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Allopregnanolone-based treatments for postpartum depression: Why/how do they work?

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ABSTRACT

Recent FDA approval of an allopregnanolone-based treatment specifically for postpartum depression, brexanolone, now commercially called Zulresso®, is an exciting development for patients and families impacted by postpartum depression and allows us to start asking questions about why and how this compound is so effective. Allopregnanolone is a neuroactive steroid, or neurosteroid, which can be synthesized from steroid hormone precursors, such as progesterone, or synthesized *de novo* from cholesterol. Neurosteroids are positive allosteric modulators at $GABA_A$ receptors ($GABA_ARs$), a property which is thought to mediate the therapeutic effects of these compounds. However, the durability of effect of brexanolone in clinical trials questions the mechanism of action mediating the remarkable antidepressant effects, leading us to ask why and how does this drug work. Asking why this drug is effective may provide insight into the underlying neurobiology of postpartum depression. Exploring how this drug works will potentially elucidate a novel antidepressant mechanism of action and may provide useful information for next generation drug development. In this review, we examine the clinical and preclinical evidence supporting a role for allopregnanolone in the underlying neurobiology of postpartum depression as well as foundational evidence supporting the therapeutic effects of allopregnanolone for treatment of postpartum depression.

1. Introduction

Recent FDA approval of an allopregnanolone-based treatment specifically for postpartum depression, brexanolone, now commercially called Zulresso®, is an exciting development for patients and families impacted by postpartum depression and allows us to start asking questions about why and how this compound is so effective. Allopregnanolone is a neuroactive steroid, or neurosteroid, which can be synthesized from steroid hormone precursors, such as progesterone, or synthesized *de novo* from cholesterol. Neurosteroids are positive allosteric modulators at $GABA_A$ receptors ($GABA_ARs$), a property which is thought to mediate the therapeutic effects of these compounds. However, the durability of effect of brexanolone in clinical trials questions the mechanism of action mediating the remarkable antidepressant effects, leading us to ask why and how does this drug work. Asking why this drug is effective may provide insight into the underlying neurobiology of postpartum depression. Exploring how this drug works will potentially elucidate a novel antidepressant mechanism of action and may provide useful information for next generation drug development. In this review, we examine the clinical and preclinical evidence supporting a role for allopregnanolone in the underlying neurobiology of postpartum depression as well as foundational evidence supporting the therapeutic effects of allopregnanolone for treatment of postpartum depression.

2. Postpartum depression

Postpartum depression is reported to impact approximately 10–20% of postpartum women (Gavin et al., 2005;O'Hara and Swain, 1996); however, the actual incidence is thought to be much higher due to the lack of proper screening, stigma surrounding postpartum depression, and resultant underdiagnosis (Ramsay, 1993; Whitton et al., 1996) (for review see (Halbreich and Karkun, 2006)). In fact, postpartum depression is the most common complication of childbirth, and the magnitude of the problem is reflected in the fact that suicide accounts for approximately 20% of postpartum deaths (Lindahl et al., 2005). It is also essential to highlight that the impact of postpartum depression is far-reaching, affecting the family unit as a whole and leading to long-term negative outcomes on infant behavioral, emotional, and cognitive development (Feldman et al., 2009; Halligan et al., 2007; Lyons-Ruth

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et al., 1986; Murray, 1992; Murray and Cooper, 1997a, 1997b; Righetti-Veltema et al., 2002, 2003). Thus, the benefits from the development of an effective treatment for postpartum depression cannot be understated.

Numerous pathological mechanisms have been proposed to contribute to postpartum depression, including neuroendocrine changes, neuroinflammation, neurotransmitter alterations, circuit dysfunction, genetics, and epigenetics. This topic has been comprehensively reviewed recently (Payne and Maguire, 2019) and for this reason and due to the recent success of an allopregnanolone-based treatment, this review will focus on evidence suggesting a role for allopregnanolone in the underlying neurobiology of postpartum depression.

3. Allopregnanolone and $GABA_AR$s

Allopregnanolone is a neuroactive derivative of progesterone and a positive allosteric modulator at $GABA_AR$s. $GABA_AR$s are heteropentameric receptors formed from a combination of 19 known subunits: α1-6, β1-3, γ1-3, δ, ε, θ, π and ρ1-3 (Barnard et al., 1998; Whiting et al., 1999), typically composed of 2 αs, 2 βs, and either the γ2 or the δ subunit. $GABA_AR$ subunit composition dictates the anatomical distribution (Pirker et al., 2000) and subcellular localization (Kittler et al., 2002), kinetics, and pharmacology of these receptors (Hevers and Luddens, 1998; Mody and Pearce, 2004). The unique properties conferred by specific $GABA_AR$ subunit combinations give rise to two distinct forms of GABAergic inhibition: phasic inhibition, which is transient and mediated by synaptically-localized receptors, and tonic inhibition, which is a persistent form of inhibition mediated largely by extrasynaptic $GABA_AR$s (Farrant and Nusser, 2005). Extrasynaptically localized δ subunit-containing receptors have been shown to confer neurosteroid sensitivity (Belelli et al., 2002; Brown et al., 2002; Mihalek et al., 1999; Spigelman et al., 2002; Wohlfarth et al., 2002); however, the neurosteroid binding site has been localized to the α-subunit transmembrane domain (Laverty et al., 2017). Further complicating the roles of these receptor subtypes, δ subunit-containing receptors have recently been demonstrated to contribute to the phasic component of inhibition to some degree (Sun et al., 2018). Notwithstanding the complexity in the contribution of different $GABA_AR$ subtypes to the different forms of inhibition and pharmacological sensitivity, it is clear that neurosteroids like allopregnanolone act as positive allosteric modulators at these receptors.

4. Allopregnanolone in postpartum depression

Changes in steroid hormone levels and associated changes in allopregnanolone levels occur throughout the peripartum period (Mastorakos and Ilias, 2000; MASTORAKOS and ILIAS, 2003; Bloch et al., 2003a) and the dramatic decline of these hormones during the postpartum period has been proposed to contribute to the development of mood disorders (for review see (Meltzer-Brody, 2011; Schiller et al., 2015)) (for review see (Bloch et al., 2003a)) (Table 1). In particular, allopregnanolone has been implicated in postpartum mood disorders due to the precipitous decline in allopregnanolone levels following delivery (Schüle et al., 2014). It has also been well-established that allopregnanolone possesses anxiolytic and antidepressant effects (for review see (Schüle et al., 2014)). Decreases in allopregnanolone levels have been implicated in major depressive disorder and antidepressant treatment has shown to increase allopregnanolone levels (Romeo et al., 1998; Schüle et al., 2005, 2011; Uzunova et al., 1998), implicating allopregnanolone as a potential mediator of depression. The following section reviews clinical and preclinical evidence pointing to a role for allopregnanolone in postpartum depression.

4.1. Clinical evidence of a role for allopregnanolone in postpartum depression

The most convincing evidence for a role for allopregnanolone in postpartum depression comes from the robust antidepressant effects demonstrated in clinical trials with an allopregnanolone analog in postpartum women (Kanes et al., 2017a, 2017b; Meltzer-Brody et al., 2018a). These studies lead to the first FDA-approved drug for the treatment of postpartum depression, brand name Zulresso®. It is unlikely that treatment with Zulresso ®is correcting the underlying biology in this diverse patient population. Therefore, these remarkable clinical findings suggest that allopregnanolone is capable of exerting robust antidepressant effects independent of the underlying etiology of disease. Understanding how allopregnanolone exerts these broad antidepressant effects may provide insight into the underlying neurobiology of postpartum depression. As this treatment goes to market we will likely learn more about the larger population response to this novel antidepressant treatment.

Hormonal fluctuations have been proposed to underlie postpartum mood disorders (Table 1) based on the timing of symptom onset which coincides with a precipitous decline in steroid hormone levels, including estrogen and progesterone (for review see (Meltzer-Brody, 2011)). Despite the seemingly obvious relationship between hormonal changes and symptom onset, studies attempting to empirically demonstrate this relationship have been inconclusive. Some studies demonstrate a correlation between reproductive hormone levels and postpartum depression (Abou-Saleh et al., 1998; Feksi et al., 1984; Harris et al., 1994), whereas, others have failed to observe this relationship (Chatzicharalampous et al., 2011; Harris et al., 1996; Heidrich et al., 1994; Klier et al., 2007; Kuevi et al., 1983) (for review see (Bloch et al., 2003a; Schiller et al., 2015; Yim et al., 2015)). A compelling, transformative study demonstrated an altered sensitivity to steroid hormones only in patients with a history of postpartum depression (Bloch et al., 2000), suggesting that absolute hormone levels may not be altered, but altered sensitivity to steroid hormone may underlie the risk to postpartum depression. While little progress has been made in identifying the potential underlying causes for altered steroid hormone sensitivity associated with postpartum depression at the clinical level, preclinical research supports this notion and will be discussed in greater depth below.

Similarly, inconsistent findings have been found regarding the relationship between allopregnanolone levels and postpartum mood. Although several studies have measured lower levels of allopregnanolone associated with postpartum depression (Nappi et al., 2001a; Hellgren et al., 2014; Osborne et al., 2017; Crowley et al., 2016) and identified lower allopregnanolone levels as a risk factor for postpartum depression (Deligiannidis et al., 2013a, 2016), many others fail to demonstrate such a relationship (Deligiannidis et al., 2013a, 2016; Epperson et al., 2006a, 2006b). Those studies that do suggest a relationship demonstrate reductions in allopregnanolone levels in women with a risk of developing postpartum depression (Osborne et al., 2017), a reduction in women experiencing postpartum blues (Nappi et al., 2001b), and a negative correlation with depression symptoms in postpartum women (Hellgren et al., 2014); whereas, others have failed to find a relationship between allopregnanolone levels and postpartum depression (Deligiannidis et al., 2013a, 2013b, 2016; Epperson et al., 2006a, 2006b). In fact, one study measured elevated levels of allopregnanolone in women with postpartum depression (Deligiannidis et al., 2019), although this increase is proposed to be a compensatory mechanism (personal communication with Dr. Kristina Deligiannidis), and positively correlates with observed differences in the connectivity of the dorsomedial prefrontal cortex within the default mode network which are correlated with depression scores (Deligiannidis et al., 2019). In fact, alterations in neurosteroid levels, particularly allopregnanolone, have been proposed to mediate affective switching in relation to reproductive mood disorders (Schiller et al., 2014). While this idea is

Table 1
Potential mechanisms implicated in the underlying neurobiology of PPD in relation to potential mechanisms of action mediating the antidepressant effects of allopregnanolone.

Mechanisms of Action of Allopregnanolone	Implicated in the Underlying Neurobiology of PPD	Potential Mechanisms Mediating the Antidepressant effects of Allopregnanolone
GABAergic Dysfunction	+	+
HPA Axis Dysfunction	+	+
Neurosteroid Deficits	+	+
Altered Network Communication	+	?
Neuroprotection	–	–
Neuroinflammation	+	?
Genetic Predisposition	+	?
Actions on pregnane X receptors/transcriptional changes and gene regulation	–	?
Actions on membrane progesterone receptors/G-protein-coupled receptors	–	?
Metabotropic Regulation of GABA receptors	–	?

+ indicates a strong relationship, - indicates no known interaction, ? Indicates the relationship is currently undetermined.

appealing, data have fallen short in supporting the role of allopregnanolone in mediating mood disorders and future studies are required to investigate the ability of allopregnanolone to mediate affective switching, i.e. the alteration in network activity from a healthy to pathological state.

The consistently inconsistent clinical findings attempting to associate either steroid hormone or neurosteroid levels with postpartum depression summarized above are likely due to the diverse underlying etiologies in the patient population. The methodology, particularly the timing of sample collection, also introduces variability in the results and needs to be appreciated when interpreting these findings. While it is likely that there is a role for altered steroid hormones and/or neurosteroids in postpartum depression, the factors discussed above make it challenging to study this in the clinical population and, therefore, preclinical studies are necessary to empirically test this relationship. These will therefore be discussed in the following section.

4.2. Preclinical studies implicating allopregnanolone in postpartum depression

This section will focus on preclinical investigations specifically related to allopregnanolone in postpartum depression, rather than attempting to comprehensively review the preclinical studies of postpartum depression (recently reviewed (Payne and Maguire, 2019)). Animal models have been employed in an effort to better understand the relationship between steroid hormones and neurosteroids in postpartum depression (reviewed in (Perani and Slattery, 2014)). Given the timing of symptom presentation, pseudo-pregnancy and hormone withdrawal models have been developed which recapitulate depression-like behaviors and anhedonia in animal models (Galea et al., 2001; Stoffel and Craft, 2004; Green et al., 2009; Navarre et al., 2010). Further studies specifically implicated neurosteroids, rather than steroid hormones themselves, in mediating the effects of steroid hormone withdrawal on depression-like behaviors. For example, treatment with finasteride, a 5α-reductase inhibitor which blocks the conversion of progesterone to allopregnanolone, induces depression-like behaviors in animal models (Frye and Walf, 2004). Further, the predominant site of neurosteroid action, namely δ subunit-containing $GABA_AR$s, have also been implicated in postpartum depression. Mice which lack (*Gabrd*$^{-/-}$ mice) or have deficits in $GABA_AR$ δ subunit expression (*Gabrd* $^{\pm}$ mice) exhibit depression-like behaviors restricted to the postpartum period and deficits in maternal care (Maguire and Mody, 2008). Similar to the robust antidepressant effects of neurosteroid-based treatments in patients with postpartum depression (Kanes et al., 2017a, 2017b; Meltzer-Brody et al., 2018a), a similar compound, SGE-516, exhibits robust antidepressant effects in preclinical mouse models of postpartum depression (Melón et al., 2018). Collectively, these findings suggest that deficits in neurosteroid signaling are sufficient to induce depression-like behaviors, with potential relevance to mood disorders related to the postpartum period.

4.3. Diverse etiology of postpartum depression with relevance to allopregnanolone

As mentioned above, there is a likely a diverse etiology of disease related to the underlying neurobiology of postpartum depression (Table 1). Here we discuss proposed mechanisms of disease with relevance to postpartum depression in relation to allopregnanolone and stress; specifically, $GABA_AR$ deficits and hypothalamic-pituitary-adrenal (HPA) axis dysfunction. The potential contribution of these mechanisms to postpartum depression has recently been comprehensively reviewed (Payne and Maguire, 2019).

4.3.1. Evidence for $GABA_AR$ deficits

A GABAergic hypothesis has been proposed for major depressive disorder (MDD) (Lüscher and Möhler, 2019; Luscher et al., 2011) and GABAergic deficits have also been implicated in postpartum depression (Table 1). Peripartum GABA levels were found to be significantly lower in women at risk for developing postpartum depression and negatively correlated with the severity of depression and anxiety symptoms (Deligiannidis et al., 2016). GABA levels also correlated with observed differences in the connectivity of the dorsomedial prefrontal cortex within the default mode network and those differences also correlated with depression scores in women with postpartum depression (Deligiannidis et al., 2019). However, observed changes in GABA levels are also inconsistent among the patient population. Occipital GABA levels are reduced in postpartum women, but not linked to postpartum depression; in fact, there is a trend towards an increase in women with postpartum depression compared to health postpartum women (Epperson et al., 2006b). Although the clinical studies do not paint a clear picture of changes in GABA associated with postpartum depression, the findings do not support GABAergic deficits associated with postpartum depression in the clinical population. Frankly, there is a limited number of studies that have attempted to examine potential changes in GABAergic signaling related to postpartum depression due to the lack of attention on this women's health issue. Those elegant studies that have begun to examine potential contributions of GABAergic mechanisms related to postpartum depression are promising and more, similarly well-controlled studies are necessary.

Preclinical studies lend more evidence suggesting that GABAergic deficits could contribute to depression (Table 1). Similar to the observations in humans, GABA levels are altered throughout the peripartum period (Lonstein et al., 2014), although deficits have not been linked to postpartum mood disorders. A moderate reduction in

forebrain expression of synaptic $GABA_ARs$ is sufficient to induce anxiety- and depression-like phenotypes (Earnheart et al., 2007), supporting the GABAergic hypothesis of depression (Lonstein et al., 2014). Studies related to postpartum depression have focused more on neurosteroid-sensitive, extrasynaptic $GABA_ARs$ (Maguire and Mody, 2009). $GABA_AR$ δ subunit expression is regulated by steroid hormones and neurosteroids, exhibiting altered expression over the estrous cycle and throughout the peripartum period in mice (Maguire and Mody, 2008, 2009; Maguire et al., 2005). Withdrawal from progesterone has been shown to increase $GABA_AR$ δ subunit expression (Sundstrom-Poromaa et al., 2002), which has been proposed to be a necessary homeostatic mechanism (Maguire et al., 2009). $GABA_ARs$ incorporating the α4 subunit, which is known to partner with the δ subunit, has also been shown to be regulated by steroid hormones and neurosteroids (for review see (Smith et al., 2007)). These receptors have been shown to be altered during puberty (Shen et al., 2007) and in hormone withdrawal models (Smith et al., 1998, 2006, 2007; Smith, 2002). Alterations in $GABA_ARs$ in hormone withdrawal models has particular potential relevance to postpartum depression. Withdrawal from prolonged exposure to either progesterone or allopregnanolone increased α4 expression in the hippocampus (Smith et al., 1998; Gulinello et al., 2002; Hsu and Smith, 2003) and in vitro (Follesa et al., 2001) with corresponding changes in pharmacology (Wafford et al., 1996). (for review see (Smith et al., 2007)). Alterations in $GABA_AR$ subunit composition following progesterone or neurosteroid withdrawal are associated with behavioral deficits, including an increase in anxiety- and depression-like behaviors (Stoffel and Craft, 2004; Smith et al., 2006). Further, mice lacking the $GABA_AR$ δ subunit have been demonstrated to exhibit depression-like behaviors that are restricted to the postpartum period and deficits in maternal care (Maguire and Mody, 2008). These data demonstrate that GABAergic deficits are sufficient to induce depression-like behaviors, but the relevance to the clinical condition remains uncertain.

4.3.2. Evidence for HPA axis dysfunction: role of allopregnanolone and $GABA_ARs$

In addition to the neuroendocrine changes implicated in postpartum depression described above, such as the dramatic changes in steroid hormone and neurosteroid levels, hypothalamic-pituitary-adrenal (HPA)axis dysfunction has also been implicated in postpartum depression (Pariante and Lightman, 2008) (Table 1). Stress and previous adverse life events are major risk factors for postpartum depression (Pariante and Lightman, 2008; Meltzer-Brody et al., 2018b). The body's physiological response to stress is mediated by the HPA axis, which constitutes the neuroendocrine response to stress involving corticotropin-releasing hormone (CRH) release from the paraventricular nucleus of the hypothalamus (PVN), signaling the release of adrenocorticotropic hormone (ACTH) from the pituitary, followed by cortisol release from the adrenal cortex in humans (corticosterone in mice). Hypercortisolism, or excessive cortisol levels, indicating HPA axis dysfunction, is a hallmark feature of major depressive disorder and, thus, has similarly been implicated in postpartum depression (Pariante and Lightman, 2008). However, similar to assessments of reproductive hormones, there have been inconsistent findings regarding alterations in stress hormones associated with postpartum depression. There is evidence that cortisol, ACTH, and CRH levels are altered in women with postpartum depression (Bloch et al., 2003b). There is also evidence that the regulation of the HPA axis may be dysfunctional in women with postpartum depression, including evidence that women with a history of postpartum depression demonstrate an increase in stimulated cortisol release (Bloch et al., 2005), decreased responsiveness to the dexamethasone suppression test (Bloch et al., 2003b), and an altered ratio of ACTH to cortisol levels (Jolley et al., 2007). Diurnal cortisol assessments suggest an increase in baseline morning cortisol levels, but a blunted morning rise in cortisol, associated with postpartum depression (Taylor et al., 2009). In a more nuanced study, cortisol levels were assessed in response to a memory encoding task during pregnancy which were negatively correlated with postpartum depression scores (Williams and Frey, 2017). Exogenous CRH-stimulated cortisol release are higher in women with a history of postpartum depression (Bloch et al., 2005). A relationship between gestational levels of CRH were found to predict development of postpartum depression and was proposed to be a diagnostic criterion (Yim et al., 2009a, 2009b)); however, other studies have failed to find a relationship between CRH levels and postpartum depression (Meltzer-Brody et al., 2011) and the utility as a diagnostic marker was openly questioned (Rich-Edwards et al., 2009). Similarly, there are conflicting studies on reproductive hormones, the methods for sample collection, timing, context, etc. which introduces variability that further complicates the comparison between studies. A recent study has employed measurements of hair cortisol levels to get a broader and more unified picture of stress hormone changes throughout the peripartum period in relation to postpartum depression, and demonstrated that hair cortisol levels along with measurements of psychopathological symptoms and pregnancy-specific stress can predict the occurrence of postpartum depression symptoms (Caparros-Gonzalez et al., 2017). A review of the literature regarding cortisol and postpartum depression suggested that hypercortisolemia is associated with transient mood states; whereas, hypocortisolemia is associated with postpartum depression (Seth et al., 2016). Thus, the relationship between stress hormone levels and postpartum depression remains unclear in the clinical population. Further, to our knowledge no clinical studies have attempted to examine the impact of allopregnanolone on HPA axis dysregulation associated with postpartum depression. However, there is ample preclinical evidence that allopregnanolone is capable of regulating HPA axis function.

CRH neurons at the apex of HPA axis control are tightly regulated by GABAergic inhibition (for review see (Decavel and van den Pol, 1990; Herman et al., 2004)). In fact, CRH neurons have been shown to be regulated by tonic GABAergic inhibition mediated by neurosteroid-sensitive, δ subunit-containing $GABA_ARs$ (Sarkar et al., 2011). Neurosteroids have been shown to influence HPA axis function (for review see (Crowley and Girdler, 2014; Wirth, 2011)). For example, pretreatment with allopregnanolone decreases the neuroendocrine response to stress, resulting in a decrease in circulating levels of stress hormones (Owens et al., 1992; Patchev et al., 1996). Allopregnanolone has been shown to alter the expression of CRH in the PVN (Patchev et al., 1994, 1996), indicating regulation of the HPA axis at the level of the hypothalamus either indirectly through the numerous brain regions impinging on this system or directly via actions on δ subunit-containing $GABA_ARs$ on CRH neurons in the PVN. These data suggest that alterations in reproductive steroid hormone or neurosteroid signaling may impact HPA axis function, providing a potential mechanistic link related to postpartum depression.

Preclinical studies have demonstrated that HPA axis dysfunction is sufficient to induce postpartum depression-like behaviors (Maguire and Mody, 2016a; Mel+¦n et al., 2018). In two independent preclinical models of postpartum depression, the inability to suppress the stress-induced activation of the HPA axis during the postpartum period is associated with depression-like behaviors restricted to the postpartum period and correlates with deficits in maternal care (Maguire and Mody, 2008; Mel+¦n et al., 2018) (Table 1). Further, artificially activating the HPA axis during the postpartum period is sufficient to induce abnormal postpartum behaviors, including depression-like behaviors and deficits in maternal care (Mel+¦n et al., 2018). These behavioral impairments are thought to be due to excessive glucocorticoid signaling given that exogenous corticosterone treatment can induce deficits in postpartum behaviors (Brummelte and Galea, 2010; Brummelte et al., 2006; Maguire and Mody, 2016b), similar to effects observed with chronic stress during late pregnancy (Maguire and Mody, 2016a). Interestingly, a neurosteroid-based treatment, related to the recently FDA-approved treatment for postpartum depression, is effective at restoring normal HPA axis function and decreasing depression-like behaviors and

improving maternal care in two independent preclinical models of postpartum depression (Melón et al., 2018) (Table 1).

5. Allopregnanolone as a treatment for postpartum depression

5.1. Clinical studies supporting allopregnanolone as a treatment for postpartum depression

Antidepressant treatment with selective serotonin reuptake inhibitors (SSRIs) has been shown to increase allopregnanolone levels (Romeo et al., 1998; Schüle et al., 2005, 2011; Uzunova et al., 1998) and, unlike the effects on the serotonergic system, the changes in neurosteroid levels occur on a time scale relevant to their antidepressant effects. These findings sparked the idea that the antidepressant effects of SSRIs may be mediated, at least in part, by the production and actions of neurosteroids.

The most direct, clinical evidence for a demonstration of the antidepressant effects of allopregnanolone fist came from an open-label, proof-of-concept study in women with severe postpartum depression using a synthetic analog of allopregnanolone, brexanolone (Kanes et al., 2017b). This study was followed by a successful double-blind, randomized, placebo-controlled trial, demonstrating a dramatic reduction in HAM-D scores in women with severe postpartum depression (Kanes et al., 2017a). This allopregnanolone-based compound also demonstrated success in a two multicenter, double-blind, randomized, placebo-controlled, phase 3 trials, again demonstrating a dramatic reduction in HAM-D scores at two different doses in both women with moderate and severe postpartum depression (Meltzer-Brody et al., 2018a). Brexanolone also significantly decreased MADRS scores across these trials (Clemson et al., 2019) and demonstrated rapid and durable antidepressant effects with a favorable safety profile (Meltzer-Brody et al., 2018c). Brexanolone, under the brand name Zulresso®, received FDA approval on March 19, 2019 (Hellwig, 2019; Scott, 2019; Canady, 2019), representing a major breakthrough as the first FDA-approved drug specifically for postpartum depression, making strides in efforts against disparities in women's health as well as demonstrating success in bench to bedside research for mental health disorders.

5.2. Preclinical studies suggesting GABA positive allosteric modulators as treatments for postpartum depression

The timeline from the first demonstration of deficits in δ subunit-containing $GABA_A$Rs contributing to postpartum depression in preclinical models and subsequent amelioration with a positive allosteric modulator of these receptors (Maguire and Mody, 2008) to FDA approval of Zulresso® took a mere 10 years (Mody, 2019). The first observation implicating deficits in neurosteroid signaling in postpartum depression in preclinical models came from the demonstration that mice that lack (*Gabrd*$^{-/-}$ mice) or have a reduction (*Gabrd* $^{\pm}$ mice) in expression of the $GABA_A$R δ subunit exhibit depression-like behaviors and anhedonia restricted to the postpartum period (Maguire and Mody, 2008). Further, *Gabrd*$^{-/-}$ and *Gabrd* $^{\pm}$ dams exhibit profound deficits in maternal care, resulting in an increase in pup mortality due to cannibalism and/or neglect (Maguire and Mody, 2008). It was proposed that impairment in neurosteroid signaling through δ subunit-containing $GABA_A$Rs during the postpartum period underlies these postpartum depression-like behaviors (Maguire and Mody, 2009). This hypothesis was tested by treating mice with a positive allosteric modulator acting preferentially at δ subunit-containing $GABA_A$Rs, which was effective at improving the postpartum behaviors and reducing pup mortality (Maguire and Mody, 2008). These studies were the first demonstration that positive allosteric modulators of $GABA_A$Rs may be useful for the treatment of postpartum depression (Maguire and Mody, 2008). Further, these data specifically implicated deficits in neurosteroid signaling in postpartum depression and suggested that neurosteroid treatment may be useful for the treatment of postpartum depression (Maguire and Mody, 2008).

6. Proposed therapeutic mechanism of action

The mechanism of action of allopreganolone is largely thought to be mediated by its ability to act as a positive allosteric modulator at $GABA_A$Rs (Table 1). However, allopregnanolone has also been shown to act on pregnane X receptors, which mediate transcriptional changes and gene regulation, as well as membrane progesterone receptors, which are G-protein-coupled receptors and mediate a variety of intracellular effects (Frye et al., 2014; Guennoun et al., 2015) (Table 1). In fact, metabotropic effects of allopregnanolone have been shown to alter the expression of $GABA_A$Rs (Comenencia-Ortiz et al., 2014; Abramian et al., 2014; Modgil et al., 2017), increasing the complexity of the impact of neurosteroids on GABAergic inhibition (Table 1). Through these diverse actions, and perhaps others that remain undiscovered or indirect, allopregnanolone has been shown to exert numerous effects such as neuroprotective effects, anti-inflammatory effects, and anxiolytic and antidepressant effects (for review see (Reddy, 2010)) (Table 1). The antidepressant effects of allopregnanolone are thought to be mediated by the positive allosteric modulation of $GABA_A$Rs. However, the durability of effect observed in clinical trials, demonstrating antidepressant effects lasting a month after the cessation of treatment, is not easily explained by the direct actions of allopregnanolone on these receptors. Thus, a better understanding of the mechanism of action mediating the rapid and prolonged antidepressant effects of Zulresso® will provide insight into potentially novel targets for the development of next generation drugs.

7. Next generation treatments

Zulresso® has shown remarkable antidepressant effects in clinical trials; however, there are limitations regarding this transformative treatment. Zulresso® treatment is administered intravenously (i.v.) and requires a Risk Evaluation and Mitigation Strategy (REMS) program, which involves administration by a healthcare provider with continuous monitoring of the patient, limiting treatment accessibility and increasing cost. Hopefully, these requirements may loosen over time with more information regarding patient's responses and tolerability. A similar oral compound developed by SAGE Therapeutics, SAGE-217, is currently in clinical trials (Hoffmann et al., 2019), which will be an improvement for dosing, accessibility, and cost.

One might argue that the antidepressant effects of Zulresso® and SAGE-217 are so striking that we need not bother investigating and developing next generation drugs. However, given the diverse effects of allopregnanolone on numerous processes, exogenous administration, particularly chronically, may have adverse side effects. Ideally, more information about the mechanism of action mediating the antidepressant effects of allopregnanolone would enable us to develop more targeted interventions for treatment (for review see (Payne and Maguire, 2019)). Thus, the development of next generation drugs requires more mechanistic information about the antidepressant effects of allopregnanolone.

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