






## CASE REPORT

# A case series of serious and unexpected adverse drug reactions under treatment with cariprazine

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## Abstract

Reporting of new or unexpected adverse drug reactions of medicines that are subject to additional monitoring (“black triangle” label), such as the antipsychotic drug cariprazine, is of paramount importance to improve pharmacotherapy safety.

## KEYWORDS

adverse drug reactions, cariprazine, dopamine supersensitivity psychosis, drug safety, hyperprolactinemia

## 1 | INTRODUCTION

Cariprazine is a dopamine receptor partial agonist (DRPA) that was approved for the treatment of schizophrenia in adult patients in Germany in 2017.<sup>1</sup> Cariprazine has proven especially effective in the treatment of negative symptoms of schizophrenia with regard to self-care, interpersonal relationships, and socially useful activities.<sup>2</sup> In the United States (US), where cariprazine has been on the pharmaceutical market since 2015, the substance is additionally approved

for the treatment of manic or mixed episodes associated with bipolar I disorder in adults.<sup>3,4</sup> Cariprazine is currently being investigated as an adjunctive treatment for unipolar major depressive disorder.<sup>5</sup> The pharmacological class of DRPAs currently comprises three drugs (aripiprazole, brexpiprazole, and cariprazine) among which cariprazine displays the highest affinity to the dopamine D<sub>3</sub> receptor.<sup>6</sup> In fact, cariprazine has an even higher affinity to D<sub>3</sub> receptors than endogenous dopamine itself.<sup>7</sup> Dopamine D<sub>3</sub> receptors are considered to play an important role in mediating negative and cognitive

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symptoms of schizophrenia.<sup>2</sup> Cariprazine also binds to dopamine D<sub>2</sub> receptors with high affinity. Cariprazine displays either agonistic or antagonistic activity, depending on the functional status of a neuronal system. In systems with normal or increased dopaminergic transmission, cariprazine acts as an antagonist. Conversely, in systems with low dopaminergic transmission, cariprazine exerts agonistic activity.<sup>8</sup> Apart from dopamine receptors, cariprazine also binds to serotonin 5-HT<sub>2B</sub> receptors with high affinity and to serotonin 5-HT<sub>1A</sub> and 5-HT<sub>2A</sub> receptors with moderate affinity.<sup>5,9</sup> Cariprazine exerts little to no anticholinergic activity.<sup>6</sup>

Cariprazine is primarily metabolized via the cytochrome P450 isoenzyme (CYP) 3A4 and, to a lesser extent, by CYP2D6.<sup>10</sup> Two active metabolites of cariprazine, desmethyl cariprazine (DCAR) and didesmethyl cariprazine (DDCAR), substantially contribute to the drug's antipsychotic activity.<sup>10</sup> While cariprazine displays a half-life of 2–4 days, its major metabolite DDCAR has a half-life of up to 3 weeks, the longest of any atypical antipsychotic.<sup>5</sup> The extended half-life can be favorable since missing doses even over several days may not necessarily lead to a recurrence of the underlying psychiatric condition. On the other hand, the long half-life may be disadvantageous as adverse drug reactions (ADRs) can persist for weeks after discontinuation.

Akathisia has been described as the clinically most relevant ADR of DRPAs.<sup>6</sup> According to the German summary of product characteristics (SPC), common ADRs of cariprazine (affecting 1%–10% of treated patients) include—but are not limited to—sedation, blurred vision, and arterial hypertension. In comparison, akathisia and Parkinsonism both constitute very frequent ADRs of cariprazine (affecting >10% of treated patients).<sup>1</sup> Similarly, the US SPC agrees that extrapyramidal symptoms (EPS), especially akathisia, belong to the clinically most relevant ADRs of cariprazine, along with sedation, dyspepsia, vomiting, and restlessness.<sup>3</sup> In this article, we present four ADRs of cariprazine, including two previously unreported ADRs: exacerbation of psychosis and hyperprolactinemia.

All presented cases have been documented in “*Arzneimittelsicherheit in der Psychiatrie*” (“Drug Safety in Psychiatry”; AMSP), a trinational postmarketing pharmacovigilance program comprising 52 participating psychiatric hospitals in Germany, Austria, and Switzerland.<sup>11</sup> Since 1993, AMSP has been systematically monitoring the occurrence of serious, new, and unexpected ADRs of psychotropic drugs in the routine treatment of psychiatric inpatients. In accordance with the Guideline for Good Clinical Practice (GCP) of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH),<sup>12</sup> a *serious* ADR within the AMSP program is defined as an ADR that (a) results in death, (b) is life-threatening, (c) requires inpatient hospitalization or prolongation of existing hospitalization, (d) results in persistent or significant disability/incapacity, or (e) is a congenital anomaly/birth defect. Three of

the four ADRs presented in this case series were classified as serious, while one ADR was considered unexpected. Written informed consent for patient information to be published was provided by all patients or a legally authorized representative.

The aim of this article is to disseminate existing and newly acquired knowledge about the side-effect profile of cariprazine to other healthcare professionals in psychiatry and beyond in order to facilitate recognition of (serious) ADRs of cariprazine and improve patient safety in the future.

## 2 | CASE PRESENTATIONS

### 2.1 | Case 1

A 30-year-old female patient suffering from an exacerbation of paranoid schizophrenia with persecutory delusions and distortions of self-experience was admitted to the hospital. The psychiatric condition had been diagnosed 3 years earlier and had previously been treated with quetiapine 900 mg per day (mg/d) and aripiprazole 20 mg/d. Moreover, the patient was suffering from a substance use disorder of alcohol and amphetamines for which she tested positive upon admission. The patient had discontinued her medication 4 months before hospitalization.

Since quetiapine had been well tolerated in the past, treatment with quetiapine 300 mg/d was resumed. Despite displaying significant clinical improvement of her psychotic symptoms, however, the patient requested to discontinue quetiapine. The reduction and subsequent termination of quetiapine triggered an exacerbation of psychotic symptoms which again required antipsychotic medication. Eight days after admission to the hospital, treatment with cariprazine 1.5 mg/d was commenced and increased to 3 mg/d 5 days later. Due to increased drive with euphoric affect, aggressive behavior, and sleeplessness, treatment with quetiapine 300 mg/d was reinitiated 1 day prior to the dosage increase of cariprazine from 1.5 to 3 mg/d. Twelve days after treatment initiation with cariprazine, 7 days after the restart of quetiapine, and 6 days after the dosage increase of cariprazine to 3 mg/d, the patient complained of restlessness in her lower extremities, anxiety, and an uncontrollable urge to move around. The patient paced back and forth along the hospital ward, being unable to sit still. While the patient's psychotic symptoms appeared significantly improved, the described symptoms of akathisia caused the patient great distress and impairment. Therefore, cariprazine was reduced to 1.5 mg/d 3 days after the onset of akathisia. Another 2 days later, cariprazine was stopped. On the other hand, treatment with quetiapine was maintained for 21 days thereafter, with no effect on akathisia. Three days after the discontinuation of cariprazine, the patient complained of persisting akathisia—albeit slightly improved—for another 5 weeks; then, the patient appeared

calmer and less distressed. However, some degree of akathisia persisted for the remainder of her inpatient treatment (ie, another 3 weeks).

Alternatively, antipsychotic treatment with risperidone was started with the aim to establish monthly risperidone injections. Under risperidone 5 mg/d, the patient developed Parkinsonism, again necessitating a change of medication. Treatment with amisulpride was established and titrated to 500 mg/d and augmented with lamotrigine 100 mg/d as well as quetiapine 150 mg/d under which the patient's mental status stabilized significantly, albeit without achieving full remission.

## 2.2 | Case 2

A 22-year-old male patient was admitted to the hospital due to paranoid schizophrenia, from which he had been suffering since the age of 17 years. The patient had previously been treated with various antipsychotic drugs but was unmedicated when admitted to inpatient care. Antipsychotic treatment was initiated with risperidone 0.5 mg/d and gradually increased to 3 mg/d over the course of two and a half weeks. As the patient displayed a multitude of negative symptoms, including blunted affect, asociality, and avolition, treatment with cariprazine 1.5 mg/d was instituted 1 week after the introduction of risperidone and further increased to 3 mg/d after 2 weeks. Eighteen days after the start of treatment with risperidone and 11 days after the start of cariprazine, the patient developed hypokinesia with a forward-flexed posture and reduced arm swing when walking. Hence, the patient was prescribed biperiden 4 mg/d. Despite the treatment with biperiden, however, hypokinesia progressed. Twenty and 13 days after the start of treatment with risperidone and cariprazine, respectively, the patient showed symptoms of severe Parkinsonism with bradykinesia, postural instability, dysdiadochokinesia, difficulty raising from a sitting or supine into a standing position, rigor of his extremities, and pronounced tremor of his hands, leading to an inability to drink from a glass or bottle without spilling fluid. Due to his extreme immobility, the patient repeatedly wet himself. He required substantial assistance from the nursing staff for nearly all activities of daily living. Symptoms were most prominent 3 days after the dosage increase of cariprazine from 1.5 to 3 mg/d. Magnetic resonance imaging did not reveal any signs of organic brain disorder. Furthermore, electroencephalography was inconclusive. After excluding alternative causes and a continuous progression of symptoms, the described Parkinsonism was suspected as ADR of the antipsychotic treatment.

Consequently, risperidone was decreased to 1 mg/d which did not result in an improvement of symptoms. The patient was treated with cariprazine at an unaltered dose of 3 mg/d for another 10 days before the dosage was reduced to 1.5 mg/d.

Treatment with risperidone was fully discontinued 14 days later (ie, 25 days after the onset of Parkinsonism). The patient was also treated with biperiden 4 mg/d for a total of 5 weeks. The reduction and ultimately termination of risperidone, the reduction of cariprazine, and the administration of biperiden led to a slow but full recovery of the patient over 5 weeks. Cariprazine 1.5 mg/d was maintained as antipsychotic therapy.

## 2.3 | Case 3

A 52-year-old male patient with a 30-year history of paranoid schizophrenia was admitted to the hospital due to the exacerbation of psychotic symptoms following the patient's decision to discontinue his antipsychotic medication (haloperidol 5 mg/d and aripiprazole 15 mg/d). Besides presenting with delusional content, the patient also displayed disorganized behavior during acute psychosis. The patient was unable to recollect when precisely he had stopped taking his medication. Since the patient had suffered from severe negative symptoms of paranoid schizophrenia in the past, an antipsychotic treatment with cariprazine 1.5 mg/d was established. Additionally, the patient was treated with pipamperone 40 mg/d, taking advantage of the drug's sedating effects. One week later, cariprazine was increased to 3 mg/d and another 5 days later to 4.5 mg/d. The patient benefitted from this drug regimen as he appeared more structured in his behavior, was able to sleep during the night, and less frequently reported delusional content. One day after the last dosage increase of cariprazine, however, the patient suddenly appeared extremely restless, especially at night, and displayed an inappropriate, bizarre behavior. For instance, he emptied a garbage can, poured water over it, and subsequently spread the trash all over the lawn of the hospital garden. Moreover, he sprayed shaving cream on a tree. Six days after the onset of this bizarre behavior, olanzapine 10 mg/d was added to the patient's medication regimen, while pipamperone was discontinued. In response, the patient's sleep disturbances significantly improved and the patient was able to sleep throughout the entire night. Furthermore, the patient appeared much calmer than during previous days, and the bizarre behavior had vanished.

The patient's legal guardian, who had accompanied him for almost the entire duration of his psychiatric condition, confirmed that the behavior the patient had displayed after the increment of cariprazine to 4.5 mg/d had been very much reminiscent of previous episodes of acute psychosis. After the behavioral changes had subsided, the patient was asked to reflect on his actions. The patient merely replied that his actions had been "just for fun" and that now he no longer experienced the urge to perform such actions, stating that he felt mentally stable. The patient was discharged from the hospital with a medication consisting of cariprazine 4.5 mg/d and

olanzapine 10 mg/d. At discharge, the patient did not appear to be suffering from acute psychosis or substantial negative symptoms.

## 2.4 | Case 4

A 22-year-old female patient, who had first been diagnosed with paranoid schizophrenia 3 years earlier, was treated with risperidone 2 mg/d after a complete diagnostic work-up had not revealed any physical abnormalities. Even though prolactin levels were normal, the patient developed amenorrhea and Parkinsonism. The medication was changed to aripiprazole 20 mg/d. Unfortunately, this did not provide sufficient control of her psychotic symptoms and she experienced imperative voices for the first time. Consequently, her medication was reevaluated. During cross-titration from aripiprazole to amisulpride, elevated levels of prolactin were detected (max. 3554  $\mu\text{U/mL}$ , reference value <496  $\mu\text{U/mL}$ ) under aripiprazole 10 mg/d and amisulpride 250 mg/d. After excluding prolactinoma via magnetic resonance imaging, the patient's medication was switched to monotherapy with cariprazine. This was a precautionary measure because the patient had a positive family history of breast cancer. Following discontinuation of amisulpride, prolactin levels normalized. Treatment with cariprazine was initiated with 1.5 mg/d and increased to 3 mg/d, 4.5 mg/d, and 6 mg/d after 2, 4, and 12 weeks, respectively. Thirteen months after the start of treatment with cariprazine, elevated prolactin levels (2449  $\mu\text{U/mL}$ ) were detected in a routine control. Due to the uncommon relationship with a DRPA, further diagnostic work-up of hyperprolactinemia was initiated. Again, magnetic resonance imaging was performed, but remained inconclusive. As the patient did not suffer from galactorrhea or amenorrhea, the medication was continued under regular gynecological and endocrinological surveillance.

## 3 | DISCUSSION

As of January 2021, cariprazine is subject to additional monitoring in the European Union (EU), indicated by the “black triangle” label in the drug's SPC and package leaflet.<sup>13</sup> Generally speaking, medicinal products labeled with a black inverted triangle are under additional monitoring in the EU because they are new to the pharmaceutical market, and comparatively, little information is available on their long-term use.<sup>14</sup> For this reason, reporting newly recognized ADRs of cariprazine—such as exacerbation of psychosis (case 3) and hyperprolactinemia (case 4)—is particularly important in order to improve drug safety. Furthermore, ADRs of cariprazine, which are in principle known from previous clinical

trials (such as EPS),<sup>6</sup> but whose severity exceeds the usually expected intensity (cases 1 and 2) should be shared with the medical community.

Cases 1-3 have in common that the dosage of cariprazine was increased at a rather fast pace. In case 1, the dosage of cariprazine was raised to 3 mg/d 5 days after treatment initiation, as was the case in the dose escalation from 3 to 4.5 mg/d in case 3. In case 2, an increment in dose of 1.5 mg/d was performed after 1 week. The German SPC of cariprazine remains surprisingly vague on how quickly the dosage should be increased, stating only that this should be done “slowly”.<sup>1</sup> The US SPC of cariprazine, on the other hand, is more precise, recommending increasing the dose from 1.5 to 3 mg/d as early as on day 2 of treatment.<sup>3</sup>

Due to the long half-life of cariprazine's active metabolites, especially DDCAR, it may take up to 3 weeks for a steady state to be reached.<sup>3</sup> Therefore, changes in dose will not be fully reflected in plasma concentrations for several weeks. Furthermore, it must be considered that the time for DDCAR to reach a steady state shows an appreciable interindividual variability. After administration of 1 mg cariprazine, DDCAR remains detectable in plasma for 8 weeks.<sup>1,3</sup> Accordingly, dose adjustments should be performed with great caution and prescribers should monitor patients for ADRs and treatment response for several weeks after the start of treatment. Considering the long half-life of DDCAR,<sup>3</sup> it seems reasonable to recommend that the dosage of cariprazine should not be increased earlier than 1 week after treatment initiation. Some patients may require an even more cautious approach, increasing the dosage of cariprazine only 2-4 weeks after the start of treatment or last increase of dosage.

In the following, the presented ADRs will be analyzed from both a pharmacological and a pharmacovigilance viewpoint. The evaluation of the relationship between cariprazine and the suspected ADRs will be performed in accordance with the World Health Organization—Uppsala Monitoring Centre (WHO-UMC) system for standardized case causality assessment.<sup>15</sup>

### 3.1 | Cases 1 and 2—extrapyramidal symptoms

In general, EPS are very common ADRs of antipsychotic drugs even though the exact pathophysiology still remains poorly understood. Alongside other postulated mechanisms, blockade of dopamine D<sub>2</sub> receptors in basal ganglia is thought to play a decisive role in EPS development. In contrast, antagonism of serotonin 5-HT<sub>2A</sub> receptors may lower the risk of akathisia and ameliorate EPS.<sup>16</sup> High-potency first-generation antipsychotics such as haloperidol or benperidol are infamous for causing severe movement disorders due to their high affinity for dopamine D<sub>2</sub> receptors where



they exert antagonistic effects.<sup>17</sup> However, EPS may also arise during treatment with second- or third-generation antipsychotics and have been reported as a very frequent ADR of cariprazine, affecting  $\geq 10\%$  of treated patients.<sup>1</sup> All three DRPAs—aripiprazole, brexpiprazole, and cariprazine—display a high affinity for dopamine D<sub>2</sub> receptors where they act as partial agonists. Cariprazine has the lowest intrinsic D<sub>2</sub> receptor activity and, therefore, most likely exerts antagonistic effects. Aripiprazole, on the other hand, shows higher intrinsic D<sub>2</sub> receptor activity and, therefore, higher D<sub>2</sub> agonism.<sup>6</sup> EPS arising under treatment with cariprazine most commonly manifest as akathisia.<sup>6</sup> In general, EPS show a dose-dependent relationship.<sup>18</sup> Studies have suggested that efficacious antipsychotic activity of cariprazine can be obtained by using lower doses than those required to trigger EPS.<sup>9</sup>

### 3.2 | Case 1—akathisia

The akathisia described in case 1 was classified as a *serious* ADR since it required cessation of cariprazine and led to a prolongation of inpatient care.<sup>12</sup> Among DRPAs, cariprazine is most likely to induce akathisia.<sup>6</sup> Akathisia is characterized by a subjective feeling of inner restlessness in combination with an irrepressible urge to move around and may cause great distress to affected patients. In fact, akathisia has even been associated with aggressive and suicidal behavior<sup>6</sup> and commonly necessitates discontinuation of the causative drug(s). Akathisia most frequently presents during the first weeks of antipsychotic treatment.<sup>6</sup>

In case 1, the patient was treated with both cariprazine and quetiapine at the onset of akathisia. Cariprazine had been increased to 3 mg/d 1 week prior to the start of symptoms, which is in line with the assumption that akathisia is a dose-dependent ADR.<sup>6</sup> Quetiapine had been added to the patient's medication 8 days earlier. Even though quetiapine had been well tolerated in the past, that is, without occurrence of akathisia or other EPS, a pharmacodynamic interaction between cariprazine and quetiapine cannot be ruled out. In general, quetiapine appears to have a lower overall risk of akathisia than cariprazine<sup>6</sup>; nevertheless, reports of severe quetiapine-induced akathisia do exist.<sup>19</sup> Because akathisia persisted despite the discontinuation of cariprazine, the other antipsychotic drugs the patients was treated with (ie, risperidone and amisulpride) seem to have contributed to the persistence of symptoms.

According to the WHO-UMC system,<sup>15</sup> the causality between cariprazine and the development of akathisia in case 1 was judged as *possible* because there was a reasonable time relationship to the intake of cariprazine although the symptom could also be explained by other antipsychotics.

### 3.3 | Case 2—Parkinsonism

The Parkinsonism described in case 2 was classified as a *serious* ADR because it had resulted in significant handicap and led to the prolongation of inpatient care.<sup>12</sup> Parkinsonism occurs in approximately 10% of patients treated with cariprazine.<sup>20</sup> While advanced age is generally considered a risk factor for drug-induced Parkinsonism,<sup>21,22</sup> case 2 describes the onset of Parkinsonism in a 22-year-old adult. Since EPS also represent a very common ADR of risperidone (affecting  $\geq 10\%$  of treated patients),<sup>23</sup> a pharmacodynamic interaction between risperidone and cariprazine seems likely and may have played a decisive role in the presented case as both drugs exert antagonistic effects on dopamine D<sub>2</sub> receptors.<sup>17</sup> An exacerbation of symptoms after dose escalation of cariprazine is consistent with the aforementioned dose-dependent nature of cariprazine-induced EPS. However, because the patient showed full remission of symptoms under continuation of treatment with cariprazine 1.5 mg/d, it cannot be fully excluded that Parkinsonism was primarily caused by risperidone and would have progressed to this extent without the addition of cariprazine. Parkinsonism persisted at an unaltered intensity after the initial dose reduction of risperidone and did not improve until the dosage of cariprazine was lowered. Symptoms improved continuously over the course of several weeks, which is best explained by the long half-life of cariprazine and its active metabolites,<sup>5</sup> whereas the longest half-life of risperidone's active metabolites is approximately 24 hours,<sup>23</sup> suggesting that symptoms would have improved much more rapidly if they had solely been evoked by risperidone.

The extent of Parkinsonism was so debilitating that the patient required assistance even for basic activities of daily living such as personal hygiene. Symptoms persisted for nearly 1 month after discontinuation of risperidone and reduction of cariprazine, which may be a consequence of the long half-life of cariprazine's major metabolite, DDCAR.

According to the WHO-UMC system,<sup>15</sup> the causality between cariprazine and the development of Parkinsonism in case 2 was assessed as *possible* because of the reasonable time relationship to the intake of cariprazine. However, the symptom could also have been caused at least partly by risperidone.

### 3.4 | Case 3—exacerbation of psychosis

The patient's bizarre behavior and psychotic symptoms in case 3 necessitated urgent medical intervention (ie, treatment with olanzapine) and led to the prolongation of inpatient care. Accordingly, the suspected ADR was classified as *serious*.<sup>12</sup>

Since the patient immediately responded to treatment with olanzapine, the described symptoms were interpreted as an exacerbation of his underlying schizophrenia. Of course, it is impossible to attribute the observed psychotic exacerbation to cariprazine with absolute certainty as psychotic symptoms are also intrinsic to paranoid schizophrenia itself. While the patient appeared to have taken his antipsychotic medication as prescribed, nonadherence to the psychopharmacological regimen cannot be fully excluded, which might have left him potentially unmedicated at the time of symptom onset. However, considering the long half-life of cariprazine and its active metabolites, missed doses for even several days in a row would not exclude the drug's involvement in a psychotic exacerbation. Even though not explicitly stated in the German SPC, aripiprazole has been implicated in the exacerbation of psychotic symptoms under certain circumstances.<sup>24</sup> Higher doses of aripiprazole may exert an increasing dopamine-agonistic activity.<sup>24</sup> A similar rationale may apply to cariprazine.

Another aspect that should be discussed is the role of pipamperone. Pipamperone was discontinued, upon which the patient's psychotic symptoms subsided, therefore showing a clear temporal relationship to the improvement of psychosis. However, induction of psychosis is not a known ADR of pipamperone and therefore seems highly unlikely to have triggered the patient's psychotic symptoms.

Prior treatment with the high-potency antipsychotic haloperidol in case 3 may have further increased the risk of psychotic exacerbation.<sup>25</sup> Recent use of antipsychotic drugs with a high affinity to dopamine D<sub>2</sub> receptors can lead to an upregulation of D<sub>2</sub> receptors, causing supersensitivity of neurons to dopamine.<sup>26</sup> The addition of cariprazine may then trigger an abrupt exacerbation of psychosis by over-proportionately stimulating D<sub>2</sub> receptors via partial-agonistic effects,<sup>24</sup> a phenomenon that has been termed “dopamine supersensitivity psychosis” by Nakata and colleagues.<sup>26</sup> Even though it remained unclear when exactly the patient had discontinued treatment with haloperidol, the onset of dopamine supersensitivity psychosis has been described with a latency of up to 6 weeks after discontinuation of previous antipsychotic treatment.<sup>26</sup>

Similar to cases 1 and 2, a *possible* causality between cariprazine and the exacerbation of psychosis in case 3 according to the WHO-UMC system<sup>15</sup> was assumed because of the reasonable time relationship to the intake of cariprazine although it cannot be excluded that the symptom was evoked by the underlying disease (ie, paranoid schizophrenia).

### 3.5 | Case 4—hyperprolactinemia

The hyperprolactinemia described in case 4 was assessed as an unexpected ADR of cariprazine because it is not listed in

the SPC. It was classified as nonserious, as no seriousness criterion was met. Blockade of dopamine D<sub>2</sub> receptors on lactotroph cells of the pituitary gland causes hyperprolactinemia due to removal of the main inhibitory influence, that is, dopamine.<sup>6</sup> DRPAs are thought to have a low risk of hyperprolactinemia due to their partial-agonistic effects. DRPAs have even proven effective in lowering prolactin concentrations in patients with hyperprolactinemia induced by other (antipsychotic) drugs.<sup>6</sup> Compared to high-potency first-generation antipsychotic drugs, which cause treatment-emergent prolactin elevation in 40%-90% of treated patients,<sup>6</sup> prevalence of hyperprolactinemia under treatment with aripiprazole is 3.1%-9.0%.<sup>27</sup> To the best of our knowledge, this is the first published case of hyperprolactinemia under monotherapy with cariprazine. In a post hoc analysis of two 48-week open-label, flexible-dose extension studies to evaluate the long-term safety of cariprazine, mean prolactin levels showed a decrease among all dose groups.<sup>28</sup> In the case presented here, an alternative cause for the elevated prolactin levels could not be identified despite thorough investigation. Based on the time relationship and the lack of alternative explanations, the causality between cariprazine and the development of hyperprolactinemia in case 4 was judged as *probable*, according to the WHO-UMC system.<sup>15</sup> The correlation might be similar to cases of hyperprolactinemia under treatment with aripiprazole—unexpected but not exclusionary. Cases such as case 4 underscore the importance of prolactin monitoring during psychopharmacological treatment, even if the applied substance rarely leads to elevated prolactin levels or has not at all been implicated in hyperprolactinemia thus far.

## 4 | LIMITATIONS AND CONCLUSION

Limitations of this case series mainly arise from the comedication and the differential diagnoses, making it difficult—if not impossible—to attribute the presented ADRs solely and undoubtedly to cariprazine. However, within the field of pharmacovigilance, it is neither necessary nor reasonable to merely report cases in which an adverse event can be ascribed to a single agent with absolute certainty. On the contrary, reporting of suspected ADRs—as in this case series—fulfills an important purpose, namely the detection of risk signals.<sup>29</sup> This is especially true for medicines under additional monitoring,<sup>13</sup> such as cariprazine.<sup>1</sup>

Our case series reports on four suspected ADRs of cariprazine, namely akathisia, Parkinsonism, exacerbation of psychosis, and hyperprolactinemia. To the best of our knowledge, exacerbation of psychosis and hyperprolactinemia have not previously been described as ADRs of cariprazine in the literature. Further pharmacovigilance surveillance is needed to assess their frequency. Reporting

newly recognized and/or unusually severe ADRs to the medical community remains a cornerstone of pharmacovigilance. We would like to share our observations with healthcare professionals in the field of psychiatry and beyond in order to promote the timely detection of (serious) ADRs of cariprazine in the future, thus pursuing the ultimate goal of improving patient safety.

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Published with written consent of the patient.

## CONFLICT OF INTEREST

JS took part in an educational event sponsored by Otsuka/Lundbeck. ST is a member of the advisory board for Otsuka and Janssen-Cilag and has received speaker's honoraria from Janssen-Cilag, Lundbeck/Otsuka, and Servier. As Drug Commissioner of Hannover Medical School, DOS is an independent expert and not affiliated with AMSP. DOS, JH, AG, CG, DD, GRS, IA, MS, RG, ER, CS, and SB state that they have no conflicts of interest to declare. The AMSP drug safety project is facilitated by nonprofit associations in Germany, Austria, and Switzerland. The AMSP project has been supported with unrestricted educational and research grants since 1993 by the following companies: German companies: Abbott GmbH & Co. KG, AstraZeneca GmbH, Aventis Pharma Deutschland GmbH GE-O/R/N, Bayer Vital GmbH, Boehringer Mannheim GmbH, Bristol-Myers-Squibb, Ciba Geigy GmbH, Desitin Arzneimittel GmbH, Duphar Pharma GmbH & Co. KG, Eisai GmbH, Esparma GmbH Arzneimittel, GlaxoSmithKline Pharma GmbH & Co. KG, Hoffmann-La Roche AG Medical Affairs, Janssen-Cilag GmbH, Janssen Research Foundation, Knoll Deutschland GmbH, Lilly Deutschland GmbH Niederlassung Bad Homburg, Lundbeck GmbH & Co. KG, Novartis Pharma GmbH, Nordmark Arzneimittel GmbH, Organon GmbH, Otsuka-Pharma Frankfurt, Pfizer GmbH, Pharmacia & Upjohn GmbH, Promonta Lundbeck Arzneimittel, Recordati Pharma GmbH, Rhone-Poulenc Rohrer, Sanofi-Synthelabo GmbH, Sanofi-Aventis Deutschland, Schering AG, SmithKlineBeecham Pharma GmbH, Solvay Arzneimittel GmbH, Synthelabo Arzneimittel GmbH, Dr Wilmar Schwabe GmbH & Co., Thiemann Arzneimittel GmbH, Troponwerke GmbH & Co. KG, Upjohn GmbH, Wander Pharma GmbH, and Wyeth-Pharma GmbH. Austrian companies: AstraZeneca Österreich GmbH, Boehringer Ingelheim Austria, Bristol-Myers Squibb GmbH, CSC Pharmaceuticals GmbH, Eli Lilly GmbH, Germania Pharma GmbH, GlaxoSmithKline Pharma GmbH, Janssen-Cilag Pharma GmbH, Lundbeck GmbH, Novartis Pharma GmbH, Pfizer Med Inform, and Wyeth Lederle Pharma GmbH. Swiss companies: AHP (Schweiz) AG, AstraZeneca AG, Bristol-Myers Squibb AG, Desitin Pharma GmbH, Eli Lilly (Suisse) SA, Essex Chemie AG, GlaxoSmithKline AG, Janssen-Cilag AG, Lundbeck

(Suisse) AG, Organon AG, Pfizer AG, Pharmacia, Sanofi-Aventis (Suisse) SA, Sanofi-Synthelabo SA, Servier SA, SmithKlineBeecham AG, Solvay Pharma AG, Wyeth AHP (Suisse) AG, and Wyeth Pharmaceuticals AG.

## AUTHOR CONTRIBUTIONS

JH, JS, AG, CG, and ST: involved in writing the first draft of manuscript. CS: contributed special expertise in pharmacovigilance. DOS, CS, GRS, DD, IA, MS, RG, ER, and SB: commented on previous versions of the manuscript. All authors: read and approved the final manuscript.

## ETHICAL APPROVAL

Evaluations based on the AMSP database have been approved by the Ethics Committee of Ludwig Maximilian University of Munich and by the Ethics Committee of Hannover Medical School (No. 8100\_BO\_S\_2018). This study adheres to the Declaration of Helsinki and its later amendments. The AMSP project is a continuous observational postmarketing drug surveillance program that does not interfere with the ongoing clinical treatment of the patients under surveillance.

## DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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