**Cariprazine-induced mania: A case series report**

María T. Pons-Cabrera¹,² | Roberto Palacios-Garrán³ | Laia Tardón-Senabre¹,² | Tabatha Fernández-Plaza¹,² | Oriol Marco-Estrada¹,² | Santiago Madero¹,² | Gerard Annella¹,² | Lluc Colomer¹,² | Mauro Druetta¹,² | Anna Giménez-Palomó¹,² | Lourdes Navarro-Cortés¹,² | María Sagué-Vilavella¹,² | Carlos Sánchez-Sierra¹,² | Norma Verdolini¹,² | Rosa Catalan⁴,⁵,⁶ | Miquel Bioque⁴,⁵,⁶ | Jose M. Goikolea¹,² | Eduard Vieta¹,² | Isabella Pacchiarotti¹,²

¹Bipolar and Depressive Disorders Unit, Hospital Clinic, Institute of Neurosciences, University of Barcelona, Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain
²Centro de Investigación Biomédica en red en salud Mental (CIBERSAM), Barcelona, Catalonia, Spain
³Department of Psychiatry, Mental Health, and Addiction, GSS–Hospital Santa Maria, Lleida, Spain
⁴Barcelona Clinic Schizophrenia Unit (BCSU), Neuroscience Institute, Hospital Clínic de Barcelona, Barcelona, Catalonia, Spain
⁵Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Catalonia, Spain
⁶Department of Medicine, Centro de Investigación Biomédica en red en salud Mental (CIBERSAM), University of Barcelona, Barcelona, Spain

Correspondence
Prof. Eduard Vieta and Isabella Pacchiarotti, Bipolar and Depressive Disorders Unit, Hospital Clinic, University of Barcelona, Institute of Neuroscience, IDIBAPS, CIBERSAM, 170 Villarroel st, 12-0, 08036, Barcelona, Catalonia, Spain.
Email: evieta@clinic.cat (E. V.); pacchiar@clinic.cat (I. P.)

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1 | BACKGROUND

Bipolar depression is the most prevalent phase of bipolar disorder (BD). The depressive bipolar phase is also the most challenging, considering the efficacy and safety of currently available treatment options, and that it is associated with a worse course of the illness both in terms of morbidity and mortality.¹

The management of bipolar depression is especially difficult because of the risk of inducing treatment-emergent affective switches (TEAS) with antidepressants (ADs), mostly in monotherapy.

Clinical guidelines do not recommend the use of ADs as a first-line treatment for bipolar depression, and if they are used, it is recommended to introduce them while the patient is treated with effective doses of

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**Key message**

Cariprazine has proved its efficacy in randomized clinical trials for the treatment of depressive and manic episodes in BD-I. However, three BD-I patients in a depressive phase presented a manic switch in the context of low-dose cariprazine treatment. Cariprazine may induce TEAS but this hypothesis needs confirmation within further research. Moreover, it should be explored if a dose increase of cariprazine could address the manic emerging symptoms associated with a low dose.
mood stabilizers (MS).
Current evidence focuses on the short-term efficacy of several second-generation antipsychotics (SGAs) for bipolar depression, including cariprazine, a dopamine-serotonin partial agonist. Cariprazine was initially approved by the Food and Drug Administration (FDA) for the acute treatment of schizophrenia (1.5–6 mg/day) and acute mania/mixed mania in BD type 1 (BD-I) disorder (3–6 mg/day). Recently, cariprazine has also received FDA approval as a monotherapy for BD-I depression (1.5–3.0 mg/day).

Although TEAS induced by SGAs are not frequent, several cases have been reported. In reviewing the literature, we found TEAS with the use of olanzapine, risperidone, ziprasidone, aripiprazole, quetiapine, and other SGAs. To our knowledge, cariprazine-induced TEAS in bipolar depression have not been described to date. To our knowledge, there is no evidence of cariprazine-induced TEAS in bipolar depression.

We describe below three clinical cases of BD patients admitted at the psychiatric ward of the Bipolar and Depressive Disorders Unit at the Hospital Clinic of Barcelona. All of them developed a manic episode presumably induced by the introduction of low doses of cariprazine.

2 | CASE 1

A 56-year-old man with BD-I disorder and Asperger Syndrome was hospitalized due to the onset of a depressive episode for 2 months. His first mood episode was at the age of 26, with a depressive predominant polarity. His home medication was divalproex sodium 500 mg twice a day and immediate release quetiapine 50 mg as supportive medication for insomnia.

The main symptoms were low mood, anhedonia, apathy and avolition, anxiety, suicidal thoughts with neglect of hygiene and social activities, and complete isolation at home. He had a previous history of AD-induced TEAS.

During the hospitalization, cariprazine 1.5 mg once a day was initiated as an add-on treatment for depressive symptoms to avoid the use of ADs. After an initial and sudden improvement of depressive symptoms and suicidal thoughts (within 4 days), the patient developed elevated energy, dysphoric mood, anxiety, irritability, distractibility, suspiciousness, racing thoughts, pressured speech with loose associations and psychomotor agitation, and decreased need for sleep. Therefore, cariprazine was discontinued and lurasidone 37 mg a day was started. A progressive improvement of the symptomatology was observed within 10 days, with reduced anxiety, irritability, and returning to a euthymic state. Finally, the patient was discharged to a therapeutic community to continue his recovery.

The main clinical features of the three cases are shown in Table 1.

3 | CASE 2

A 24-year-old female college student, with severe type I Diabetes Mellitus and diagnosed with bipolar type schizoaffective disorder and severe obsessive-compulsive disorder (OCD), was admitted to the psychiatry ward due to a depressive episode with suicidal thoughts. She also presented with psychotic symptoms and exacerbation of the OCD symptomatology, mainly contamination phobia and compulsive handwashing leading to severe contact dermatitis that needed specialized dermatologic care. In this episode, as well as in the previous one, she discontinued her treatment including insulin therapy.

Previous to the mentioned depressive episode which required hospitalization, treatment with low doses of cariprazine was initiated in combination with 800 mg of lithium carbonate a day, because of resistant depression symptoms and considering the favorable metabolic profile. Following the introduction of cariprazine 1.5 mg a day in an out-patient setting, she started with racing thoughts, expansive mood, inflated self-esteem, distractibility, impulsivity (as she reported: “I started to make improvised and imprudent decisions”), as well as irritability and grandiose and mystic-religious delusions. The patient herself decided, against psychiatric advice, to discontinue treatment with cariprazine. She eventually developed a depressive recurrence which precipitated hospitalization.

4 | CASE 3

A 29-year-old woman, diagnosed with BD-I disorder in 2011, was hospitalized due to a manic episode. Her illness followed a seasonal pattern, with depressive episodes in winter and manic symptoms in summer. The patient had maintained stability for the last 4 months. In the last appointment with her psychiatrist due to the presence of subthreshold depressive symptoms, cariprazine 1.5 mg a day was added to her maintenance treatment with lithium carbonate 1200 mg/day as a mood stabilizer and immediate-release quetiapine 50 mg/day as supportive medication for insomnia.

Four weeks later, in October, and opposite to her usual seasonal pattern, she presented with expansiveness and mood lability, elated mood, delusions with mystic and magical content, decreased need for sleep, behavioral disorganization, and aggressiveness. Once admitted to the hospital, cariprazine was progressively increased to

LEARNING POINTS

• Cariprazine is a dopamine D2 and D3 receptor partial agonist, approved by the Food and Drug Administration (FDA) for the acute treatment of schizophrenia (1.5–6 mg/day), acute mania/mixed mania in BD type 1 (BD-I) disorder (3–6 mg/day), and for BD-I depression (1.5–3.0 mg/day).

• In previous studies, cariprazine has not significantly arisen alerts for treatment-emergent affective switches. According to our experience, cariprazine may induce affective switches in BD-I patients. Information regarding early warning symptoms must be delivered.
6 mg. The symptoms remitted after 15 days of hospitalization with the mentioned treatment.

5 | DISCUSSION

Cariprazine is a dopamine D2 and D3 receptor partial agonist with preferential binding to D3 receptors. Cariprazine would be preferable at higher doses (3.0–6.0 mg/day) for mania to enhance its dopamine-antagonistic actions and at low doses (1.5–3 mg/day) for depression, to emphasize its agonistic actions and potentially its unique D3-preferred properties whose receptor is expressed in brain regions controlling reward, emotions, and motivation.3

In our series, two of the patients met the DSM-5 criteria for BD-I, depressive episode, and one of them met DSM-5 criteria for schizoaffective disorder, bipolar type. A summary of the patient's clinical characteristics is shown in Table 1. All patients were initially treated with low doses of cariprazine (1.5 mg) during a depressive phase of BD-I or schizoaffective disorder. All three cases were simultaneously treated with mood stabilizers, lithium in two of the patients, and valproate in one. In these cases, despite the ongoing MS treatment, all three patients switched to a manic episode when cariprazine was initiated. Adherence to the MS was confirmed in all cases by blood levels.

In one of the patients, TEAS occurred during the first 4 days of treatment with cariprazine, being hospitalized for a depressive episode, and in the other two cases, cariprazine was prescribed by their outpatient psychiatrist during a depressive episode or to treat subthreshold depressive symptoms (in case 3). Moreover, in case 3, the switch to mania reversed the usual seasonal pattern observed since the beginning of her illness. Patient 1 had the previous history of AD-induced TEAS, but cases 2 and 3 had no previous history of TEAS. It is noteworthy that in previous studies, assessing the efficacy and side effects profile of cariprazine in depressive episodes of BD-I, TEAS have not been significant. However, according to our experience, cariprazine may have induced affective switches in BD-I patients. Nevertheless, as a limitation of our observations, the low number of cases limit the strength of our results. We should also keep in mind that mood elevations and changes in cycle frequency may occur unpredictably in the natural course of BD, and consequently, it is difficult to distinguish spontaneous from drug-induced switching during the recovery phase of a depressive episode.2

In patient 3, once the dose was titrated to 6 mg, an improvement of manic symptoms was observed. As above-mentioned, cariprazine, at a high dose could be used to treat manic or mixed episodes associated with BD-I, as it emphasizes its D2 antagonistic properties.3 Thus, as a potential strategy in cases of TEAS induced by cariprazine a dose increase might be effective. However, based on our findings, patients and psychiatrists should receive information regarding early warning symptoms and monitor possible cariprazine-induced mood switching.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding authors.
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