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New Findings and Emerging Trends in Postpartum Mental Illness: Risk Factors and Treatments

Kathleen Kendall-Tackett, PhD, IBCLC, FAPA

Department of Pediatrics, Texas Tech University Health Sciences Center, Amarillo, Texas, USA.

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ABSTRACT

Research on postpartum depression and co-occurring conditions, such as anxiety and posttraumatic stress disorder (PTSD), continues to accumulate at a rapid rate, with recent identification of new risk factors and treatments. This article highlights these recent findings. Recent studies have identified several groups of women more at risk for depression postpartum: women in the military; refugees, asylum seekers, and immigrants; women who gave birth during COVID, and women who smoke. In addition, there are several emerging treatments for depression that are promising that include non-pharmacologic and pharmacologic modalities. Among the non-pharmacologic treatments are acupuncture and repetitive transcranial magnetic stimulation (rTMS). New medications include ketamine and esketamine, and brexanolone and zuranolone. All these medications reduce symptoms quickly and have been approved to treat severe depression. Ketamine and esketamine have been approved for depression in general, while brexanolone and zuranolone specifically treat postpartum depression.

Keywords: postpartum, depression, military, asylum seekers, COVID, smoking, esketamine, brexanolone, zuranolone.

Depression, anxiety, and posttraumatic stress disorder are common in pregnant and postpartum women, with some groups at especially high risk. Many recent findings expand our thinking about mental health in the perinatal period. This article highlights some trends on risk factors and treatment innovations that emerged from a recent a large review that resulted in a two-volume book (Kendall-Tackett, 2023, 2024). This review was the result of a comprehensive literature search that was conducted over a 2-year period (2021-2022) and continued until the books were complete. Articles were gathered from around the world but were limited to articles published in English.

Searches were conducted on PubMed, CINAHL, Cochrane databases, and Google scholar with a wide range of search terms including postpartum/postnatal depression, anxiety, and posttraumatic stress disorder (PTSD). These terms were combined with more specific terms, such as treatment, assessment, symptoms, or risk factors. The searches became more specific as different terms emerged (e.g., acupuncture, military mothers, and immigrants). These searches yielded 1,010 articles; 851 were included in the final review. The articles not included were rejected because they were either not methodologically rigorous or they were older and repeated content already included in earlier editions of the book. The goal of the review was to not simply add new literature to an existing volume, but to understand how these new studies fit or changed the interpretation of previous findings.

This present article is an excerpt and reworking of text from the larger review focusing on articles that represent genuine change in what we know about perinatal risk factors and treatment innovations. Since these areas are new, the text included in this article represents what we know so far. The goal of the present article is to make this information more readily accessible to clinicians. The selection of topics I have highlighted is admittedly subjective but reflects novel areas of study, with a particular focus on the past 5 years. I have included some older studies in this review that are important for context. The first section describes risk factors for depression.

Risk Factors

VIOLENCE AGAINST WOMEN

Violence is a well-established risk factor for depression, anxiety, and PTSD in perinatal women. Recent research has confirmed that relationships, particularly studies on adverse childhood experiences and intimate partner violence. In addition, recent studies have identified a new population at risk for violence: women in the military.

Adverse childhood experiences

Adverse childhood experiences (ACEs) include childhood physical and sexual abuse; emotional abuse; neglect (physical and emotional); witnessing parental intimate partner violence; parental mental illness, substance use, and criminal activity. The more types of ACEs people experience, the higher their ACE score, which can lead to potentially worse outcomes as adults (Anda et al., 2009).

A Chinese study assessed women in late pregnancy, and at 1 and 4 weeks postpartum (Li et al., 2017). Physical neglect was the strongest predictor for both prenatal and postpartum depression. The effects of ACEs were also cumulative: women who experienced more ACEs had higher depression throughout the perinatal period.

A large, prospective study from France (N=3,310) compared risk factors for early- (n=250) and late-onset (n=235) postpartum depression (Tebeka et al., 2021). Early-onset depression (up to 8 weeks) was related to childhood sexual abuse, stressful life events, personal history of depression, or co-occurring chronic disease. Late-onset depression was associated with childhood emotional abuse, stressful life events, unemployment, personal or family history of mood disorders, cannabis use, and an emergency condition during pregnancy.

Intimate partner violence

All around the world, women are beaten or raped

by their intimate partners during pregnancy or postpartum. Recent data from the U.S. PRAMS study found that 13% of mothers are depressed (Bauman et al., 2020). However, 33% of women have depression if they experienced partner violence before or during pregnancy.

Partner violence increased the risk of depression by 5 times in a Nigerian study of 250 mothers (Adeyemo et al., 2020). Of the 40 who reported partner violence, 65% reported verbal abuse, 28% were beaten, and 8% were raped. A study of 500 women from Tanzania found that 19% experienced physical or sexual partner violence while pregnant: 39% reported childhood physical or sexual abuse, and 10% experienced both (Mahenge et al., 2018). The risk of depression increased 5.8 times if they were abused by a partner during pregnancy, and 2.7 times if they were abused as children.

A sample of 210 women from Mexico City found that 11% reported partner violence during pregnancy and postpartum (Navarrete et al., 2021). Partner violence increased the risk of depression during pregnancy by 3.5 times, and by 18.3 times at 6 months postpartum. It also increased the risk of anxiety by 6 times. Women with low-income and education were most vulnerable to partner violence.

In a sample of 239 low-income pregnant American women who were part of a nurse home-visitation program following recent partner violence, 40% had PTSD (Kastello et al., 2016). Forty-three percent reported physical, sexual, and psychological abuse within the past year. Age was the strongest predictor of PTSD; 80% of women 30 or older had PTSD, possibly due to a cumulative effect of lifetime trauma. Interestingly, 65% of participants said that other events—not partner violence—caused their PTSD. Women at particular risk for IPV were unmarried, low-income, and with low education.

Military sexual trauma

Women in active military service are a newly identified at-risk population. All women in the military are at high risk for depression, but women who have experienced military sexual trauma are at especially high risk. Military sexual trauma ranges from offensive remarks to rape. The effects of military sexual trauma are so devastating that they can exceed those of combat. It has been linked to depression, PTSD, anxiety, and adverse birth outcomes. So far, all studies have been in the U.S., but other countries may have similar issues.

A longitudinal study followed 620 U.S. female veterans during pregnancy and 452 postpartum (Gross et al., 2020). Fifty-two percent reported sexual harassment and 30% reported sexual assault. Seventy-one percent of women who were harassed were depressed compared to 41% of non-harassed women, which is also a high rate. In addition, 56% had PTSD and 56% had an anxiety disorder compared to 24% of non-harassed women. Among the women who were sexually assaulted, 77% were depressed (vs 48% of non-assaulted women), 65% had PTSD (vs 30%), and 60% had anxiety disorders (vs 41%). These results show very high rates of depression, anxiety, and PTSD for all women in the military, with exceedingly high rates for women who have been assaulted.

Another U.S. study included 911 women who delivered a baby after entering the military (Nillni et al., 2020). Fifty-nine percent reported military sexual trauma and 36% reported combat exposure. Among the entire sample, 29% had a preterm birth (the U.S. national rate is 11%), and 45% had postpartum depression or anxiety. Military sexual trauma increased these rates. After controlling for age, racial/ethnic minority status, childhood violence, and warfare exposure, every increase on the sexual harassment scale decreased birthweight by 17 g and increased depression by 9%.

In a sample of 697 pregnant U.S. veterans, military sexual trauma negatively affected mother-infant bonding (Creech et al., 2022). Fifty-two percent reported harassment and 30% reported abuse or rape. Twenty-eight percent of women who experienced military sexual trauma were depressed. Military sexual trauma increased the risk of depression, which was related to poorer mother-infant bonding.

GLOBAL EVENTS AND MATERNAL MENTAL HEALTH

New mothers are not immune to what is happening in the world. Terrorism, war, and global pandemic have all affected women's mental health. Below is a brief summary of recent findings on the effect of COVID-19 and immigration and forced migration on maternal mental health.

Covid-19

The COVID-19 pandemic had a devastating effect on new mothers. An international study, conducted in 12 languages and 64 countries while COVID still raged, examined its effects in a sample of 6,894 pregnant and postpartum women (Basu et al., 2021). Forty-three percent were at or above the cutoff for posttraumatic stress disorder, 31% for anxiety or depression, and 53% for loneliness. The more worries mothers identified, the higher their depression, anxiety, PTSD, and loneliness scores were.

COVID-19 also impacted birth outcomes. A study compared 1,611 mothers who gave birth at the height of COVID-19 to 640 mothers who had given birth before (Mayopoulos et al., 2021). Mothers in the COVID-19 group had more acute stress, childbirth-related PTSD, and breastfeeding problems compared to mothers who delivered before COVID-19. COVID mothers also had bonding difficulties compared to non-COVID mothers.

A similar study from Russia included 611 women who gave birth before the pandemic and 1,645 who gave birth during it (Yakupova et al., 2022). In Russia, the rates of depression and PTSD rates were already high, so did not increase during the pandemic. However, obstetric violence significantly increased during COVID, particularly verbal aggression, bullying, and ignoring the needs of the birthing woman. Seventy-three percent of COVID mothers gave birth with no labor support. Eighteen percent had PTSD and 46% were depressed. The authors concluded that COVID-19 compounded pre-existing problems with birth in Russia.

In Mexico City, 293 women at 4 to 12 weeks postpartum had significant symptoms due to COVID lockdowns: 39% were depressed, 46% had anxiety, and 58% reported stress (Suarez-Rico et al., 2021). Pre-lockdown rates for depression were 25% and 23% for anxiety with comparable samples. An astonishing 69% had cesareans and 35% had adverse perinatal outcomes. Mothers who tested positive for COVID while pregnant were significantly more likely to be depressed.

Immigration, forced migration, and refugee status

Women leave their countries for many reasons. Even if mothers migrate for positive reasons, being in a new country—possibly learning a new language, culture, and customs—is highly stressful. Migrating may also mean leaving support behind. Refugee women may be fleeing war or violence and may have experienced the violent death of family members, sexual violation, or possible separation from other children. Not surprising, these women are at high risk for perinatal mental illness.

A study from Ontario, Canada included 519 immigrant women (Gannan et al., 2016). They found that immigrant women were more likely to be depressed if they had been living in Canada for less than 2 years, had previous depression and low support, and/or were living in low-income immigrant communities. Another Canadian study of 1,125 women found that 10% of the overall sample were depressed at 16 weeks postpartum. However, rates varied based on immigration status: 18% for refugees, 24% for asylum-seekers, 14% for non-refugee immigrants, and 7% Canadian-born women (Dennis et al., 2016).

Immigrant vs Native-born

Acculturation refers to the cultural adaptation immigrants experience as they adapt to a new country. It can include learning the language or how to navigate essential systems, such as housing, transportation, and food, while maintaining their original culture (Knipscheer & Kleber, 2006). Non-acculturated immigrants are at higher risk for depression. This can be seen in studies that compared immigrant and native-born mothers. In

every study, immigrant mothers were more likely to be depressed, even if they had been in their current country for many years.

A study from the Netherlands (N=5,109) found that non-Dutch immigrants were more likely to be depressed (Walker et al., 2021). Similarly, a Canadian population study (N=6,237, unweighted, N=74,231 weighted) compared three groups of new mothers: Indigenous, Canadian-born non-Indigenous, and immigrants (Daoud, O'Brien, et al., 2019). The rates for severe depression were 6% for non-Indigenous mothers, 11% for Indigenous, and 12% for immigrant mothers. For mild depression, the rates were 13% for non-Indigenous Canadian-born, 21% for Indigenous, and 24% for immigrants.

A study from Israel included a stratified sample of 1,128 new mothers that included three groups: Palestinian-Arab, Jewish immigrant, and non-immigrant Jewish (Daoud, Saleh-Darawshy, et al., 2019). Palestinian-Arab women had the highest rates of postpartum depression (21%), followed by Jewish immigrants (9%), and non-immigrant Jewish (6%). A key finding was the interaction between multiple forms of discrimination and women's identity (Palestinian-Arab, immigrant, or non-immigrant) that affected Palestinian-Arab and immigrant Jewish mothers. Among Palestinian-Arab mothers, those who experienced multiple forms of discrimination were at highest risk for depression.

SMOKING

Smoking is another risk factor that recently emerged. Whether it *causes* depression, or is simply a marker for it, remains to be seen. However, the results have been remarkably consistent. Pregnant women (N=5,109) who smoked were more likely to be depressed in a study from the Netherlands (Walker et al., 2021). A study from Shanghai (N=1,204) had similar findings: smoked during pregnancy, mother-infant separation, lower education, and breastfeeding difficulties all increased the risk of depression (Liu et al., 2020). A prospective study of 236 new mothers found that smokers had the highest rates of depression (Mbah et al., 2013). The more a mother smoked, the higher her depression score. In U.S. PRAMS data (N=134,435), prenatal smoking increased the risk of depression by 41%. Postpartum smoking increased the risk by 33%. If women smoked during both pregnancy and postpartum, depression risk increased by 54% (Barber & Shenassa, 2021). The authors proposed screening for smoking as a tacit screen for depression as so many depressed mothers smoked.

NON-PHARMACOLOGIC TREAMENTS

Acupuncture

Acupuncture effectively treats major depression in pregnant and postpartum women. It reduced symptoms of major depression in pregnant women in two older American studies (Manber et al., 2004; Manber et al., 2010). In the first study, the response rate was 69% for acupuncture, compared to 47% for sham acupuncture, and 32% for massage, with 20 pregnant women in each group (Manber et al., 2004). Sham acupuncture involves using small, metal "needles" that appear to puncture the skin, but do not. In the second study, 150 pregnant women with major depression were also randomized to three conditions: acupuncture specific for depression, acupuncture not specific for depression, and massage (Manber et al., 2010). The remission rates were 63% for acupuncture for depression, 44% for non-specific acupuncture, and 38% for massage.

Not surprisingly, more recent studies have come from China. A recent review included 887 patients with postpartum depression from 12 randomized trials (Tong et al., 2019). Of these, 443 were treated with acupuncture and 444 were in control groups. Patients in the treatment group had significantly better scores on the Hamilton Rating Scale for Depression (HAM-D) and Edinburgh Postnatal Depression Scale (EPDS) compared to those in the control group. However, the authors were circumspect regarding their findings. Interestingly, the control groups in the 12 studies all had active treatments: 12 studies used medications, 1 included therapy, 2 used Traditional Chinese Medicine, and

1 used massage. In addition, the acupuncture studies did not include acupuncture alone: 3 also included psychological interventions and 3 included Traditional Chinese Medicine. However, even compared to all these other treatments, acupuncture was superior.

Another review included 15 studies of acupuncture and Chinese herbal medicine from both English and Chinese databases (Yang et al., 2018). When acupuncture and Chinese herbal medicine were used alone, or with antidepressants, they reduced depression symptoms on the EPDS compared to a placebo or antidepressants. There was no significant difference between acupuncture and antidepressants, and adverse effects were rare. However, they rated the evidence as low quality (per the Cochrane risk-of-bias tool).

The mechanism by which acupuncture influences mental health is unclear. A recent study of 52 women with postpartum depression (22 of whom had acupuncture) and 24 non-depressed controls found that women with postpartum depression had decreased gray matter volume in sub-regions of the amygdala (left and right lateral) compared to the healthy postpartum women (Huang et al., 2023). The HAM-D scores improved for the depressed women after being treated with acupuncture and the gray matter volume marginally improved. The treated women also showed a significantly enhanced resting-state on functional magnetic resonance imaging (fMRI). They concluded that acupuncture may improve symptoms because it changes the amygdala sub-region structure and the functional connections of brain areas that process negative emotions.

REPETITIVE TRANSCRANIAL MAGNETIC STIMULATION

Repetitive transcranial magnetic stimulation (rTMS) is a gentle brain-stimulation technique that does not require anesthesia and has few side effects. rTMS is a neuro*modulator*, which stimulates nerves to provide a natural biological response. It uses a gentle magnetic pulse and stimulates the brain by passing electrical current through a magnetic coil, which creates a magnetic field over the scalp. The tiny currents stimulate neuronal activity, and it stimulates the right and left dorsolateral prefrontal cortex. Repetitive transcranial magnetic stimulation effectively treats depression, OCD, and PTSD, as well as pain, stroke, and several diseases. There is much research to support this modality and it has been FDA cleared for treating depression. Recent European evidence-based guidelines found that rTMS was effective at Level A (definite efficacy) or Level B (probable efficacy) for depression and other conditions (Lefaucheur et al., 2020).

A consensus statement included 118 articles plus expert opinion on rTMS for treating major depression (McClintock et al., 2018). They found that multiple randomized controlled trials supported the safety and efficacy of rTMS as an antidepressant therapy. The authors wrote this statement on behalf of the National Network of Depression Centers rTMS Task Force and the American Psychiatric Association's Council on Research Task Force on Novel Biomarkers and Treatments.

A small study used repetitive transcranial magnetic stimulation to treat 6 postpartum women with depression (Cox et al., 2020). The women received 20 sessions of 10 Hz rTMS over the left dorsolateral prefrontal cortex over 4 weeks. Researchers measured depression, anxiety, and breastfeeding practices at baseline and at 3 and 6 months postpartum. There was no control group, which does not account for the placebo effect. However, depression and anxiety scores declined over the 4-week treatment period. Depression was lower at 3 and 6 months. Of the six patients, 4 achieved remission.

A review of 14 studies (N=884 participants) found that rTMS reduced scores on the HAM-D and EPDS, and improved cognitive function in patients with postpartum depression (Peng et al., 2020). They included studies from both English and Chinese databases. The studies were all randomized trials and included either a control or sham-treatment group.

One recent study provided a possible mechanism by which rTMS might decrease depressive

symptoms. In a functional-imaging study, 32 women with postpartum depression were compared with 32 age-matched healthy controls (Zhang et al., 2022). Prior to treatment, women with postpartum depression had reduced voxel-mirrored homotopic connectivity in the amygdala, insula, and medial frontal gyrus of the brain compared to healthy volunteers. These regions renormalized after rTMS. In addition, increased connectivity between the right and left insula was correlated with improved EPDS scores. They concluded that intrinsic functional architecture of the interhemispheric communication was disrupted in postpartum depression, which they believed provided evidence for the pathophysiological mechanisms and effects of rTMS.

Repetitive transcranial stimulation (rTMS) has a strong evidence base supporting its use in the general population. Perinatal studies have been promising. This procedure should not be confused with electroconvulsant therapy (ECT). ECT requires anesthesia and can cause memory loss and confusion. In contrast, rTMS is gentle and safe, with minimal side effects. It also requires no anesthesia and is far preferable to ECT.

FAST-ACTING MEDICATIONS FOR SEVERE DEPRESSION: KETAMINE AND BREXANOLONE

Two new medications represent a breakthrough for quickly treating depressive symptoms, particularly when they are severe. Ketamine and brexanolone produce rapid results and treat severe depression and suicidal ideation. The US Food and Drug Administration (FDA) approved both for treating depression in 2019: esketamine for treating depression in the general population and brexanolone for postpartum depression.

These medications work differently than traditional antidepressants. Rather than targeting levels of the monoamine neurotransmitters (serotonin, norepinephrine, and dopamine), ketamine and brexanolone work on GABA (γ-Aminobutric acid) and glutamate receptors. Ketamine and brexonalone are usually given via intravenous (IV) infusion, but esketamine, a variant of ketamine, can be delivered intranasally, and zuranolone is taken orally.

Ketamine

Ketamine is an anesthetic medication with an off-label use to treat severe, refractory depression, especially depression with suicide risk (Preston et al., 2022). Around 60% of patients respond 4.5 hours after a single dose, which lasts 24 hours. The response rate is over 40% after 7 days (Molero et al., 2018). Repeat doses (2 to 4 times per week) sustain the response for several weeks. Ketamine is administered in a clinic via IV over a 2-to-3-hour period with healthcare providers monitoring for possible dissociative and psychotic (temporary) symptoms.

Ketamine is an antagonist of NMDA receptors and blocks their activity and includes racemic and S-ketamine. IV ketamine infusions use both S- and R-ketamine. In their review of 3 randomized trials, 8 open-label trials, and 30 case reports, Smith-Apeldoorn and colleagues (2022) noted that ketamine has been administered intravenously, intranasally, orally, and possibly intramuscularly. Side effects were uncommon but included possible elevated blood pressure and mild dissociative and psychotomimetic effects. They concluded that ketamine had "therapeutic potential" (p. 907) and that maintenance ketamine treatment sustains its antidepressant effect.

Another review and meta-analysis of 24 trials (N=1,877) compared the efficacy of racemic vs esketamine for depression and bipolar major depression (Bahji et al., 2021). Racemic ketamine produced a greater treatment response, higher remission rates, and lower dropouts due to adverse effects compared to esketamine. Ketamine works quickly and lowers depression with suicidal ideations, so could be effective for some high-risk mothers.

Esketamine

Esketamine (Spravato) is a recent iteration that uses only the S isomer. The US Food and Drug Administration (FDA) approved esketamine to treat depression and lower suicide risk on March 5, 2019. Intranasal esketamine was comparable to IV infusions in its antidepressant effect and the FDA

designated it a breakthrough therapy (Molero et al., 2018). Esketamine is a glutamate NMDA antagonist, but its specific mechanism vis-a-vis depression is unknown. Effects are seen within minutes to hours.

A recent phase-2, double-blind, randomized placebo-controlled trial compared esketamine in three different dosages (28, 56, and 84 mg) to a placebo administered twice a week (Daly et al., 2018). The final sample included 67 participants with treatment-resistant major depression that had not responded to two or more antidepressants. Participants continued taking their antidepressants during the trial. Esketamine was superior to the placebo in all three groups and symptom improvement was sustained despite reduced frequency of use. The results persisted for more than 2 months.

An expert opinion article noted that ketamine produced rapid antidepressant effects (Nikayin et al., 2022). Regarding safety for racemic ketamine and esketamine, they noted that high-dose ketamine can cause long-term cognitive impairment, but esketamine did not have these effects with no increased risk for cognitive impairment when used appropriately.

Questions remain, however, regarding how to maintain ketamine's antidepressant effect after acute administration and the safety of ketamine and esketamine long term. Specific concerns are neurocognitive and urologic toxicity, addiction, and possible substance use (Molero et al., 2018).

Brexanolone

Brexanolone is a medication specifically designed to treat postpartum depression and it received FDA-approval in 2019. It rapidly treats depression, with a quick drop in symptoms and remission that is sustained for at least 30 days. It is a synthetic version of allopregnanolone, a neurosteroid and metabolite of progesterone that acts on GABA receptors (Walkery et al., 2021). The theory behind this medication is that the core component of the pathophysiology of depression is a brain network dysregulation and excitation-inhibition imbalance (Deligiannidis, Meltzer-Brody, et al., 2023). Allosteric modulators of $GABA_A$ receptors are believed to restore dysregulated brain networks.

Sage Therapeutics, maker of brexanolone, notes that SSRIs do not reduce symptoms for at least 6 weeks. Brexanolone is marketed as superior to SSRIs. The manufacturers concede that cost and side effects, such as loss of consciousness, remain "sizeable obstacles" (p. 389) that will need to be overcome (Gerbasi et al., 2021). However, they still consider brexanolone a cost-effective option if considered over an 11-year period compared with treating someone with SSRIs for the same amount of time.

A recent review included three studies that tested the efficacy and safety of brexanolone in treating postpartum depression. One study was a phase-2 trial, and two were phase-3. None of the mothers were breastfeeding. The initial trial had a small sample (n=4 in the treatment group and n=8 in the placebo group). The second study included 138 women randomized into three treatment groups (two different dosages of brexanolone or a placebo). The depression scores at the end of the infusion were significantly lower and a higher percentage of women in the treatment groups achieved remission compared to the placebo group. The third trial included 108 patients: 54 received brexanolone and 54 received the placebo. The remission rates were higher in the treatment group, but the effect was not maintained at follow-up. In all three studies, there was no difference between brexanolone and the placebo after 30 days (Walkery et al., 2021). Two authors disclosed financial connections to the manufacturer of brexanolone.

A recent network meta-analysis compared efficacy of brexanolone injections with SSRIs for treating postpartum depression in 6 studies (Cooper et al., 2019). The study designs were brexanolone vs placebo and SSRIs vs placebo at day 3, week 4, and last observation. At all time points, change from baseline was greater for brexanolone than for

SSRIs, but the difference between the two treatments was less at every assessment point. SSRIs do not become effective until 4 to 6 weeks after administration. Brexanolone treats symptoms more quickly than SSRIs (as it is designed to do) but is not necessarily better than SSRIs over the long term. In cases of severe depression, both could be used: brexanolone to address immediate symptoms and SSRIs to maintain recovery.

LIMITATIONS OF BREXANOLONE

Brexanolone has been heavily marketed to practitioners and influencers in the postpartum depression field. Many were excited about a depression treatment that targeted GABA receptors, feeling that this was a "new" model of treatment that reverses depression quickly. However, in some ways, it is not new at all. Allopregnanolone is a metabolite of progesterone, which has a long, and now discredited, use as a treatment, and mutes my enthusiasm.

There are also practical downsides. Brexanolone requires IV infusion over 60 hours and must be administered in the hospital (Walkery et al., 2021) because of its black-box warning for "potential excessive sedation and sudden loss of consciousness" (p. 451) (Fantasia, 2019). Approximately, 30% of women experience a significant drop in symptoms that lasts at least a month. But most patients are co-treated with other antidepressants. The cost of the medication is significant (approximately $34,000 plus fees for the hospital stay and for clinician care) (Cornett et al., 2021). It also involves being separated from their infants during that time. Finally, breastfeeding women were specifically excluded from trials, possibly because a progesterone metabolite might cause breastfeeding to fail. Progesterone specifically blocks the hormone prolactin, which is necessary for milk production.

Zuranolone

Zuranolone, a variant of brexanolone, addresses some of these concerns. Zuranolone also treats depressive symptoms via the GABA receptors and is similar in pharmacokinetic profile to brexanolone. Rather than using an IV and requiring hospitalization, it is administered orally once a day. In a randomized trial, 150 patients with depression received either a placebo or 30 mg of zuranolone (Deligiannidis et al., 2021). Patients receiving zuranolone had lower symptoms by Day 3, which is unusual for an antidepressant. By Day 15, patients in the zuranolone group had significantly lower scores on the Hamilton Rating Scale for Depression. The effect was sustained through Day 45.

Similarly, a double-blind phase-3 trial randomized women with severe postpartum depression to either a placebo or 50 mg/day of zuranolone for 14 days (N=170) (Deligiannidis, Meltzer-Brody, et al., 2023). Women in the zuranolone group had significantly lower HAM-D scores at day 15, with improvement in symptoms at days 3, 28, and 45. No loss of consciousness was reported, but some reported dizziness. A similar double-blind trial randomized women to 30 mg of zuranolone or a placebo for 14 days (Deligiannidis, Citrome, et al., 2023). Women in the zuranolone group had lower depression and anxiety scores and improved perceived functional health compared to women in the placebo group at days 3, 15, and 45.

Conclusions

The findings presented in this article demonstrate that there have been significant advances in our understanding of postpartum depression and co-occurring conditions. Organizations concerned with maternal mental health have often stated that 10% to 15% of new mothers are depressed. That number may be true in the aggregate but is not true for higher-risk groups. One of the more astonishing findings was the high percentage of women in the military who have experienced military sexual trauma, and the high rates of depression for all military mothers in the U.S. The distinction between refugees, asylum seekers, and immigrants was also new. Many previous studies have combined these groups, but findings from Canada suggest that researchers who do so lose information. Smoking is also interesting. At this

point, all we have is an association: smoking and postpartum depression often co-occur. But does smoking *cause* depression? We do not know, but the results are so consistent, it is worth following up.

Treatment options have also expanded. Many non-pharmacologic treatments are now available, but two with recent research are acupuncture and repetitive transcranial magnet stimulation (rTMS). We have some older studies in English on acupuncture for treating perinatal depression, but the advance is the number of systematic reviews that also include articles from Chinese journals. This treatment is not for everyone, but the results are promising. It is a non-invasive way to treat depression without dangerous side effects, and it is effective for severe depression.

Similarly, rTMS represents a significant treatment advance for general depression, with strong evidence to support its use. Like acupuncture, it is non-invasive, with only mild side effects. It is a far better option than electro-consultant therapy, which is still suggested. rTMS requires no anesthesia and does not cause memory problems.

Brexonalone and ketamine reflect a different biological model for depression. Rather than focusing on monoamine neurotransmitters, such as serotonin and norepinephrine, these newer medications target GABA and glutamate receptors. There are also more assessable variants of these with esketamine and zuranolone. All of these medications are effective and fast-acting. There are cautions and side-effects. Nevertheless, these medications represent a major leap forward in pharmacotherapy.

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Orcid:

https://orcid.org/0000-0003-0709-1059

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