

Table 1. Summary of the two cases of resistant late-onset schizophrenia with prominent neurocognitive deficits

Features	Case 1	Case 2
Age/Sex	54/F	68/F
Onset (DOI)*	51 (3)	65 (3)
Clinical presentation	Suspiciousness, muttering + intermittent catatonia (benzodiazepine-non-responsive) + prominent forgetfulness, inattention, and difficulty in ADLs ¹	Suspiciousness, muttering, disinhibited behaviour + intermittent catatonia (benzodiazepine-non-responsive) + prominent memory deficits and difficulty in ADLs ¹
MSE	Constricted affect, persecutory delusions, AHs (PANSS: 93), BFCRS 16	Constricted affect, persecutory delusions, AHs (PANSS: 108), BFCRS: 14
NPB [#]	Deficits in attention, new learning ability, planning, and visual-motor coordination	Deficits in attention, recent memory and constructional ability
Investigations	Thyroid profile, serology, vitamin-B ₁₂ , and anti-TPO antibody were normal	Thyroid function tests, serology, vitamin-B ₁₂ , and anti-TPO antibody were normal
MRI-Brain	Bilateral hippocampal atrophy with chronic lacunar infarcts in bilateral centrum semiovale	Non-specific white matter hyperintensities
Past failed trials	Risperidone 4mg/day, Amisulpride 600 mg/day (EPS on dose escalation), Clozapine: stopped due to intolerable giddiness	Olanzapine 15 mg/day, Amisulpride 400 mg/day (EPS on dose escalation), Clozapine: stopped due to alarming QTc prolongation
Acute ECT ²	Improvements in catatonia (BFCRS: 0), psychosis (PANSS: 38) and cognition (MoCA: 26)	Improvements in catatonia (BFCRS: 0), psychosis (PANSS: 32) and cognition (MoCA: 24)
M-ECT ³	Progressive improvement in cognition and functionality	Progressive improvement in cognition and functionality

Note: * in years; ADL: Activities of Daily Life; AH: auditory hallucinations, Mental Status Examination; PANSS: Positive and Negative Syndrome Scale; BFCRS: Bush Francis Catatonia Rating Scale; #: NIMHANS Neuropsychological Battery; anti-TPO: anti-Thyroid Peroxidase; 1: neurocognitive deficits appeared after the onset of the psychotic symptoms; 2: acute course of bifrontal ECT at frequency of thrice/week (8 sessions); M-ECT: Maintenance-ECT at frequency once/month; 3: M-ECT was given to prevent relapse; MoCA: Montreal Cognitive Assessment Scale

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MIXED STATES, PATHOPLASTICITY, AND THE BIPOLAR SPECTRUM

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Dear editor,

As a mood disorders psychiatrist, it was with great interest that I read the article by Prof. Tavormina on the clinical aspects and nosology of mixed states in bipolar disorder and its relationship with temperaments (Tavormina 2021). The author demonstrated a profound knowledge of the bipolar spectrum concept and offers valuable advice for the practicing clinician with regards to the identification and management of this condition. Nonetheless, as an academic exercise, I would like to bring up a few points that complement Prof. Tavormina's discussion on mixed states.

First, I missed a more direct reference to the concept of pathoplasticity (Widiger 2011), which can help us better understand the relationship between personality/temperament traits and mixed symptomatology. According to this model, an individual's baseline personality plays an important role in the clinical presentation of a certain psychiatric conditions, such as bipolar disorder. That may be the reason why two patients with bipolar disorder, despite suffering from the same condition, are never identical as for their psychopathological features during acute mood states and could potentially explain why some patients present with mixed symptomatology while others don't. In other

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 (HAM-D) (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 HAM-D 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 HAM-D 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