Hartz AJ, *et al.* Pooled analysis of antidepressant levels in lactating mothers, breast milk, and nursing infants. *Am J Psychiatry* 2004; 161: 1066–1078.
 49. Smit M, Dolman KM and Honig A. Mirtazapine in pregnancy and lactation – a systematic review. *Eur Neuropsychopharmacol* 2016; 26: 126–135.
 50. Phillips SJ, Tepper NK, Kapp N, *et al.* Progestogen-only contraceptive use among breastfeeding women: a systematic review. *Contraception* 2016; 94: 226–252.
 51. Lopez LM, Grey TW, Stuebe AM, *et al.* Combined hormonal versus nonhormonal versus progestin-only contraception in lactation. *Cochrane Database Syst Rev* 2015; 3: CD003988.
 52. Sharma V and Sommerdyk C. Are antidepressants effective in the treatment of postpartum depression? A systematic review.

- Prim Care Companion CNS Disord* 2013; 15: PCC.13r01529.
53. Baulieu E-E. Steroid hormones in the brain: several mechanisms? In: Fuxe K, Gustafsson J-A and Wetterberg L (eds) *Steroid hormone regulation of the brain*. Oxford: Pergamon Press, 1981, pp. 3–14.
 54. Paul SM and Purdy RH. Neuroactive steroids. *FASEB J* 1992; 6: 2311–2322.
 55. Rupprecht R. Neuroactive steroids: mechanisms of action and neuropsychopharmacological properties. *Psychoneuroendocrinology* 2003; 28: 139–168.
 56. Callachan H, Cottrell GA, Hather NY, *et al.* Modulation of the GABAA receptor by progesterone metabolites. *Proc R Soc Lond B Biol Sci* 1987; 231: 359–369.
 57. Avoli M and Krnjević K. The long and winding road to gamma-amino-butyric acid as neurotransmitter. *Can J Neurol Sci* 2016; 43: 219–226.
 58. Parakala ML, Zhang Y, Modgil A, *et al.* Metabotropic, but not allosteric, effects of neurosteroids on GABAergic inhibition depend on the phosphorylation of GABA(A) receptors. *J Biol Chem* 2019; 294: 12220–12230.
 59. Semyanov A, Walker MC and Kullmann DM. GABA uptake regulates cortical excitability via cell type-specific tonic inhibition. *Nat Neurosci* 2003; 6: 484–490.
 60. Olsen RW and Sieghart W. International Union of Pharmacology. LXX. Subtypes of gamma-aminobutyric acid(A) receptors: classification on the basis of subunit composition, pharmacology, and function. Update. *Pharmacol Rev* 2008; 60: 243–260.
 61. Sieghart W. Allosteric modulation of GABAA receptors via multiple drug-binding sites. *Adv Pharmacol* 2015; 72: 53–96.
 62. Pritchett DB, Sontheimer H, Shivers BD, *et al.* Importance of a novel GABAA receptor subunit for benzodiazepine pharmacology. *Nature* 1989; 338: 582–585.
 63. Middendorp SJ, Hurni E, Schönberger M, *et al.* Relative positioning of classical benzodiazepines to the γ 2-subunit of GABAA receptors. *ACS Chem Biol* 2014; 9: 1846–1853.
 64. Hevers W and Lüddens H. The diversity of GABAA receptors. Pharmacological and electrophysiological properties of GABAA channel subtypes. *Mol Neurobiol* 1998; 18: 35–86.
 65. Durkin EJ, Muessig L, Herlt T, *et al.* Brain neurosteroids are natural anxiolytics targeting α 2 subunit γ -aminobutyric acid type-A receptors. *bioRxiv*, 2018, <https://www.biorxiv.org/node/139737.full>
 66. Bellelli D, Hogenkamp D, Gee KW, *et al.* Realising the therapeutic potential of neuroactive steroid modulators of the GABA(A) receptor. *Neurobiol Stress* 2020; 12: 100207.
 67. Eaton MM, Lim YB, Covey DF, *et al.* Modulation of the human ρ 1 GABAA receptor by inhibitory steroids. *Psychopharmacology* 2014; 231: 3467–3478.
 68. Miller PS, Scott S, Masiulis S, *et al.* Structural basis for GABA(A) receptor potentiation by neurosteroids. *Nat Struct Mol Biol* 2017; 24: 986–992.
 69. Engin E, Benham RS and Rudolph U. An emerging circuit pharmacology of GABA(A) receptors. *Trends Pharmacol Sci* 2018; 39: 710–732.
 70. Castellano D, Shepard RD and Lu W. Looking for novelty in an ‘Old’ receptor: recent advances toward our understanding of GABA(A)Rs and their implications in receptor pharmacology. *Front Neurosci* 2020; 14: 616298.
 71. Jacob TC, Moss SJ and Jurd R. GABA(A) receptor trafficking and its role in the dynamic modulation of neuronal inhibition. *Nat Rev Neurosci* 2008; 9: 331–343.
 72. Abramian AM, Comenencia-Ortiz E, Modgil A, *et al.* Neurosteroids promote phosphorylation and membrane insertion of extrasynaptic GABAA receptors. *Proc Natl Acad Sci USA* 2014; 111: 7132–7137.
 73. Stell BM, Brickley SG, Tang CY, *et al.* Neuroactive steroids reduce neuronal excitability by selectively enhancing tonic inhibition mediated by delta subunit-containing GABAA receptors. *Proc Natl Acad Sci USA* 2003; 100: 14439–14444.
 74. Sarkar J, Wakefield S, MacKenzie G, *et al.* Neurosteroidogenesis is required for the physiological response to stress: role of neurosteroid-sensitive GABA A receptors. *J Neurosci* 2011; 31: 18198–18210.
 75. Crowley SK and Girdler SS. Neurosteroid, GABAergic and hypothalamic pituitary adrenal (HPA) axis regulation: what is the current state of knowledge in humans. *Psychopharmacology* 2014; 231: 3619–3634.
 76. Herman JP and Cullinan WE. Neurocircuitry of stress: central control of the hypothalamo-

- pituitary-adrenocortical axis. *Trends Neurosci* 1997; 20: 78–84.
77. Diotel N, Charlier TD, Lefebvre d’Hellencourt C, *et al.* Steroid transport, local synthesis, and signaling within the brain: roles in neurogenesis, neuroprotection, and sexual behaviors. *Front Neurosci* 2018; 12: 84.
 78. Murugan S, Jakka P, Namani S, *et al.* The neurosteroid pregnenolone promotes degradation of key proteins in the innate immune signaling to suppress inflammation. *J Biol Chem* 2019; 294: 4596–4607.
 79. Butterfield MI, Stechuchak KM, Connor KM, *et al.* Neuroactive steroids and suicidality in posttraumatic stress disorder. *Am J Psychiatry* 2005; 162: 380–382.
 80. Guille C, Spencer S, Cavus I, *et al.* The role of sex steroids in catamenial epilepsy and premenstrual dysphoric disorder: implications for diagnosis and treatment. *Epilepsy Behav* 2008; 13: 12–24.
 81. Bäckström T, Haage D, Löfgren M, *et al.* Paradoxical effects of GABA-A modulators may explain sex steroid induced negative mood symptoms in some persons. *Neuroscience* 2011; 191: 46–54.
 82. Luchetti S, Bossers K, Van de Bilt S, *et al.* Neurosteroid biosynthetic pathways changes in prefrontal cortex in Alzheimer’s disease. *Neurobiol Aging* 2011; 32: 1964–1976.
 83. Schiller CE, Schmidt PJ and Rubinow DR. Allopregnanolone as a mediator of affective switching in reproductive mood disorders. *Psychopharmacology* 2014; 231: 3557–3567.
 84. Deligiannidis KM, Kroll-Desrosiers AR, Tan Y, *et al.* Longitudinal proneuroactive and neuroactive steroid profiles in medication-free women with, without and at-risk for perinatal depression: a liquid chromatography-tandem mass spectrometry analysis. *Psychoneuroendocrinology* 2020; 121: 104827.
 85. Schweizer-Schubert S, Gordon JL, Eisenlohr-Moul TA, *et al.* Steroid hormone sensitivity in reproductive mood disorders: on the role of the GABA(A) receptor complex and stress during hormonal transitions. *Front Med* 2020; 7: 479646.
 86. Zulresso (brexanolone) injection [package insert]. Cambridge, MA: Sage Therapeutics, 2019.
 87. Kanes SJ, Colquhoun H, Doherty J, *et al.* Open-label, proof-of-concept study of brexanolone in the treatment of severe postpartum depression. *Hum Psychopharmacol* 2017; 32: e2576.
 88. Shear MK, Vander Bilt J, Rucci P, *et al.* Reliability and validity of a structured interview guide for the Hamilton Anxiety Rating Scale (SIGH-A). *Depress Anxiety* 2001; 13: 166–178.
 89. MartinezBotella G, Salituro FG, Harrison BL, *et al.* Neuroactive steroids. 2. 3 α -hydroxy-3 β -methyl-21-(4-cyano-1h-pyrazol-1’-yl)-19-nor-5 β -pregnan-20-one (SAGE-217): a clinical next generation neuroactive steroid positive allosteric modulator of the (Γ -Aminobutyric Acid)(A) receptor. *J Med Chem* 2017; 60: 7810–7819.
 90. Althaus AL, Ackley MA, Belfort GM, *et al.* Preclinical characterization of zuranolone (SAGE-217), a selective neuroactive steroid GABA(A) receptor positive allosteric modulator. *Neuropharmacology* 2020; 181: 108333.
 91. Bialer M, Johannessen SI, Levy RH, *et al.* Progress report on new antiepileptic drugs: a summary of the thirteenth Eilat conference on new antiepileptic drugs and devices (EILAT XIII). *Epilepsia* 2017; 58: 181–221.
 92. Gentile S. Tricyclic antidepressants in pregnancy and puerperium. *Expert Opin Drug Saf* 2014; 13: 207–225.
 93. Newton ER and Hale TW. Drugs in breast milk. *Clin Obstet Gynecol* 2015; 58: 868–884.
 94. Pinheiro E, Bogen DL, Hoxha D, *et al.* Transdermal estradiol treatment during breastfeeding: maternal and infant serum concentrations. *Arch Womens Ment Health* 2016; 19: 409–413.
 95. Moses-Kolko EL, Berga SL, Kalro B, *et al.* Transdermal estradiol for postpartum depression: a promising treatment option. *Clin Obstet Gynecol* 2009; 52: 516–529.
 96. Rasmusson AM, Marx CE, Jain S, *et al.* A randomized controlled trial of ganaxolone in posttraumatic stress disorder. *Psychopharmacology* 2017; 234: 2245–2257.
 97. Gunduz-Bruce H, Silber C, Kaul I, *et al.* Trial of SAGE-217 in Patients with major depressive disorder. *N Engl J Med* 2019; 381: 903–911.
 98. Stein DG and Sayeed I. Repurposing and repositioning neurosteroids in the treatment of traumatic brain injury: a report from the trenches. *Neuropharmacology* 2019; 147: 66–73.
 99. Sperling MR, Klein P and Tsai J. Randomized, double-blind, placebo-controlled phase 2 study of ganaxolone as add-on therapy in adults with uncontrolled partial-onset seizures. *Epilepsia* 2017; 58: 558–564.