words, their temperament would help defining the shape (and maybe the triggering) of the mood disorder among individuals who have a "bipolar disorder diathesis" but not necessarily be part of the bipolar spectrum or represent an attenuated form of bipolar disorder that could predispose the individual in question for the development of full-criteria bipolar disorder.

Second, I would like to emphasize that, as mentioned by the author, mixed mood symptomatology is a rather fluid concept and their place in psychiatric nosology seems to always be in constant motion. For example, DSM-5 eliminated the concept of mixed mood state altogether, instead replacing it with the term "mixed features", which can technically be described not only among patients with bipolar disorder but also in those with a working diagnosis of unipolar depression (Verdolini et al. 2014). While this categorical diagnostic view may seem to be in opposition to the dimensional model of mood disorders represented by the bipolar spectrum, it gives clinicians a certain latitude with regards to avoiding the premature diagnosis of bipolar disorder while still allowing them to keep in mind that major depressive disorder patients with mixed mood symptomatology should be monitored as for the future development of full bipolar disorder and often require certain adjustments with regards to their pharmacological management, such as association of mood stabilizers and/or atypical antipsychotics to their antidepressant regimen (Sanches et al. 2021).

Third, even though, as highlighted by the author, clinical experience supports the importance of irritability as a possible indicator of a mixed state in patients with depressive mood, irritable mood was not included among the criteria for the characterization of mixed symptomatology in DSM-5. As a matter of fact, the relationship between irritability and mood is not yet completely clear, with some evidence indicating it might not be a feature necessarily associated with a specific mood pole in bipolar disorder but rather represent an independent feature that may be shared by patients in mania and depressive states (Bell et al. 2020), what emphasizes the fact that a better understanding of the role of irritability across the different phases of the bipolar illness will likely help clarify its role in the characterization of mixed mood states.

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# EFFECTS OF PAROXETINE ON PLASMA LEVELS OF VASCULAR ENDOTHELIAL GROWTH FACTOR IN PATIENTS WITH MAJOR DEPRESSION

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## Dear editor,

Vascular endothelial growth factor (VEGF) signaling, which modulates angiogenesis and neurogenesis within the neurovascular unit, may play an important role in the neuro-endocrine-immune stress-adaptation system. Recent evidence indicates that it is involved in the pathophysiology of several diseases, including major depression (MD), and is influenced by antidepressants (Lang & Borgwardt 2013).

The present study aimed to investigate the effect of paroxetine, a selective serotonin reuptake inhibitor, on plasma VEGF levels in patients with MD. Twenty-eight patients who met the MD criteria as per the DSM-5 (American Psychiatry Association 2013) were enrolled in this study (age 42±8 years; male/female 15/13; single-/repeated-episode 12/16). Improvement in depressive symptoms was evaluated using the 17-item Hamilton Rating Scale for Depression (HAMD) (Hamilton 1960). The maximum dose of paroxetine at week four was 34.0±7.8 mg/day. Blood was drawn at 9:00 a.m. Plasma levels of VEGF were analyzed in duplicate, and mean values were presented for each data point. Plasma VEGF levels were measured with our quantitative sandwich enzyme assay technique using a Quantikine HS High Sensitivity Immunoassay kit (R&D Systems, Minneapolis, MN, USA). This study was approved by the ethics committee of the University of Occupational and Environmental Health, and written informed consent was obtained from all the participants. The HAMD scores significantly decreased after paroxetine treatment (week 0, 22.0±3.2; week 4, 13.0±4.7; $p<0.001$, Wilcoxon signed-rank test). The plasma levels of VEGF were not altered before or four weeks after paroxetine treatment (week 0, 29.45±8.97 pg/ml; week 4, 28.32±7.96 pg/ml; $p=0.1359$, Wilcoxon signed-rank test). No correlation was found between the changes in plasma VEGF levels and the changes in HAMD scores ($rho=-0.0577$, $p=0.7704$, Spearman rank correlation coefficient). The results of the present study suggested that treatment with paroxetine for four weeks did not alter plasma VEGF levels and that the changes in plasma VEGF levels were not related to the clinical response to paroxetine. Fornaro et al. (2013) reported that VEGF levels significantly increase in association with the clinical response to duloxetine in early responders. It has been reported that baseline VEGF levels are significantly higher in the non-responder subgroup than in the responders (Elemery et al. 2017). However, the results were not replicated in our study with paroxetine. The baseline plasma VEGF levels of responders and non-responders were

28.73±8.24 pg/ml and 29.60±8.61 pg/ml, respectively (p=0.2447, Wilcoxon signed-rank test). A recent report demonstrated that ketamine does not change plasma VEGF levels in patients with MD (Medeiros et al. 2021). Taking these data into consideration, the effect of antidepressants on plasma VEGF levels in MD remains controversial. Further studies focusing on VEGF-A, an isoform of VEGF, should be conducted.

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