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New Approaches to Postpartum Depression: GABA-A Receptor Positive Allosteric Modulators

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New Approaches to Postpartum Depression: GABA-A Receptor Positive Allosteric Modulators

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Abstract

Introduction: Postpartum depression (PPD) is a globally prevalent disorder that is characterized by the onset of depressive symptoms during the peripartum period. The pathophysiology of this disease is still very unclear; however, it seems to be related to the hormonal fluctuations that occur during this period and the consequent dysfunction of the γ -aminobutyric acid (GABA) signaling, in genetically susceptible women. PPD causes significant functional impairment and can have a detrimental impact on the well-being of both the mother and the infant, with potentially enduring consequences. Accordingly, an early diagnosis, by resorting to the valid screening tools available, and a treatment with a quick and effective response are crucial to minimize the negative outcomes of this disease.

Objectives: The aim of this review is to evaluate the available therapeutic options for postpartum depression, while compiling and summarizing available data concerning the efficacy, tolerability and clinical application of brexanolone and zuranolone in the treatment of PPD. Furthermore, this thesis intends to promote a reflection on the advantages and the limitations of the GABA-A receptor positive allosteric modulators and their potential importance in the future treatment of psychiatric disorders.

Methods: To elaborate this dissertation, the research and selection of scientific articles were carried out through the PubMed database. They were based on the keywords mentioned below and comprehended articles written in English and in Portuguese, published between January 2014 and April 2024. Complementary bibliography was also included by manual research.

Discussion: While in mild to moderate PPD the first-line treatment is psychotherapy, in severe episodes, pharmacotherapy is recommended. The traditionally prescribed antidepressants fall short to accomplish a satisfactory response when treating PPD, because of their late onset of action, mediocre rates of remission and lack of fast improvement in suicidality. Recently, the US Food and Drug Administration (FDA) has given approval, specifically, for the treatment of PPD to the first two drugs: brexanolone (administered by intravenous infusion) and zuranolone (administered orally). Acting by enhancing the inhibitory activity of the GABA-A receptors, these neuroactive steroids have shown promising results in previous clinical trials, demonstrating a quick onset of action, high response rates, great tolerability and a good safety profile while breastfeeding.

Conclusion: Although brexanolone and zuranolone have obvious and useful advantages, further investigation is needed to evaluate their long-term safety and efficacy and to compare them with

the previously prescribed antidepressants. Major drawbacks of these neuroactive steroids include the potential risks of harming the fetus when used in pregnant women and the sedation associated with their administration.

Keywords: Postpartum Depression; Treatment; Antidepressive Agents; GABA modulators; Brexanolone; Zuranolone; Allopregnanolone.

Resumo

Introdução: A depressão pós-parto é um distúrbio globalmente prevalente que se caracteriza pelo surgimento de sintomas depressivos no período perinatal. A sua fisiopatologia ainda não está totalmente esclarecida; no entanto, parece estar relacionada com as flutuações hormonais que ocorrem no período perinatal e com a consequente disfunção da sinalização GABAérgica, em mulheres geneticamente suscetíveis. A depressão pós-parto causa disfunção significativa e pode ter um impacto negativo no bem-estar da mãe e do recém-nascido, com consequências potencialmente duradouras. Desta forma, um diagnóstico precoce, com recurso a ferramentas de rastreio validadas, e um tratamento com resposta rápida e eficaz são cruciais para melhorar o prognóstico desta patologia.

Objetivos: O objetivo desta revisão consiste em avaliar as opções terapêuticas disponíveis para a depressão pós-parto, fazendo uma compilação da informação disponível relativamente à eficácia, tolerância e aplicação clínica da brexanolona e da zuranolona. Para além disso, esta dissertação pretende promover a reflexão quanto às vantagens e limitações dos moduladores alostéricos positivos do recetor GABA-A e à sua potencial importância no tratamento de distúrbios psiquiátricos no futuro.

Metodologia: Para elaborar esta dissertação, procedeu-se à pesquisa e seleção de artigos científicos através da base de dados PubMed. Foram baseadas nas palavras-chave referidas de seguida e abrangeram artigos escritos em inglês e em português, publicados entre janeiro de 2014 e abril de 2024. Foi também incluída bibliografia complementar, pesquisada manualmente.

Discussão: Enquanto que, na depressão pós-parto leve a moderada, a primeira linha de tratamento é a psicoterapia, em episódios severos, está recomendada farmacoterapia. Os antidepressivos tradicionalmente prescritos não apresentam uma resposta satisfatória no tratamento desta patologia, devido ao seu início de ação tardio, taxas de remissão medíocres e ausência de uma rápida melhoria dos comportamentos suicidas. Recentemente, a FDA aprovou, especificamente para o tratamento da depressão pós-parto, os primeiros dois fármacos: brexanolona (administrada intravenosamente) e zuranolona (administrada por via oral). Estes fármacos, cuja ação aumenta a atividade inibitória dos recetores GABA-A, mostraram resultados promissores, com um rápido início de ação, elevadas taxas de resposta, tolerância razoável e um bom perfil de segurança na amamentação.

Conclusão: Ainda que a brexanolona e a zuranolona apresentem vantagens bastante óbvias, é necessária investigação adicional para avaliar a sua eficácia e segurança a longo prazo e para as

comparar com os antidepressivos previamente existentes. As suas maiores limitações são o potencial risco de causar danos no feto, quando administrados em mulheres grávidas, e a sedação associada à sua toma.

Palavras-chave: Depressão Pós-parto; Tratamento; Agentes Antidepressivos; Moduladores GABA; Brexanolona; Zuranolona; Alopregnanolona.

Abbreviation List

AP – Allopregnanolone

CBT – Cognitive Behavioral Therapy

CNS – Central Nervous System

CYP3A4 – Cytochrome P450 3A4

DSM-5 – Diagnostic and Statistical Manual of Mental Disorders – fifth edition

ECT – Electroconvulsive Therapy

eGFR – Estimated Glomerular Filtration Rate

EMA – European Medicines Agency

EPDS – Edinburgh Postnatal Depression Scale

FDA – Food and Drug Administration

GABA – γ -Aminobutyric Acid

HAM-D – Hamilton Rating Scale for Depression

HPA – Hypothalamic-Pituitary-Adrenal

ICD-11 – International Classification of Diseases – eleventh revision

IPT – Interpersonal Psychotherapy

MAOIs – Monoamine Oxidase Inhibitors

MDD – Major Depressive Disorder

PAM – Positive Allosteric Modulator

PPD – Postpartum Depression

PRIME – Priority Medicines

REMS – Risk Evaluation and Mitigation Strategy

SNRIs – Serotonin and Norepinephrine Reuptake Inhibitors

SSRIs – Selective Serotonin Reuptake Inhibitors

TCAs – Tricyclic Antidepressants

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Introduction

According to the Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-5), Postpartum Depression (PPD) is defined as a major depressive disorder (MDD) with peripartum onset, occurring during pregnancy or in the 4 weeks following delivery. On the other hand, the International Classification of Diseases – eleventh revision (ICD-11) requires that the episode starts within 6 weeks of delivery and some authors even consider a bigger time frame, up to 12 months after childbirth.¹⁻⁸

1. Epidemiology and Risk Factors

Globally, PPD affects 10 to 20 percent of women who have given birth,⁹⁻¹² although this disease is often underdiagnosed due to lack of provider's awareness, barriers to access health care and negative social stigma.^{7,10,11,13} According to a population-based study published in 2011, the prevalence of PDD in Portugal from birth to the third month postpartum is 11.7%, using DSM - fourth edition diagnostic criteria, and 16.6%, using ICD - tenth revision diagnostic criteria.¹⁴

Multiple risk factors for PPD were identified. A prior history of perinatal or nonperinatal depression is one of the factors that most increases the likelihood of having PPD, for instance, women with previous history of PPD have 50% chance of going through it again in a future pregnancy.^{6,8,15} Other risk factors include: stressful life events (such as marital conflict or emigration); lack of social and financial support; mother age under 25 or over 35; low self-esteem; single marital status; intimate partner violence or history of physical or sexual abuse; unwanted pregnancy; fear of childbirth; multiparity; poor perinatal health (for example, gestational diabetes or obesity); adverse pregnancy or neonatal outcomes (such as stillbirth, preterm birth or very low birth weight); breastfeeding difficulties; childcare stress (including difficult infant temperament and inconsolable infant crying); delivery during the time of the year when daylight is diminished; postpartum blues symptoms; family history of PPD or any psychiatric disease; history of premenstrual syndrome or premenstrual dysphoric disorder; perinatal anxiety or sleep disorders.^{3,8,10,13,15-17}

2. Pathophysiology

The mechanisms underlying the development of PDD remain unclear,^{8,9,13,18-20} as well as to what degree the pathogenesis of PPD differs from the pathogenesis of nonperinatal depression.⁸ However, it is generally believed that the pathophysiology of PPD is multifactorial, including hormonal fluctuations during pregnancy, γ-aminobutyric acid signaling (GABA) signaling

dysfunction, genetic susceptibility, epigenetic changes and neuroinflammatory responses as well as environmental factors, such as social problems and stressful life events.^{8,11,13,19–22}

The perinatal period is marked by significant changes in the serum concentration of the reproductive hormones. During the third trimester of pregnancy, the levels of estrogen and progesterone increase by 10 to 50-fold, compared to the normal levels before pregnancy.^{23–25} After childbirth and placental expulsion, these hormone levels decrease abruptly.^{23–25} Allopregnanolone (AP), also known as $3\alpha,5\alpha$ -tetrahydroprogesterone, is a progesterone metabolite (synthesized in the central nervous system (CNS), corpus luteum and placenta) and a neuroactive steroid that is thought to act on the GABA-A receptor as a Positive Allosteric Modulator (PAM).^{11,25–28} GABA-A receptors are pentameric channels composed by a combination of up to 19 identified subunits ($\alpha 1$ -6, $\beta 1$ -3, $\gamma 1$ -3, $\rho 1$ -3, δ , ϵ , θ and π).^{10,26,29–31} When GABA binds to this receptor, a chloride channel opens and allows selective permeability of the chloride ion, which causes cell hyperpolarization and can lead to two different types of inhibition, depending on the location and composition of the receptor: if it is a synaptic receptor, there is phasic inhibition, which is transient and intense; if it is an extrasynaptic receptor, the inhibition is tonic, which is more sustained but less intense.^{10,21,28,30–34} Although it can bind to different GABA-A receptor subtypes, AP acts preferentially on δ -containing receptors, only found at extrasynaptic sites, meaning AP is mostly responsible for tonic inhibition.^{7,10,26,30,32,35–37} In contrast to the synaptic receptors, extrasynaptic receptors can be activated by low concentrations of GABA and neurosteroids.^{20,26} In addition to being a PAM of this receptors, AP can also have metabotropic effects on GABAergic inhibition through the activation of the G protein-coupled membrane progesterone receptors, leading to an higher cell surface expression of GABA-A receptors and, therefore, a sustained elevation in tonic current.³¹ GABAergic neurons are found in areas of the CNS that are associated with regulating mood, emotions, memory, cognitive abilities, sleep, motivation and decision-making, therefore, AP is considered to act as a neuroprotector, with antidepressant, antistress, anxiolytic and sedative effects.^{26,31,36,38,39}

During the peripartum period, AP levels fluctuate alongside progesterone levels.^{11,13,26,28,32,40,41} Multiple pieces of evidence confirmed that changes in GABAergic signal transduction and neuroactive steroid concentrations were related to the pathogenesis of PPD. Firstly, decreased levels of AP in the peripheral blood and cerebrospinal fluid have been associated with an increased risk of developing PPD^{18,21,32,41–43} and antidepressant therapy has been shown to elevate AP levels.^{7,26,42,44} However, low AP levels have not been consistently demonstrated in women with PPD.^{10,13,27,39,45} It is thought that the rapid decline of the AP level after childbirth may represent a trigger in women with greater sensibility to the fluctuation of the neurosteroid levels, likely due to

genetic vulnerability.^{7,19,23,34,40,44,46,47} During pregnancy, the increasing levels of AP cause a compensatory down-regulation of the GABA-A receptors, which is usually followed by an up-regulation after childbirth.^{7,13,30,32,39} This physiological compensation may be impaired in women who suffer from PPD, which leads to a failure in the adaptation of GABA-A receptors and to a disruption in GABA signaling.^{7,11,20,30–32,39,41,42,45,48}

Additionally, alterations in the hypothalamic-pituitary-adrenal (HPA) axis have been implied in the pathogenesis of PPD, since there is a rise in the cortisol secretion during pregnancy followed by its marked reduction and hypofunction of the HPA axis after childbirth.^{13,44,49} Although there have been conflicting findings about the absolute changes of the stress hormone levels, the contribution of this axis to the development of PPD is undeniable, being related to the psychological stressors and the increased sensitivity to such stressors, which are important risk factors for PPD.^{10,13,41,44,48} Δ -containing GABA-A receptors are also responsible for controlling corticotropin-releasing neurons and, therefore, regulating the HPA axis.^{13,23,24,26,27,31,40,44,49}

The reproductive hormones and the neuroactive steroids may also interfere with the immune system, by exerting anti-inflammatory actions,^{7,19,46} and with the regulation of neurotransmitters, such as serotonin, dopamine, norepinephrine and glutamate.^{8,12,23,31,39,46}

Genetic differences and epigenetic changes have also been implicated in the pathophysiology of PPD, predisposing women to the impairment of GABA signaling. Studies have shown that the contribution of genetic factors for PPD was close to 40 percent.^{8,44} Genetic studies identified some genetic variations in patients with PPD, such as in the kynurenine-3-monooxygenase.²⁰ Epigenetic changes, such as the estrogen-induced epigenetic DNA methylation, also appear to increase susceptibility to PPD.^{5,19}

3. Clinical Presentation

The clinical presentation of PPD varies largely according to the severity of the symptoms and the time of onset. The common signs and symptoms of PPD are similar to those that occur in MDD outside postpartum period.^{8,13,17} Depressed mood, ranging from subjective changes, such as sadness, irritability, anxiety or frustration to an important functional impairment and suicidal ideation, may be present in women suffering from PPD.^{8,13} This condition can also present with loss of interest or pleasure in previous enjoyable activities, lack of energy, changes in appetite or weight, sleep disturbances and neurocognitive dysfunction with impaired ability to concentrate and make decisions.^{8,16,17} Additionally, women with PPD can exhibit ruminative thoughts, feelings of worthlessness or excessive guilt and persistent doubts about their capacity to look after their offspring.^{7,8,17,34}

PPD can also give rise to somatic symptoms, such as changes in sleep, appetite and energy level, which can be difficult to distinguish from normal changes that occur in postpartum women that are not depressed. Therefore, these symptoms should be assessed taking into account their severity and the context in which they occur.⁸

Comorbid psychiatric illness, such as anxiety, eating and obsessive-compulsive disorders, are common and frequently associated with higher symptom severity and increased treatment resistance.^{8,11,50}

The course of illness is uncertain since PPD may resolve spontaneously without treatment, improve after therapy or evolve into a persistent depressive disorder. In 30 to 50 percent of the patients, the episode of PPD lasts for at least one year.^{4,8}

4. Adverse Consequences

PPD can have a detrimental impact on the well-being of both the mother and the infant, with enduring consequences.^{4,10}

When the onset occurs during pregnancy, it is associated with adverse pregnancy outcomes, such as preterm delivery and infant low birth weight, and an increased risk of preeclampsia, gestational diabetes and maternal substance abuse.^{13,50,51}

Adverse outcomes for the mother may include marital discord, social isolation and impaired bonding with the infant.¹⁵ Moreover, if left untreated or undiagnosed, PPD increases the risk of maternal suicide, which is the leading cause of death in postnatal women, occurring in approximately 1 to 5 per 100000 live births.^{8,15} Additionally, PPD can cause ruminative thoughts about harming the baby, that are perceived as scary, unacceptable and intrusive. These symptoms should motivate an evaluation for psychotic syndromes, since rumination with intent is typical of postpartum psychosis. However, infanticide is rare and frequently followed by maternal suicide attempt.^{8,50}

On the other hand, PPD can have serious consequences for the infants, including poor health and nutrition, since the woman's ability to take care of the baby is impaired. Mothers with PPD are less likely to discuss their problems with their healthcare providers, to properly position their infants to sleep, to take their children to receive vaccinations and to fulfill safety practices, such as using infant car seats.^{8,11,12,18} PPD can also impact breastfeeding, being associated with lower rates and decreased duration compared to mothers who don't suffer from this disorder, due to the development of negative feelings toward nurturing the offspring this way.^{8,18} Furthermore, PPD has been reported to interfere with the infant's cognitive, neuropsychological and emotional

development, causing developmental delays, insecure or disorganized attachment to the mother and abnormal emotional regulation and social behavior.^{8,10,18} Cognitive impairment of the offspring is frequently associated with PPD and encompasses dysfunction in the general performance, language development, intelligence and executive functioning.^{8,51} Additionally, PPD increases the risk of infants developing psychiatric disorders, from childhood through adulthood, namely depression, anxiety, attention deficit hyperactivity disorder, conduct disorder (presenting with rule-breaking and aggressive behaviors) and oppositional defiant disorder (presenting with an angry and irritable mood).^{8,52}

At last, PPD can also have a significant impact on the partner of the mother, leading to paternal depression and paternal stress.^{15,41}

5. Screening

Consensus guidelines recommend primary care clinicians to screen for depression at least twice, during the pregnancy and the postpartum period, since PPD is a serious, prevalent and treatable disease, with valid screening tools available.^{8,11,53,54} According to the Portuguese national program for the surveillance of pregnancy, this screening should be applied between the 14th and the 16th week of pregnancy and the 4th and 6th week postpartum.⁵³ The screening should be carried in places that guarantee follow-up for diagnosis and treatment.⁸ Patients can also be taught to recognize the first symptoms of PPD, in order to promote earlier diagnosis and faster treatment response.⁸

The most widely used screening test is the Edinburgh Postnatal Depression Scale (EPDS)⁵⁵ (Annex 1), which is a very practical ten-item self-report scale that can be completed in less than 5 minutes.^{4,8,50} The scale takes into account both depressive and anxious symptoms and doesn't include items asking about somatic symptoms that are commonly experienced by postpartum women who are not depressed (for example, changes in sleep and appetite or fatigue), increasing the specificity of this screening tool.^{4,8,15} The answers to items are scored from 0 to 3, with a maximum score of 30. In Portugal, the cutoff used is 12, which means that if the score is equal or greater than this, the woman is very likely to suffer from depression.^{15,53} The last item evaluates suicidal ideation, that should be addressed independently.¹⁵

Other validated screening tools include the self-report two-item and the nine-item Patient Health Questionnaire, the Beck Depression Inventory and the Hamilton Rating Scale for Depression (HAM-D)⁵⁶ (Annex 2), which is a scale with different versions that also evaluates the severity of the depression, despite not being specific for PPD.^{4,8,10,15}

If the screening is positive, either by applying a screening instrument or by asking a few clinical questions, the patients should be evaluated through a clinical interview in order to confirm the diagnosis.^{6,8,15} This evaluation should comprehend the characterization of the symptoms and the impairment caused by the disease, the complete personal and family history and the assessment of substance abuse and comorbid symptoms, such as anxiety or panic. The presence of symptoms of mania or psychosis should be ruled out, as well as signs and symptoms of alternative causes, such as hypothyroidism.^{8,15} Suicidal ideation should be addressed and identification of imminent risk should prompt immediate psychiatric care.^{8,15}

6. Diagnosis

The diagnosis of PPD is based on the DSM-5 diagnostic criteria for MDD, which requires the presence of 5 or more of the following symptoms during the same two week period: (1) depressed mood, (2) markedly diminished interest or pleasure in all, or almost all, activities - at least one of the two previous symptoms must be present -, (3) significant weight loss or gain, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feeling of worthlessness or excessive inappropriate guilt, (8) indecisiveness or reduced ability to think or concentrate, (9) recurrent thoughts of death or suicidal ideation. Additionally, symptoms must cause significant distress or impairment in social, occupational or other important areas of functioning, be unrelated to the physiological effects of a substance or medical condition and be unexplained by schizophrenia or other psychotic disorder. The patient shouldn't have had any prior manic or hypomanic episode. Lastly, the episode must occur during the peripartum period, described above.¹

Objectives

After this review of the most relevant characteristics of PPD, this dissertation has the following objectives:

- Reviewing the available therapeutic options for PPD, including psychotherapy, pharmacotherapy and neuromodulation techniques;
- Promoting knowledge about the mechanism of action and pharmacological properties of GABA-A receptor PAMs;
- Compiling and summarizing available data concerning the efficacy and tolerability of brexanolone and zuranolone in the treatment of PPD, including their safety while breastfeeding;
- Providing insight into the current clinical orientations regarding the use of brexanolone and zuranolone in women with PPD;
- Promoting a reflection on the advantages and the limitations of the GABA-A receptor PAMs and their potential importance in the future treatment of psychiatric disorders.

Methods

To elaborate this dissertation, the research and selection of scientific articles were carried out through the PubMed database. The research comprehended articles written in English and in Portuguese and published between January 2014 and April 2024. The following keywords were used: “postpartum depression”, “treatment”, “antidepressive agents”, “GABA modulators”, “brexanolone”, “zuranolone”, “allopregnanolone”. The initial selection of articles was executed based on the title and the abstract, according to the following inclusion and exclusion criteria.

The inclusion criteria enclosed: (1) articles concerning the epidemiology, the pathophysiology and the clinical management of PPD; (2) articles concerning the mechanism of action and the pharmacological properties of GABA-A receptor PAMs; and (3) articles concerning the use of brexanolone and zuranolone in the treatment of PPD. The exclusion criteria included: (1) articles only regarding other psychiatric disorders, such as MDD or menstrual dysfunction disorder; (2) articles focusing on other experimental treatments for PPD besides the GABA-A receptor PAMs; (3) articles without an abstract; and (4) articles whose full-text version wasn't available online.

Complementary bibliography, such as diagnostic criteria, prescribing information and clinical guidelines, was also included by manual research.

From a total of 242 articles, based on the selection criteria, 160 were excluded from this review. Ultimately, including the results from manual research (16 articles), 98 articles were considered relevant for the elaboration of this thesis.

Discussion

1. Management

Treating PPD requires a comprehensive and multidisciplinary approach, ranging from psychotherapy and psychosocial strategies to pharmacological and neuromodulatory interventions, depending on the severity of the disease.^{15,17,19,26,33,46,47,57–59}

According to the expressed symptoms and their severity, PPD can be classified in mild, moderate and severe.^{18,19,60} Mild to moderate episodes manifest through five or six depressive symptoms, not being associated with marked social and functional impairment, suicidal behaviors or other complications such as psychotic features.^{19,60} On the other hand, severe episodes are defined by the presence of seven to nine depressive symptoms, can be associated with the features mentioned above and frequently require referral to a psychiatrist or hospitalization.^{60,61} By using EPDS, mild, moderate and severe episodes of PPD can be empirically defined as an average score of 11, 15 and 20, respectively.⁶⁰

In mild to moderate episodes of PPD, the recommended first-line treatment is psychotherapy, progressing to pharmacotherapy if the response is insufficient.^{18,46,60,62} In patients with severe PPD, pharmacotherapy is indicated, alone or in combination with psychotherapy.^{18,46,58,61–63} Neuromodulation is also a therapeutic option in certain cases of severe PPD.⁶¹ Adjunctive therapies, including psychosocial strategies and other psychotropic medications to treat comorbidities, can also be prescribed, depending on each patient.^{19,61}

1.1 Psychotherapy

Different types of psychotherapy have been applied to the treatment of PPD, with a proved positive effect on parental adjustment, child behavior and infants nurturing.¹⁹ This approach is approved for woman with mild to moderate episodes of PPD, in combination with pharmacotherapy for woman with severe episodes of PPD and for patients who are not interested in receiving pharmacological treatment, most frequently due to the risk of infant's exposure to antidepressant through breastfeeding.^{4,50,51,61} In fact, this therapy has no impact on breastfeeding and no adverse effects on the mother or the infant.⁶³

One of the best-studied techniques is cognitive behavioral therapy (CBT) that intends to develop better emotional control and coping strategies to overcome current daily difficulties.^{15,33,60} Behavioral activation is one of the skills of CBT used to treat PPD, by encouraging the participation in positive and rewarding activities in order to improve the woman's mood and diminish

avoidance behaviors.⁶⁰ On the other hand, interpersonal psychotherapy (IPT) focuses on fixing interpersonal relationships or circumstances in order to relieve the woman's symptoms and improve interpersonal functioning.^{15,33,60} CBT and IPT are the psychotherapies with more evidence of their efficacy in the treatment of PPD, reducing depressing symptoms and improving the overall well-being of these women, both immediately after treatment and during the 6 months after.^{6,15,19,26,33,51,60} IPT has been demonstrated to have greater effect compared to CBT.^{15,19,51}

However, there are reasonable alternatives to CBT and IPT.^{19,60} Nondirective counseling or listening visits intend to help the patients understand and accept their own feelings and behaviors by encouraging them to speak, without offering any explanation or advice. This intervention was designed to be delivered at home by nurses.^{15,60} Psychodynamic psychotherapy aims to improve patients' self-awareness of unresolved conflicts, by identifying patterns of relationships, feelings and behaviors, enabling the patient to build up new coping mechanisms.⁶⁰

Typically, psychotherapy is time-limited, intended to be completed in 6 to 12 sessions or 12 to 20 weeks, although the optimal length of treatment is yet to be defined.^{33,60}

Although individual psychotherapy is considered more effective, CBT and IPT have been successfully adapted to group format, taking advantage of the communication between peers and the support given by people that are experiencing similar problems and reducing social isolation and feelings of hopelessness.^{15,51,60} Psychotherapy can also be beneficial if delivered virtually, guaranteeing privacy, accessibility and scheduling flexibility.^{15,19,60} Maternal preferences should always be taken into account, if possible.¹⁹

If women with mild to moderate PPD episodes don't achieve full response to the chosen type of psychotherapy, the number and frequency of sessions can be increased, the type of psychotherapy can be switched or pharmacological therapy can be introduced.⁶⁰

Limitations to the participation in psychotherapy include the social stigma, the lack of trained therapists specializing in CBT or IPT, the need to invest a lot of time to complete the therapy's plan, the difficulty in arranging childcare needs, the lack of transportation and the associated costs.^{6,19,33,64}

1.2 Pharmacotherapy

The previously existing pharmacological options for treating women with PPD have been adapted from the treatment of MDD, although neither of them has been approved by the US Food and Drug Administration (FDA) for the use in PPD.^{4,7,11,13,17,46,50,57,65,66} The most common off-label choices are selective serotonin reuptake inhibitors (SSRIs), serotonin and norepinephrine reuptake

inhibitors (SNRIs) and tricyclic antidepressants (TCAs).^{12,13,67,68} Other antidepressants that may be used are mirtazapine, bupropion and monoamine oxidase inhibitors (MAOIs).^{17,31,59}

Pharmacotherapy is usually recommended in women with moderate to severe PPD, that were previously treated pharmacologically for depression or that don't have access or a successful response to psychotherapy.^{60–62} Antidepressants were proven efficacious and are widely available, fomenting their use in the treatment of PPD.^{18,19,61} Before deciding which medication to introduce, it's important to take into account if the patient has been responsive to an antidepressant prior to the development of PPD.^{18,61} If a woman was successfully treated before, it is recommended to resume the same antidepressant, warranting its compatibility with breastfeeding, if needed.^{18,61} Otherwise, selective serotonin reuptake inhibitors (SSRIs) were considered the first choice.^{12,18,46,69,70}

SSRIs were the best pharmacological option available for treating PPD during the past decades because of their efficacy, tolerability and availability.^{4,46,50,61} However, there is limited evidence of their effectiveness specifically in the postpartum period,^{38,57,69} as stated in a Cochrane systematic review,⁷¹ and the proportion of women successfully treated with PPD varies largely (43 to 88%), rarely surpassing 50%.^{31,33,38,65,72} Between SSRIs, they appear to have similar effectiveness.⁶¹ Compared to SNRIs and TCAs, SSRIs demonstrated similar efficacy yet fewer adverse effects than TCAs, since SSRIs only significantly interfere with the serotonergic activity.^{31,61} The most common adverse effects are gastrointestinal disturbances, such as nausea and diarrhea, but the presence of xerostomia, insomnia, sexual dysfunction, anxiety, agitation, headache, drowsiness and weight changes is also experienced.^{33,62,63,73} Previously, there was a concern that the use of SSRIs during pregnancy was associated with major organ malformation and cardiac defects on the fetus, however, no statistically significant increased risk was detected.^{51,70} SSRIs also have a very good safety profile for breastfeeding, with minimal expression into breastmilk (less than 10% of the maternal level), except for fluoxetine, whose use is usually discouraged due to its long half-life and bigger presence in the milk.^{19,46,60,61,63}

For patients with poor response to SSRIs, it is recommended to switch antidepressants rather than resort to augmentation with other type of drug.⁶¹ Options include serotonin and norepinephrine reuptake inhibitors (SNRIs), mirtazapine or tricyclic antidepressants (TCAs).^{12,13,15,16,50,61,67,68} Adverse effects of SNRIs are similar to the adverse effects of SSRIs, despite usually manifesting with greater intensity, and may also include constipation and increased blood pressure.³¹ The TCA with the best safety profile is nortriptyline, which can be used, with caution, while breastfeeding.^{15,19,46,58,74} On the other hand, doxepin is contraindicated given reports of serious

adverse events in breastfed infants.^{19,46,58,74} In addition, TCAs are associated with a wide range of adverse effects, due to their inhibition of cholinergic, α -1 adrenergic and histaminergic receptors, possibly causing blurred vision, constipation, xerostomia, urinary retention, confusion, sexual dysfunction, tachycardia, orthostatic hypotension, dizziness, sedation, increased appetite and weight gain.^{31,75} These drugs are also more likely to induce toxicity, therefore they are not typically chosen for an initial approach.³¹ Bupropion and monoamine oxidase inhibitors (MAOIs) may also be an option to treat PPD, however, bupropion is contraindicated while breastfeeding and IMAOs are associated with potentially fatal reactions (such as increased blood pressure, stroke and acute coronary syndrome) and not recommended while breastfeeding as well.^{4,31,50,74} At last, if there is a partial response to an antidepressant, a second drug can be added, such as a second-generation antipsychotic.^{61,74}

Some patients and clinicians may be hesitant to initiate pharmacotherapy while breastfeeding, due to the potential adverse effects on the infant.^{18,19,51,61,62,64} Uncommon side effects may include sedation, poor feeding and sleep disturbances.^{58,61} However, the general consensus is that, when indicated, the benefits of antidepressants outweigh their potential risks.^{61,62,64,76} According to LactMed,⁷⁴ treatment plans including SSRIs (preferably not fluoxetine), SNRIs, TCAs (except for doxepin), mirtazapine, second-generation antipsychotics or lithium are largely considered compatible with breastfeeding healthy full-term infants.^{19,61,74} The risk of breastfeeding while taking antidepressants in premature or medically ill infants should be individually evaluated by the pediatrician.¹⁹

Unfortunately, most of the antidepressants discussed take a long time to achieve maximal symptom improvement (from weeks to months) which, apart from decreasing patients' compliance and, consequently, the antidepressants' efficacy, is very detrimental in the perinatal period, taking into account the negative consequences of with PPD, that can potentially affect the infant's health and well-being permanently.^{11,12,15,17,31,36,57,62,66,72,77} It is also established that antidepressants that target the monoaminergic system may increase the risk of suicidal thoughts and behaviors in patients aged 24 years and younger.¹⁰ In addition, the unsatisfactory rates of remission (around 50%) and the lack of fast improvement in suicidality^{17,36} warranted the development of a more effective drug, with a more targeted mechanism of action, originating the GABA-A receptor PAMs (discussed below).^{11,38,70,72}

1.3 Neuromodulation therapy

Neuromodulation therapies are recommended in severe cases of PPD when psychotherapy and pharmacotherapy do not induce remission or women decline the use of antidepressants while

breastfeeding.^{4,19,50,61} Furthermore, specific indications for this treatment include the presence of psychotic symptoms, severe suicidal behaviors and rejection of food and fluid intake causing malnutrition and dehydration.^{4,19,50,61}

One of the most important neuromodulatory therapies in the treatment of PPD is the electroconvulsive therapy (ECT), which has been considered very effective and well tolerated.^{50,51,59,61} Although ECT requires general anesthesia, it's considered a safe treatment option during all the trimesters of pregnancy as well as during the postpartum period.^{19,51} Concerning breastfeeding, the risk of anesthetic drugs passing into milk appears to be low, meaning breastfeeding can be resumed once the patient recovers from anesthesia, and adverse effects upon lactation are unknown.⁶¹

Additionally, other techniques can be used, such as transcranial direct current stimulation and repetitive transcranial magnetic stimulation.^{4,19,50} These non-invasive brain stimulation techniques are safe, widely available and effective in alleviating symptoms of depression by the end of the treatment phase.^{4,19,50,51,64,65} However, larger trials to better evaluate the safety and efficacy of these therapies are necessary.^{4,19,50,51}

1.4 Adjunctive Therapies

The aim of psychosocial interventions is to enhance mental health by promoting the development of practical and emotional social support and reducing the impact of negative life events or stressors in the well-being of women who suffer from PPD; therefore, these strategies are recommended to be applied as adjunctive therapies in all patients.^{19,33} Psychosocial interventions include: aerobic exercise, if the patient has enough energy and motivation to engage this activity;^{19,51,61} infant behavioral sleep interventions, to improve the mother's amount and quality of sleep and, therefore, her mood;¹⁹ peer support, in which the peer has experimental knowledge of a similar situation - in women with mild PPD this measure may be helpful on its own;¹⁹ social support, for example, by hiring a doula or a dry nurse;⁶⁰ and parenting education.⁶⁰

Furthermore, other psychotropic medications can be used as adjunctive therapy to treat comorbidities or to augment antidepressant medication response.^{19,33} For comorbid anxiety and insomnia, monotherapy with the prescribed antidepressant is usually preferred, unless the woman experiences severe symptomatology. In these cases, a benzodiazepine can be added to the treatment plan for a relatively short period and then, once the symptoms start regressing, progressively discontinued.^{19,33,61} In women who present with PPD with psychotic features, an antipsychotic must be associated to the antidepressant medication.⁶¹ The safety profile of the adjuvant drug that is being introduced should always be evaluated, not only regarding its passage

into breast milk and the possible adverse effects on the infant, but also its interactions with the already prescribed medications.¹⁹

2. GABA-A Receptor Positive Allosteric Modulators

Since previously existing antidepressant therapies fall short in treating PPD successfully, the development of GABA-A receptor PAMs was crucial to the progress of the treatment of psychiatric illnesses.^{54,58,78,79} Recently, based on promising results in preclinical and clinical trials, FDA has given approval, specifically, for the treatment of PPD to the two first drugs: brexanolone, an intravenous analogue of AP, in March 2019; and zuranolone, an oral neuroactive steroid, in August 2023.^{9,15,24,26,33,54,65,68,72,77,78,80–82} Both of these drugs are already commercially available with prescription in the USA.^{9,81,83} The European Medicines Agency (EMA) has also granted the Priority Medicines (PRIME) designation to brexanolone although it hasn't approved the marketing authorization yet.⁸⁴

2.1 Mechanism of action

Along the lines of the pathophysiology of PPD, the exact neurobiological mechanisms behind the effects of GABA-A receptor PAMs are yet to be understood.^{80,81,85}

Brexanolone is an aqueous preparation of synthetic AP in a cyclodextrin solution.^{6,10,24,31,46,51,68,86,87} When administered, it can provide equivalent AP levels to those measured during the third trimester of pregnancy.^{10,26,54,87} On the other hand, zuranolone is a novel synthetic compound, different from AP, that also acts as a potent neuroactive steroid capable of modulating the activity of both synaptic and extrasynaptic GABA-A receptors.^{3,23,33,67,72,80,85}

By uniquely targeting both synaptic and extrasynaptic GABA-A receptors and positively modulating their activity, brexanolone and zuranolone enhance the receptor response to GABA and increase both tonic and phasic inhibition.^{5,72,81,85,88} In addition, these PAMs can also increase the cell surface expression of GABA-A receptors, by activating G protein-coupled membrane progesterone receptors, even further contributing to a sustained elevation in tonic current.^{31,33} Since PPD is associated with a dysregulation in the excitation-inhibition balance, these PAMs are beneficial by rapidly enhancing inhibitory GABAergic signaling and, therefore, restoring the network balance.^{5,31,33,51,68,72,85,86} Consequently, this results in an improvement of mood and anxiety symptoms.^{54,85,86,89}

The mechanism of action of these neuroactive steroids is different from the ones of other GABA-A allosteric modulators, such as benzodiazepines and barbiturates. Unlike brexanolone and zuranolone, benzodiazepines only target synaptic receptors, only enhancing phasic inhibition, and are associated with the downregulation of these receptors, which is a limitation to their efficacy.^{23,31,79,87}

2.2 Brexanolone

2.2.1 Administration

Brexanolone is currently administered through continuous infusion over 60 hours, via a programmable peristaltic pump with the following dosage regimen: 30 µg/kg/h during the first 4 hours; 60 µg/kg/h from hour 4 to 24; 90 µg/kg/h from hour 24 to 52 (if this dosage is not well tolerated, it can be reduced to 60 µg/kg/h); 60 µg/kg/h from hour 52 to 56; and 30 µg/kg/h from hour 56 to 60.^{5,10,46,58,61,83} A single 60-hour infusion is prescribed for each episode of PPD after delivery.⁸³

Brexanolone is only available for patients that enroll the Risk Evaluation and Mitigation Strategy (REMS) program, which entails the administration of brexanolone to occur at a certified inpatient health care facility, under close supervision of a clinician and monitorization of hypoxia through continuous pulse oximetry.^{3,23,61,67,83,87} Clinicians should screen for excessive sedation or sudden loss of consciousness and, if present, the infusion must be stopped. After dose interruption, these adverse effects are expected to last for 15 to 60 minutes and, after the resolution of the symptoms, the infusion can be resumed with the same or a lower dose, as clinically appropriate.^{87,90} On the other hand, if the patient becomes hypoxic, the infusion must be immediately stopped and should never be resumed again.^{87,90}

Due to the brexanolone's risk of sedation, patients must be accompanied when interacting with their offsprings and should be advised against engaging in any potentially dangerous activities, such as driving or operating machinery, until the sedative effects entirely resolve.^{87,90} Although drug interactions have not been widely tested in combination with brexanolone, when administered with other CNS depressants, such as benzodiazepines, opioids or alcohol, a higher percentage of patients presenting with adverse effects was registered. Therefore, it is recommended that patients discontinue or reduce by 50% the dosage of these drugs, prior to the infusion.^{10,23,87,90}

2.2.2 Pharmacokinetics and Pharmacodynamics

Brexanolone exhibits poor absorption when taken orally, with an oral bioavailability of less than 5%, therefore it is administered intravenously.^{3,10,31,87} This drug has dose-proportional pharmacokinetics over a dose range of 30 µg/kg/h to 270 µg/kg/h and a mean state exposure at 60 µg/kg/h and 90 µg/kg/h of around 52 ng/mL and 79 ng/mL, respectively.^{87,90}

The brexanolone's volume of distribution is approximately 3 L/kg, indicating extensive distribution into tissues.^{10,87,90} It binds extensively to plasma proteins (more than 99%) and has a terminal half-

life of approximately 9 hours, with a total plasma clearance of nearly 1 L/h/kg.^{10,58,87,90,91} Brexanolone is metabolized by non-cytochrome P450 pathways via keto-reduction, glucuronidation and sulfation, originating three major circulating metabolites that are pharmacologically inactive.^{10,58,87,90,91} The excretion of brexanolone is mostly in fecal and urinary (47% and 42%, respectively), with less than 1% of unchanged brexanolone remaining.^{5,10,87,90}

Although no significant differences in the pharmacokinetics of brexanolone were associated with renal or hepatic impairment, the use of brexanolone is not recommended in patients with end-stage renal disease, with an estimated glomerular filtration rate (eGFR) inferior to 15 mL/min/1.73m², due to the possible toxic accumulation of a solubilizing agent.^{58,87,90}

Brexanolone is a lipophilic molecule that readily passes through the blood-brain barrier, potentiating GABAergic effects in cells expressing $\alpha 1\beta 2\gamma 2$, $\alpha 4\beta 3\delta$ and $\alpha 6\beta 3\delta$ receptor subunits.^{10,24,90} The pharmacodynamics of brexanolone, including exposure-response relationships, is yet to be determined.⁹⁰ A study evaluated the effect of brexanolone on the QT interval and concluded that brexanolone did not prolongate the QT interval to a clinically relevant extent, when administered 1,9-times the maximum infusion rate recommended.⁹⁰

2.2.3 Efficacy

Brexanolone's approval by FDA was based on 4 published studies – an open-label proof of concept study,³⁸ a small randomized controlled phase II trial⁹² and two large randomized controlled phase III trials⁹¹ – all of them showed clinical benefit in treating PPD with brexanolone, with a consistent and fast reduction of depressive symptoms. The patients were followed up until day 30.^{10,39} All of them had similar inclusion and exclusion criteria and included women within 6 months of childbirth.²³ HAM-D remission is considered when there is a total score of <10 and >50% reduction.¹⁰

The phase II trial³⁸ was a double-blind placebo-controlled study of a single, continuous 60-hour infusion of brexanolone, at the maximum rate of 90 µg/kg/h, in 21 women with severe PPD (HAM-D score ≥ 26). The primary study endpoint was the change from baseline in the 17-item HAM-D score. After the infusion, the mean change of the HAM-D score among the patients who received brexanolone was 21 points, compared to 8.8 points in the placebo group. These positive results led to the phase III trials.^{10,19,23,24,86}

The phase III trials⁹¹ were two multicenter, double-blinded, randomized, placebo-controlled trials. In study 1, 138 women with HAM-D scores ≥ 20 were randomly assigned to receive brexanolone at 90 µg/kg/h, brexanolone at 60 µg/kg/h or placebo. After infusion, the least-squares mean

reduction in HAM-D total score from baseline was 19.5 points in the brexanolone 60 µg/kg/h group and 17.7 points in the brexanolone 90 µg/kg/h group compared to 14.0 points in the placebo group. In study 2, 108 women with HAM-D scores ≥ 25 were randomly assigned to receive brexanolone at a maximum rate of 90 µg/kg/h or placebo. After infusion, the least-squares mean reduction in HAM-D total score from baseline was 14.6 points in the brexanolone group and 12.1 points in the placebo group.^{10,23,39,86} A sustained reduction in the HAM-D score 30 days after infusion was reported in both clinical trials.⁹¹

Although placebo's response was notable (as it usually was in MDD clinical trials), these studies demonstrated statistically significant and clinically meaningful reductions on the women's symptomatology after 60-hour infusion, with rapid onset of action and sustained treatment response.^{10,23,24,39,86}

Furthermore, an improvement in mood beyond 30 days was recently reported in an open-label, single-institution, follow-up study of PPD patients treated with brexanolone (with a follow-up time ranging from 3 to 16 months postinfusion).^{31,86,93}

The efficacy, tolerability and safety of brexanolone were also evaluated by several meta-analysis, with similar results showing significant differences in HAM-D response and remission compared to placebo.^{9,10,26,94} A meta-analysis of the existing data from brexanolone and SSRIs concluded, by using indirect comparison, that patients treated with brexanolone had a greater change from baseline in HAM-D scores at all time points, compared to patients treated with SSRIs.^{10,57}

In a post hoc analysis,⁸⁶ it was also assessed the effect of brexanolone on the reduction of anxiety and insomnia in women with PPD, which demonstrated that the symptoms of both conditions were significantly diminished when treated with brexanolone - a great advantage compared to SSRIs, since these antidepressants often don't improve insomnia's symptoms.^{9,86}

2.2.4 Adverse Effects

Throughout all phases of clinical trials, brexanolone was generally well tolerated, with low rates of discontinuation due to adverse effects.^{9,23,61} The most common side effects include sedation/somnolence (15%), dizziness/vertigo/presyncope (12%), xerostomia (5%), sudden loss or altered state of consciousness (4%), flushing, headache and nausea/vomiting.^{9,10,23,58,68,83,87}

Due to the risk of sedation and loss of consciousness, in clinical practice, brexanolone is only available through the REMS program, discussed above, and is a Schedule IV medication with a black box warning for excessive sedation and sudden loss of consciousness.^{23,46,51,58,68,83,87} However, in a postmarketing surveillance data analysis, [7](#) excessive sedation and loss of

consciousness were reported at lower rates than in the previous clinical trials and were most commonly associated with the concomitant use of CNS depressants.^{10,46,83,90}

In spite of the majority of the adverse events being mild, severe adverse reactions have also been rarely documented, such as suicidal ideation, homicidal ideation, agitation, anxiety disorder, panic disorder and psychotic disorder.^{10,68,83} Some of these adverse reactions cannot be easily distinguished from PPD symptoms, which is important to take into account.⁶⁸ If the patient's symptoms worsen or suicidal ideation takes place, it should be considered changing the therapeutic regimen or stopping the treatment with brexanolone completely.⁸⁷

Regarding specific populations, patients with end-stage renal disease are not recommended to take brexanolone.^{10,26,90} The use of brexanolone in pregnant women wasn't properly assessed yet, which means there isn't any available data on the associated risks of major birth defects, miscarriage or adverse maternal or fetal outcomes; however, findings from animal studies of other drugs that enhance GABAergic inhibition indicate that brexanolone may cause fetal harm.^{10,24,90} In animal studies, only plasma levels of brexanolone of ≥ 2 times the maximum recommended dose in humans resulted in adverse outcomes.⁹⁰

2.2.5 Safety while Breastfeeding

A recent study in 12 women treated with brexanolone, at a maximum perfusion rate of 90 $\mu\text{g/kg/h}$, evaluated the AP levels in their blood and breast milk, during 7 days.⁹⁵ Breast milk concentrations of AP demonstrated a parallel temporal profile to the blood concentrations, with maximum concentrations of AP between hour 24 and 48 (when the maximum dosage was infused).^{10,74,95} The average peak AP breastmilk level was 125 $\mu\text{g/L}$.⁷⁴ After the end of the 60-hour infusion, breast milk AP levels fell below the limit of detection (5 $\mu\text{g/L}$) in most women in 3 days.^{3,51,74,87,95} This study predicted milk AP (natural and synthetic) levels inferior to 10 ng/mL 36 hours after the end of the infusion in 95% of the patients.^{74,90,95} The calculated relative infant dose was low, 0.69% to 1.3% of the maternal weight-adjusted dosage.^{46,74,95} There were no reports of effects on lactation or milk production.^{74,90}

Although there isn't any published data on the levels and effects of AP in breastfed infants, the low amounts of brexanolone in milk and low oral bioavailability (less than 5%) has led to expect the infants' exposure and, therefore, the risk of adverse effects to be low.^{68,74,90,95} Although its likelihood is very low, a potential adverse effect for the infant is transient somnolence.¹⁰

In conclusion, according to LactMed,⁷⁴ given the development and health benefits of breastfeeding, if brexanolone use is required, it is not considered a reason to discontinue

breastfeeding. It is only advised the presence of a second caregiver during infusion in case of mother's excessive somnolence or sudden loss of consciousness.^{74,96} However, some authors still consider that the best procedure is to cease nursing during the treatment with brexanolone and to resume it four days after the end.^{10,61,95} More research on this topic is essential.

2.2.6 Advantages and Limitations of Brexanolone

Brexanolone was the first GABA-A receptor PAM approved for the clinical practice, a revolutionary step to improve the treatment of PPD.⁶ Besides being well tolerated, this therapeutic option offers high rates of response and remission with a rapid onset of action, in contrast to SSRIs and psychotherapy, which only achieve optimal symptom improvement weeks after starting the therapy.^{6,33,59,86,87} The fast symptom improvement is crucial while treating PPD, reducing negative outcomes caused by delays in the management of this disease.^{67,86,87} Brexanolone can also be useful as a bridge to engage in long-term psychiatric treatments.⁶ However, studies such as randomized controlled trials that directly compare the efficacy of GABA-A receptor PAMs, SSRIs and psychotherapy are mandatory to further evaluate their pros and cons.³⁶

One of brexanolone's major limitations is its pharmaceutical properties, since the lack of water solubility, poor oral bioavailability, short half-life and rapid metabolism dictate the need for a frequent or continuous intravenous administration.¹⁰ In spite of the challenging logistics involved, the intravenous administration route may be seen as an advantage for patients requiring psychiatric hospitalization and the relatively short duration of the treatment can also lessen the pill burden.^{18,26,36,61} However, on top of the need to inpatient hospitalization, brexanolone is only available through the REMS program, that requires constant monitorization in a certified health care facility.^{10,15,24,36,65,68,81} Other barriers to the clinical adoption of brexanolone are its cost, that includes not only the drug itself but also the cost of admission to a medically supervised facility, and the lack of insurance coverage, which limits the access of the lower socioeconomic classes.^{10,16,23,33,46,65,68} Since the patient shouldn't be the primary caregiver of their children during the infusion, this therapy may also be inconvenient, requiring the patient to spend time away from the family.^{23,36,68}

Furthermore, more large-scale clinical trials are needed to evaluate the long-term safety and efficacy of brexanolone in the treatment of PPD.^{5,10,68,87,89}

2.3 Zuranolone

2.3.1 Administration

Zuranolone is available in 20, 25 and 30 mg capsules and is administered as 50 mg taken orally in the evening with a fat-containing food (for example, 400 to 1000 calories, 25% to 50% fat), for 14 days.^{61,80,81,88,97} It can be used as monotherapy or in combination with other antidepressants.^{61,81,88,97} After administration, if the patient suffers from moderate to severe somnolence or other CNS depressant effects of zuranolone, the dose of this neuroactive steroid must be reduced to 40 mg once daily within the 14-day period.^{61,88,97} In case a zuranolone dose is missed, patients should maintain the regular schedule and only take the next dose the following evening.⁹⁷

A smaller dosage of zuranolone, 30 mg once daily for 14 days, is recommended for patients with severe hepatic impairment (Child-Pugh Class C), moderate or severe renal impairment (eGFR < 60 mL/min/1.73m²) and for patients taking concomitant medications that strongly inhibit the cytochrome P450 3A4 (CYP3A4), such as clarithromycin and ketoconazole.⁹⁷ If the patient is taking CYP3A4 inducers, such as carbamazepine and rifampicin, the use of zuranolone should be avoided.⁹⁷

Since Zuranolone can have CNS depressant effects, such as somnolence, disorientation and cognitive impairment, the patients should be advised not to engage in any potentially dangerous activities that require complete mental alertness, such as driving, until at least 12 hours after taking the medication.^{88,97} It should also be mentioned to the patient that they may not be able to assess the degree of driving impairment caused by zuranolone.^{88,97} The concomitant use of benzodiazepines and other CNS depressants should be avoided or at least reduced to a smaller dosage, due to the increased risk of psychomotor performance and cognitive impairment, somnolence and even respiratory depression.^{81,88,97}

2.3.2 Pharmacokinetics and Pharmacodynamics

Zuranolone concentrations increase in an approximately dose-proportional manner with doses ranging from 30 mg to 60 mg with a moderate-fat meal (700 calories, 30% fat).^{81,97} Following once daily zuranolone administration, the systemic circulation accumulated almost 1.5-fold the recommended dosage of zuranolone and the steady state was achieved in 3 to 5 days.^{81,88,97}

The maximum serum concentration of zuranolone occurs 5 to 6 hours after administration and is increased by 2-fold and 1.8-fold with a high-fat meal (800 to 1000 calories, 50% fat) and a low-fat meal (400 to 500 calories, 25% fat), respectively, compared to fasted conditions.^{80,81,88,97} The

absolute bioavailability of zuranolone in humans is yet to be determined.⁹⁷ Zuranolone's volume of distribution is superior to 500 L, with plasma protein binding greater than 99.5%.^{80,81,88,97} It has a terminal half-life of approximately 19.7 to 24.6 hours and an estimated mean clearance of 33 L/h.^{80,81,88,97} Zuranolone is extensively metabolized via CYP3A4 and none of the metabolites is considered to have pharmacological activity.^{81,88,97} Zuranolone is mostly excreted in urine (45%) and in feces (41%, with less than 2% of unchanged zuranolone remaining).^{81,88,97}

Since CYP3A4 is responsible for a majority of the metabolism of zuranolone, the concomitant use of a strong CYP3A4 inhibitors increases the risk of zuranolone-associated toxicity, which motivates dosage adjustments and monitorization of adverse effects, and the concomitant use of CYP3A4 inducers decreases the antidepressant's efficacy, thus it should be avoided. Moderate CYP3A4 inhibitors don't require a reduction of the dose of zuranolone, but it is important to monitor the patient for somnolence and sedation.^{81,88,97}

Although mild renal impairment (eGFR of 60 to 89 mL/min/1.73m²) and mild to moderate hepatic impairment (Child-Pugh class A or B) didn't alter the pharmacokinetic parameters of zuranolone, the exposure to this neuroactive steroid was increased in patients with severe hepatic and moderate to severe renal impairment.^{81,97}

Zuranolone is a neuroactive steroid that potentiates GABAergic effects in cells expressing $\alpha 1\beta 2\gamma 2$ and $\alpha 4\beta 3\delta$ receptor subunits.⁹⁷ The pharmacodynamic parameters of zuranolone require further investigation.⁹⁷ Zuranolone and benzodiazepines appear to have synergistic activity over GABA-A receptors, in a non-competitive way, meaning that a similar therapeutic effect can be reached with smaller doses of these drugs when used together rather than separately, which can be a beneficial strategy for reducing the incidence of adverse effects.^{3,80,88} Zuranolone does not have any clinically relevant effect on the QT interval, at 2 times the maximum recommended dose.^{81,97}

2.3.3 Efficacy

The efficacy of zuranolone was evaluated in two randomized, double-blind, placebo-controlled phase III trials – the ROBIN study²² and the SKYLARK study.⁹⁸ Both clinical trials included women aged 18 to 45 years, diagnosed with PPD until 4 weeks postpartum, with HAM-D scores ≥ 26 at baseline, within up to 6 or 12 months postpartum (in ROBIN and SKYLARK, respectively).^{22,67,79–81} The exclusion criteria were similar.^{22,80} Patients were allowed to use concomitant antidepressant medication if the dose was stable at least for the last 30 days.^{22,80,81} Patients were followed up until day 45.^{22,80,98} The primary endpoint in both studies was the change from baseline in HAM-D score at day 15.^{22,67,80,81,98} Several secondary outcomes were also evaluated, such as the change from baseline in HAM-D score at other time points, the HAM-D response (defined as a reduction

of at least 50% of the total score) and remission (defined as a total score ≤ 7) rate, the change from baseline of the Hamilton Anxiety Rating Scale (HAM-A) at day 15, among others.^{22,80,81,98}

In the ROBIN study,²² 153 women were randomly assigned to receive zuranolone 30 mg once daily during 14 days or placebo. At day 15, there was a significantly greater reduction from baseline in HAM-D score in the zuranolone group, 17.8 points, compared to the placebo group, 13.6 points.^{22,46,54,77,80,81} Significantly greater reductions in HAM-D score were also observed at day 3, 8 and 45.^{22,33,46,54,80,81} The proportion of patients achieving HAM-D response and remission in the zuranolone group at days 3, 15 and 45 was significantly superior to the placebo group, for instance, at day 45, HAM-D response rates were 75% vs 57% and the HAM-D remission rates were 53% vs 30% in the zuranolone and the placebo group, respectively, showing a remarkable maintenance of antidepressive effect.^{22,46,81} Regarding anxiety, significantly greater reductions from baseline in HAM-A score were reported at days 3, 15 and 45.^{22,54,79} Insomnia symptoms were also assessed, through a subscale value of HAM-D score, and considered significantly improved in patients treated with zuranolone.^{33,80,81} Furthermore, the patient-report Barkin Index of Maternal Functioning was also evaluated and revealed significant improvement compared to placebo.²² A relatively high placebo response was observed in this trial.²²

In the SKYLARK study,⁹⁸ 196 women were randomly assigned to receive zuranolone 50 mg once daily during 14 days or placebo.⁴⁶ At day 15, there was a significantly greater reduction from baseline in HAM-D score in the zuranolone group, 15.6 points, compared to the placebo group, 11.6 points.^{46,77,80,81,98} Significantly greater reductions in HAM-D score were also observed at day 3, 28 and 45, demonstrating sustained antidepressive efficacy.^{46,67,80,81,98} In the zuranolone group, the HAM-D response rates were significantly superior compared with placebo at day 15 (57% vs 38.9%) and the HAM-D remission rates were significantly greater at day 45 (44% vs 29.4%).^{46,80} In addition, treatment with zuranolone showed positive effects on insomnia and patient-reported outcomes, assessed by EPDS and 9-item Patient Health Questionnaire score.^{46,67}

Several meta-analysis^{9,72,89} were also carried out in order to better assess the efficacy and tolerability of zuranolone and reached similar conclusions to the clinical trials. The results reveal that zuranolone has a fast (by day 3) and sustained efficacy (at day 45) in improving depressive symptomatology, as well as minimizing anxiety and insomnia and promoting a better global functioning, in women with PPD.^{9,31,72,85,89}

A study⁶⁷ used previously existing clinical trials to compare, indirectly, the effectiveness of zuranolone, SSRIs and combination therapy (SSRIs and non-pharmacological interventions). Although indirect comparison has several limitations, since it relies on the assumption of

homogeneity, exchangeability and comparability between studies, this essay demonstrated that patients treated with zuranolone had larger changes from baseline in the EPDS score, even when compared data from day 45 for the zuranolone group and from the last observation timepoint for SSRIs and combination therapy, giving these therapies sufficient time to the onset of their efficacy.⁶⁷ Nevertheless, further investigation is mandatory, to directly compare the efficacy and tolerability of these therapeutic options.

2.3.4 Adverse Effects

According to multiple studies, Zuranolone is usually well tolerated, with low rates of discontinuation due to adverse effects.^{3,9,22,72,80,81} The most common side effects were somnolence, dizziness, sedation, headaches, fatigue, nausea, diarrhea, upper respiratory tract infection and urinary tract infection.^{3,22,33,46,51,54,67,77,79–81,97} However, only somnolence, dizziness and sedation were significantly more frequent in patients treated with zuranolone, compared to placebo.^{72,89} The overall incidence of serious side effects was low (<2%).^{22,31,79}

No clinically significant changes in vital signs, electrocardiogram and laboratory parameters were reported or led to dose adjustment or discontinuation.^{3,22,80,81} No loss of consciousness or withdrawal symptoms after discontinuation of zuranolone were described.^{22,33,46,81,98} No evidence for increased suicidal ideation or behaviors was observed by evaluating the Columbia Suicide Severity Rating Scale.^{3,22,46,80,81,89,98} However, regarding the increased risk of suicidal thoughts in patients treated with antidepressants (especially in younger patients), in spite of not interfering directly with monoaminergic system, it should be considered modifying the treatment regimen if the woman starts presenting with suicidal ideation or worsening depressive symptoms.⁸¹

The correct clinical use of zuranolone in specific populations, such as patients with hepatic and renal impairment, was discussed above. The use of zuranolone in pregnant women wasn't properly studied in humans, since there is insufficient data to determine the associated risks of major birth defects, miscarriage and adverse maternal or fetal outcomes.^{80,97} Nevertheless, based on numerous animal studies, zuranolone may cause fetal harm, therefore, pregnant women should be informed of the potential risks of this therapy.^{88,97} Moreover, patients in childbearing age should be advised to use appropriate contraception from the beginning of the treatment with zuranolone until one week after the final dose.^{80,88,97} In animal studies, only plasma levels of zuranolone ≥ 2 times the maximum recommended dose in humans resulted in adverse outcomes, such as fetal malformations and growth deficits.⁹⁷

At last, zuranolone has a dose-dependent abuse potential, estimated in a study in healthy individuals to be comparable to single oral doses of alprazolam and greater than placebo.^{61,81,97} This drug may also cause physical dependence.⁹⁷

2.3.5 Safety while Breastfeeding

A recent study in 14 lactating women treated with zuranolone, 30 mg once daily, for 5 days, evaluated the passage of zuranolone into breast milk.^{46,74,97} At steady state (day 5), the daily infant dose via milk was low, 0.00124 mg/kg, reflecting a mean weight-adjusted relative infant dose of 0.357%, compared to the maternal dose.^{46,74,80,97} Concentrations of zuranolone in breast milk were below the level of quantification limit by 4 to 6 days after the last dose.^{74,97} There is limited data on the effects of zuranolone in milk production, since this study reported a mean decrease of 41.2 mL (8.3%) in the milk volume at day 5, compared with baseline; however, this reduction may be due to the study design, because women stopped breastfeeding and pumped their milk.⁷⁴

Although the levels and effects of zuranolone in breastfed infants are unknown, the low amounts of zuranolone in milk predict a low risk of adverse effects in the offspring.^{74,80,97} According to LactMed, considering the developmental and health benefits of breastfeeding, it shouldn't be discontinued only because the mother requires zuranolone.^{74,97} Further safety studies are needed and the use of zuranolone while breastfeeding should be careful, therefore it is recommended infant monitorization for excessive sedation, especially in newborn and preterm infants and in higher dosages of the drug.^{3,74,80,89} If patients prefer to avoid infant exposure to zuranolone, they can temporarily bottle-feed their newborn and pump and discard their breast milk for the 14 days of treatment until a week after the last dose.^{61,80}

2.3.6 Advantages and Limitations of Zuranolone

Zuranolone's major advantage in comparison with brexanolone is its oral administration, only possible after the optimization of its pharmacologic, pharmacokinetic and pharmacodynamic properties.^{3,33} In contrast to the 60-hour continuous infusion of brexanolone requiring permanent monitorization, the therapeutic regimen of zuranolone is more practical, convenient and patient-friendly, allowing patients to take their medication at home and giving them more control over their treatment.^{26,33,59,78} However, it is important to make sure that patients are taking the prescribed dosage and adhering to the recommended schedule.^{26,78}

Regarding traditional treatment options, such as SSRIs and psychotherapy, zuranolone presents a faster onset of action, providing symptom relief in only a few days, compared to the traditional options, which take weeks to reach optimal symptom reduction.^{26,33,59} Moreover, zuranolone

demonstrated higher response and remission rates when compared, indirectly, with these therapies, revealing sustained efficacy during the month after the last dosage.^{26,33,88} Quick and effective treatment is particularly important in PPD, providing medical benefits for the entire family unit.^{67,80,88} In addition, the duration of the treatment is specified (only 14 days), reducing pill burden.^{26,80} At last, some SSRIs side effects may decrease the compliance to the therapy regimen (for example, sexual dysfunction), thus, in patients experiencing these symptoms, zuranolone might be a good alternative.⁵⁹

Nevertheless, zuranolone's depressant effects on the CNS can be an obstacle to the treatment of women with PPD, since patients may not have any additional support at home and be the only ones responsible for taking care of their children.⁸⁰ The driving impairment can also condition the daily life of the patient, who can be the only driver in their home as well.⁸⁰ Although a study⁷⁷ suggests that zuranolone is more cost-effective compared to SSRIs, the high cost of zuranolone may also limit the access to this new therapy.^{77,80} In addition, long-term safety and efficacy of zuranolone is still unknown, warranting larger trials with longer durations, as well as studies that directly compare traditional therapies to the GABA-A receptor PAMs, as previously stated.^{59,67,72,78,80,89} In spite of providing acute symptom relief in the immediate postpartum period, additional therapy may be needed long-term, to treat patients with a more chronic course of disease.^{72,80}

2.4 Application in Clinical Settings

The current American College of Obstetricians and Gynecologists guidelines for the treatment of PPD were published before the approval of zuranolone and recommend the use of brexanolone in patients with severe symptoms of PPD.⁸⁰ SSRIs and SNRIs are considered second-line options.⁸⁰

Meanwhile, with the approval of zuranolone, some authors defend that, in patients with moderate to severe PPD who haven't been treated with other antidepressants in the past, the best treatment option is zuranolone, following the administration regimen described above. Brexanolone is considered to be a good alternative therapy, if zuranolone is declined or not available or if the patient is hospitalized due to psychiatric symptoms, such as suicidal ideation. Neuroactive steroids can be used as monotherapy or in combination with other antidepressants.⁶¹

If patients don't respond to the treatment with one of the neuroactive steroids, it is recommended not to use the other one as a next step treatment, due to their similar mechanisms of action. In this case, second-line treatment with SSRIs or SNRIs must be attempted.⁶¹

Patients with complex and chronic illnesses (for example, personality or substance abuse disorders) may have a poorer response compared to patients with no previous psychiatric history.⁶¹

Conclusion

The high global prevalence of PPD, as well as its serious, and even permanent, consequences for the mother and the offspring, determine the urgent need for an effective and safe therapeutic option, in order to minimize PPD's lifelong negative impact. The unique mechanism of action, the tolerability, the quick onset of action and the high response rates of the GABA-A receptor PAMs show promising advances in our ability to improve treatment outcomes, not only of PPD but also, potentially, of other forms of depression and other psychiatric illnesses (such as Alzheimer's disease, epilepsy or essential tremor). The side effects associated with the treatment with neuroactive steroids (especially sedation) can interfere with the patients' adherence to these regimens, since they are incompatible with the constant need to be available to take care of a newborn that is characteristic of the postpartum period. The potential risks of harming the fetus when used in pregnant women are a major drawback of these innovative drugs.

Additional clinical trials, with a larger population and a longer follow-up, are warranted to evaluate the long-term safety and efficacy of brexanolone and zuranolone, as well as to compare the success of these therapies to the traditionally used ones. It should also be explored the possibility for neuroactive steroids to act as a bridge, providing acute relief of the depressive symptoms while other antidepressants or psychotherapy don't achieve optimal response, in patients suffering from PPD with chronic course.

To this date, brexanolone and zuranolone haven't received EMA's marketing authorization, delaying and preventing their use in Europe, in spite of their multiple benefits when treating PPD.

Appendix

Annex 1 – Edinburgh Postnatal Depression Scale (EPDS)

1. I have been able to laugh and see the funny side of things:

As much as I always could (0); Not quite so much now (1); Definitely not so much now (2); Not at all (3).

2. I have looked forward with enjoyment to things:

As much as I ever did (0); Rather less than I used to (1); Definitely less than I used to (2); Hardly at all (3).

3. I have blamed myself unnecessarily when things went wrong:

Yes, most of the time (3); Yes, some of the time (2); Not very often (1); No, never (0).

4. I have been anxious or worried for no good reason:

No, not at all (0); Hardly ever (1); Yes, sometimes (2); Yes, very often (3).

5. I have felt scared or panicky for no good reason:

Yes, quite a lot (3); Yes, sometimes (2); No, not much (1); No, not at all (0).

6. Things have been getting to me:

Yes, most of the time I haven't been able to cope at all (3); Yes, sometimes I haven't been coping as well as usual (2); No, most of the time I have coped quite well (1); No, I have been coping as well as ever (0).

7. I have been so unhappy that I have had difficulty sleeping:

Yes, most of the time (3); Yes, sometimes (2); No, not very often (1); No, not at all (0).

8. I have felt sad or miserable:

Yes, most of the time (3); Yes, quite often (2); Not very often (1); No, not at all (0).

9. I have been so unhappy that I have been crying:

Yes, most of the time (3); Yes, quite often (2); Only occasionally (1); No, never (0).

10. The thought of harming myself has occurred to me:

Yes, quite often (3); Sometimes (2); Hardly ever (1); Never (0).

Font: Adapted from Cox JL, Holden JM, Sagovsky R. Detection of Postnatal Depression. *British Journal of Psychiatry*. 1987;150(6):782-786. doi:10.1192/bjp.150.6.782

Annex 2 – 17-Item Hamilton Rating Scale for Depression (HAM-D)

1. DEPRESSED MOOD

0 - Absent.

1 - These feeling states indicated only on questioning.

2 - These feeling states spontaneously reported verbally.

3 - Communicates feeling states non-verbally, i.e. through facial expression, posture, voice and tendency to weep.

4 - Patient reports virtually only these feeling states in his/her spontaneous verbal and non-verbal communication.

2. FEELINGS OF GUILT

0 - Absent.

1 - Self-reproach, feels he/she has let people down.

2 - Ideas of guilt or rumination over past errors or sinful deeds.

3 - Present illness is a punishment. Delusions of guilt.

4 - Hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations.

3. SUICIDE

0 - Absent.

1 - Feels life is not worth living.

2 - Wishes he/she were dead or any thoughts of possible death to self.

3 - Ideas or gestures of suicide.

4 - Attempts at suicide (any serious attempt rate 4).

4. INSOMNIA: EARLY IN THE NIGHT

0 - No difficulty falling asleep.

1 - Complains of occasional difficulty falling asleep, i.e. more than 1/2 hour.

2 - Complains of nightly difficulty falling asleep.

5. INSOMNIA: MIDDLE OF THE NIGHT

0 - No difficulty.

1 - Patient complains of being restless and disturbed during the night.

2 - Waking during the night – any getting.

6. INSOMNIA: EARLY HOURS OF THE MORNING

0 - No difficulty.

1 - Waking in early hours of the morning but goes back to sleep.

2 - Unable to fall asleep again if he/she gets out of bed.

7. WORK AND ACTIVITIES

0 - No difficulty.

1 - Thoughts and feelings of incapacity, fatigue or weakness related to activities, work or hobbies.

2 - Loss of interest in activity, hobbies or work – either directly reported by the patient or indirect in listlessness, indecision and vacillation (feels he/she has to push self to work or activities).

3 - Decrease in actual time spent in activities or decrease in productivity. Rate 3 if the patient does not spend at least three hours a day in activities (job or hobbies) excluding routine chores.

4 - Stopped working because of present illness. Rate 4 if patient engages in no activities except routine chores, or if patient fails to perform routine chores unassisted.

8. RETARDATION

0 - Normal speech and thought.

1 - Slight retardation during the interview.

2 - Obvious retardation during the interview.

3 - Interview difficult.

4 - Complete stupor.

9. AGITATION

0 - None.

1 - Fidgetiness.

2 - Playing with hands, hair, etc.

3 - Moving about, can't sit still.

4 - Hand wringing, nail biting, hair-pulling, biting of lips.

10. ANXIETY PSYCHOTIC

- 0 - No difficulty.
- 1 - Subjective tension and irritability.
- 2 - Worrying about minor matters.
- 3 - Apprehensive attitude apparent in face or speech.
- 4 - Fears expressed without questioning.

11. ANXIETY SOMATIC

- 0 - Absent.
- 1 - Mild.
- 2 - Moderate.
- 3 - Severe.
- 4 - Incapacitating.

12. SOMATIC SYMPTOMS GASTROINTESTINAL

- 0 - None.
- 1 - Loss of appetite but eating without staff encouragement. Heavy feelings in abdomen.
- 2 - Difficulty eating without staff urging. Requests or requires laxatives or medication for bowels or medication for gastro-intestinal symptoms.

13. GENERAL SOMATIC SYMPTOMS

- 0 - None.
- 1 - Heaviness in limbs, back or head. Backaches, headaches, muscle aches. Loss of energy and fatigability.
- 2 - Any clear-cut symptom rates 2.

14. GENITAL SYMPTOMS

- 0 - Absent.
- 1 - Mild.
- 2 - Severe.

15. HYPOCHONDRIASIS

- 0 - Not present.
- 1 - Self-absorption (bodily).
- 2 - Preoccupation with health.
- 3 - Frequent complaints, requests for help, etc.
- 4 - Hypochondriacal delusions.

16. LOSS OF WEIGHT (RATE EITHER a OR b)

- a) According to the patient:
 - 0 - Less than 1 lb weight loss in week.
 - 1 - Probable weight loss associated with present illness.
 - 2 - Definite (according to patient) weight loss.
 - 3 - Not assessed.
- b) According to weekly measurements:
 - 0 - No weight loss.
 - 1 - Greater than 1 lb weight loss in week.
 - 2 - Greater than 2 lb weight loss in week.
 - 3 - Not assessed.

17. INSIGHT

- 0 - Acknowledges being depressed and ill.
- 1 - Acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
- 2 - Denies being ill at all.

Font: Hamilton M. A Rating Scale for Depression. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62.
doi:10.1136/jnnp.23.1.56

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