Increased 5-HT2C receptor expressions incite neuroinflammation, and inflammatory cytokines also raise 5-HT2C receptor editing levels. In addition, inflammatory cytokines induce serotonin transporter activity, enhancing serotonin uptake and metabolism. Conversely, melatonin exerts anti-inflammatory and antioxidant effects on microglia and astrocytes via MT1 and MT2 receptors, resulting in increased anti-inflammatory cytokines and BDNF, as well as free radical scavenging.[9] It can also reduce brain glutamate levels, preventing microgliosis and astrogliosis, potentially repairing the blood-brain barrier and reducing oxidative stress by inhibiting ROS production.[10] Therefore, agomelatine may operate through several molecular mechanisms: inhibiting cytoplasmic and nuclear STAT3 phosphorylation to reduce apoptosis, suppressing Gαi-2 through antagonistic properties on 5-HT2C receptors, which blocks transient mGluR2 inhibition on synaptic transmission, and activating the cAMP-PKA-ASK1 neuroprotective pathway.[10,11] Animal studies demonstrate promotion of hippocampal cell proliferation, maturation, and survival, while increasing BDNF in the prefrontal cortex and hippocampus, enhancing synaptic plasticity and neurogenesis.[12]

Consequently, the inhibiting 5-HT2C receptors with Gαi-2 or modifying melatonin receptors can effectively reduce neuroinflammation, abnormal autophagy, and neuronal apoptosis. Notably, in both in vivo and in vitro studies, the antidepressant, anxiolytic effects, and circadian rhythm restoration cannot be replicated by using 5-HT2C antagonists or melatonin alone.[13] Interestingly, only synergy between melatonergic and 5-HT2C receptors has been shown to be responsible for the effects on neurogenesis, cell survival, BDNF, and glutamate release.[12,13] In conclusion, this case report provides preliminary evidence suggesting that agomelatine may be a promising treatment option for individuals with PASC who experience depressive, anxiety, and sleep disturbances. This may be attributed to its unique combination of antioxidant and anti-inflammatory properties.

ACKNOWLEDGMENT

The Institute Review Board of the Tri-Service General Hospital (IRB# A202315082).

AUTHOR DISCLOSURE INFORMATION

All authors declare no conflicts of interest for this report.

This research did not receive any specific grant support from funding agencies in the public, commercial, or not-for-profit sectors.

Author contributions: C.-C.H. and T.-C.Y. conceived the concept of this article. C.-S.L. and T.-C.Y. provided the clinical insights in this case. C.-C.H. and Y.-A.K. wrote the first draft and was edited by T.-C.Y. (fantine7520@ndmctsgh.edu.tw) who contributed in conducting the critical revision of article and served as the corresponding authors. All authors approved this article.

ARTICLE INFORMATION

Received September 29, 2023; accepted after revision December 5, 2023. Y.-A.K. and C.-C.H. contributed equally to this work.
DOI: 10.1097/JCP.0000000000001823

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Rapid Improvement of Post-Partum Depression With Subanesthetic Racemic Ketamine

To the Editors:

Major depressive disorder with peripartum onset is defined as a major depressive episode characterized by the emergence of mood symptoms during pregnancy or within the initial 4 weeks after delivery.[1] Peripartum depression (PPD) represents one of the most prevalent postpartum complications, affecting 12% of pregnancies.[2] It is associated with numerous short- and long-term deleterious consequences for mothers, children, and families, including attachment and bonding issues.[3,4] Furthermore, suicide is one of the main causes of maternal death during the first year after childbirth.[5] Thus, rapid and efficacious management of PPD is of paramount importance.[6] Current guidelines recommend the use of psychotherapy and

pharmacotherapy,[6] but these treatments typically require weeks to months for optimal effects.[7] There are no treatments specifically approved for PPD in Canada. There is evidence from meta-analyses for rapid antidepressant effects of low-dose intravenous infusions of the *N*-methyl-D-aspartate antagonist ketamine, and an intranasal formulation of the s-enantiomer, esketamine, is approved by the US Food and Drug Administration for treatment-resistant depression (in conjunction with an oral antidepressant).[8,9] The therapeutic benefits of ketamine typically manifest within minutes to hours after the first dose, persisting beyond its metabolic breakdown and elimination, extending to several weeks for depression and even longer for antisuicidal effects.[8] Because of this rapid effect, ketamine is stimulating significant scientific interest as a potential treatment of PPD.[10–13] Given the paucity of clinical data in this novel context, here we report, with the patient's written consent for publication, a case study featuring a woman with PPD who experienced a rapid improvement with a brief course of ketamine.

CASE REPORT

The patient, a woman in her late 30s, had a 2-year-old child from an uneventful prior pregnancy devoid of psychiatric symptoms. She had previously been diagnosed with adjustment disorder on 3 occasions in the context of psychosocial stressors, each episode rapidly improving with short-term psychotherapy and antidepressants prescribed for anxiety, with no history of suicidal ideas or attempts. She was also known to have attention-deficit/hyperactivity disorder previously treated with lisdexamfetamine, which was discontinued at the beginning of the pregnancy, and severe asthma. The second pregnancy was marked by a COVID-19 infection during the eighth week, leading to severe pneumonitis and post-COVID syndrome with new onset postural orthostatic tachycardia syndrome and pericarditis, resulting in a Karnofsky performance status of 70 that lasted the duration of the pregnancy and beyond. The delivery was complicated, necessitating intensive care unit admission for both mother and infant, resulting in a 5-day separation. Psychiatry was consulted 12 days postpartum for increasing dysphoric mood. The patient reported sadness, diminished capacity for enjoyment, guilt regarding her perceived role in the complications of her pregnancy and childbirth, as well as distress and a sense of worthlessness associated with her indifference toward her infant. While her anxiety and difficulties with sleep were mild, she was profoundly fatigued with impaired concentration. Absence of suicidal or homicidal ideation and psychosis was noted.

The patient met the *Diagnostic and Statistical Manual of Mental Disorders* criteria for a major depressive episode, although several symptoms could be attributed to her post-COVID syndrome. The medications prescribed were not associated with neuropsychiatric adverse effects. Surprisingly, her Edinburgh Postnatal Depression Scale score was 9/30, falling below the threshold of 13 indicative of depressive illness or high risk for its development. Anticipating symptom resolution upon returning home in 2 days, the patient opted to decline initiation of antidepressant medication. However upon an outpatient evaluation 28 days postpartum, the patient's mood had not improved, and her feelings of unworthiness persisted toward supportive family members. Minimal interaction with her infant was all she could tolerate. Attention difficulties, potentially linked to both untreated attention-deficit/hyperactivity disorder and post-COVID syndrome, continued to afflict her. Given her nonbreastfeeding status and that she had not resumed psychostimulant therapy, bupropion XL was initiated and increased to 300 mg daily and was well tolerated.

Four weeks after the initiation of bupropion (8 weeks postpartum), the patient reported only mild improvements in mood and concentration, while inability to bond with her newborn persisted. In an attempt to expedite recovery, the patient consented to a trial of ketamine. In accordance with the institution's protocol, she received 2 subanesthetic doses of racemic ketamine (0.5 mg/kg of body weight); the first by 40-minute intravenous infusion at 10 weeks postpartum, and the second through intramuscular injection at 12 weeks postpartum (for enhanced feasibility). Ketamine infusions were combined with interventions using the acceptance and commitment therapy framework. Ketamine was administered with nonpharmacological treatment adjuncts inspired from the paradigm of psychedelic-assisted psychotherapy and included music, the use of blindfolds, and accompaniment by a trained physician who invited the patient to explore and make meaning of her ketamine experience.[14]

Both treatments were very well tolerated with no significant increase in blood pressure, nausea, or headache. Immediately after the first treatment, the patient experienced significant improvements in mood, anhedonia, energy, concentration, and feelings of guilt: the improvement was not reflected by the modest improvement in the BDI-II where the symptoms of her post-COVID contributed heavily to the total score. She also reported a desire to care for and cuddle her infant for the first time since birth. These beneficial outcomes were globally sustained between the initial and subsequent ketamine treatments (2 weeks later) except for the improvements in her cognitive symptoms, which waned within hours. The second treatment yielded further enhancements in mood and ability to bond with the infant, although the impact was less profound than the initial instance. These benefits persisted and extended over time. Exploration of her ketamine experiences unveiled rediscovery of pleasurable activities compatible with the physical limitations and fresh perspectives on adapting professional activities to her physical constraints, attenuating pessimistic outlooks on the future.

Five weeks after her last ketamine treatment (17 weeks postpartum), affection for her infant and the strengthening bond persisted. Notwithstanding residual cognitive symptoms, substantial fatigue, and respiratory distress, the patient engaged in some daily tasks and leisure pursuits. The Karnofsky score remained unchanged. Of note, the patient never developed psychotic symptoms or suicidal/infanticidal ideations during the course of her PPD. Wellbutrin was continued and her improvement was maintained up to 1 year later.

DISCUSSION

Although the use of ketamine is approved for the treatment of resistant depression and suicidality, our off-label administration of this agent in a woman with major depression with onset in the postpartum period resulted in a rapid improvement in her ability to develop a bond with her infant. This improvement is especially noteworthy given the patient's persisting functional limitations arising from post-COVID syndrome, leading to ongoing concerns about her ability to eventually resume her professional activities. The patient's symptoms of post-COVID syndrome partly overlapped with the manifestations of depression, limiting the precision of depression rating scales in capturing clinical improvement. We interpret the improvement in maternal bonding as indicative of improvement in mood and heightened capacity for experiencing pleasure. Examination of the psychedelic experiences that accompanied ketamine treatment aided in identifying sources of joy within the patient's constrained physical state, but this specific treatment paradigm might not be imperative for eliciting improvements.

Two fast acting antidepressants for the treatment of PPD are currently approved in the United States: brexanolone (given intravenously in a medical facility for 60 hours at a cost of approximately US $34,000)

and zuranolone, given orally (cost unknown at this time). Ketamine has numerous advantages over other treatments for PPD. It is widely accessible, inexpensive, has a favorable safety profile[8] and, in the postpartum context, its short half-life and hydrophilicity result in rapid clearance from breastfeeding such nursing mothers might only need to discard breast milk for 1 day after treatment.[15] While several antidepressants are considered safe during breastfeeding, some mothers nevertheless feel concerned about exposing their newborn to a medication and will opt to prematurely discontinue the medication; the brevity of the ketamine treatment represents an advantage in this respect.

CONCLUSIONS

Peripartum depression is a common and often devastating condition. To our knowledge, this case report represents the first documentation in North America and the second globally, of a dramatic and rapid improvement in PPD after a short course of ketamine—here administered in an approach inspired by the psychedelic paradigm.[11] Given that other treatment options for PPD remain limited and/or slow-acting,[6] this case report underscores the potential of ketamine as a therapeutic option for PPD, advocating for additional research to establish its efficacy and to facilitate evidence-based evaluation of its role in the management of PPD. Beyond individual patient response, we propose that the success of postpartum antidepressant treatment should extend to encompass the well-being of the entire family, especially the newborn. Given that ketamine treatments are already offered outside of academic institutions without the required scientific evidence, clinical studies are urgently warranted.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

ARTICLE INFORMATION

Received June 22, 2023; accepted after revision December 22, 2023.
DOI: 10.1097/JCP.0000000000001780

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