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LETTER TO THE EDITOR

Brexanolone and postpartum depression: what does it have to do with GABA?

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Puerperal depression is a form of (major depressive disorder) MDD that is universally recognized. A meta-analysis (O'Hara and Swain 1996) showed a prevalence of 13% with most cases starting in the first 3 months postpartum. Particular at-risk groups include pregnant immigrant women (Zelkowitz et al. 2008), teenage pregnancy (Bayatpour et al. 1992), assisted conception (Hammarberg et al. 2008), and previous stillbirth (Turton et al. 2001) The Edinburgh Postnatal Depression Scale (EPDS) has been developed to detect mothers suffering from postnatal depression in primary healthcare settings (Cox et al. 1987). Exact neurobiology remains elusive. Possibly hormonal (gonadal steroids) fluctuations associated with childbirth induce depression in vulnerable women (Bloch et al. 2000) . Other mechanisms at play include dysregulation of HPA axis already present in pregnancy. A study has showed a direct association between blood levels of CRH in the second trimester and development of postnatal depression (Yim et al. 2009). Associations between depressive symptoms and polymorphic variations in the expression of the serotonin transporter gene, a possible regulator of serotonergic function, have been reported (Sanjuan et al. 2008).

In March 2019, brexanolone (Zulresso) was the first drug to have ever been approved by the US FDA specifically for the treatment of postpartum depression (PPD) in adult females based on two multicentre DBRBC trials (Meltzer-Brody et al. 2018) where the administration of brexanolone injection for postpartum depression resulted in significant and clinically meaningful reductions in the HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period.

Brexanolone, the aqueous form of allopregnanolone, is a neurosteroid and acts as a positive allosteric modulator of the $GABA_A$ receptor.

As such, there seems a major paradigm shift from prototypic monoaminergic (5HT, NE, DA) hypothesis of MDD to GABAergic system. Here, I would try to briefly address the rhetorical question of GABA and MDD.

The idea linking GABAergic system to MDD is not innovative; the triazolo benzodiazepine (BDZ) alprazolam (Xanax) has been traditionally suggested to possess antidepressant properties (Warner et al. 1998). Even, a more recent meta-analysis has demonstrated BDZs to be as effective as antidepressants with a faster action in the short-term treatment of depression (Benasi et al. 2018).

MDD is characterized by decreased GABA levels and function. This has been repeatedly demonstrated across multiple levels of investigation and this has been tied to excitation-inhibition balance (EIB) changes in MDD.

MDD patients with melancholic features and especially anhedonia showed particularly robust plasma GABA deficits (Petty et al. 1992).

CSF GABA levels in MDD has shown to be decreased (Gold et al. 1980).

Utilizing proton magnetic resonance spectrometry to examine GABA levels in vivo and transcranial magnetic stimulation paired with electromyography to measure in vivo functionality of GABA neurotransmission have confirmed GABA reductions as well as decreased inhibitory function across depressive and euthymic phases. Regions of the default mode network (DMN) and dorsolateral prefrontal cortex (dlPFC) show the most robust decreases and this goes in tandem with changes in resting-state fMRI activity (Hasler et al. 2007; Levinson et al. 2010).

Moreover, in human postmortem studies, confirmation of these findings is observed (Bielau et al. 2007).

Of related interest, deficits in somatostatin (SST) neurons may underlie these general GABA deficits, as SST expression is decreased per cell across all examined layers in ACC, dlPFC and amygdala (Seney et al. 2015).

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Animal studies provide evidence that SST neurons are selectively vulnerable to stress and might be causally involved in depression (Lin and Sibille 2015).

Importantly, these changes are not unique to MDD, were replicated in other psychiatric disorders with shared symptomatology (e.g. bipolar) and might be regarded as a trait marker.

All these converge and give kudos to altered GABAergic function in MDD and hence mechanistically explain brexanolone utility for PPD.

Compliance with ethical standards

Competing interests Author declares no competing interests.

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