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Case Report

Could Cariprazine Be a Possible Choice for High Functioning Autism? A Case Report

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Abstract: This case report was conducted by searching for the following keywords on PubMed: High Functioning Autism, Autism Spectrum Disorder, cariprazine, aripiprazole, partial agonist antipsychotic, DRD2/DRD3. High Functioning Autism (HFA) is a neurodevelopmental disorder characterized by the core symptoms of autism spectrum disorder (ASD) with average intellectual abilities, behavioral symptoms such as irritability, hyperactivity, aggressiveness and mood symptoms. HFA is not a term used in the Diagnostic and Statistical Manual of mental disorders (DSM), but it is commonly used to identify patients diagnosed with Autistic Disorder (AD) or Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) with average or above average intellectual abilities. Several factors are involved in HFA development, including environmental and genetic factors. In particular, over the last several decades, dopaminergic signaling system dysfunction has been highlighted as being responsible for behavioral patterns. Nowadays, symptoms of ASD lack a specific pharmacological treatment. The only medications approved by the Food and Drug Administration (FDA) for symptoms associated with ASD, in particular the irritability, are risperidone and aripiprazole. According to the hypothesis that dopamine receptor DRD2 and DRD3 might be involved in impulsive behavior, stereotypy, repetitive behaviors and language impairment, cariprazine could be a therapeutic option. This molecule is primarily characterized by DRD3 partial agonism and serotonin 5-HT1A partial agonism, with a lower ability to activate DRD2 than other third-generation antipsychotics, such as aripiprazole. We have reported here a case study of treatment of HFA with cariprazine.

Keywords: ASD; HFA; cariprazine; DRD2/DRD3; 5HT-2B; obsessive symptoms; impulsivity

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1. Introduction

Autism is a lifelong neurodevelopmental disorder characterized by a range of conditions and symptoms that frame it as a spectrum of disorders (autism spectrum disorder, ASD), whose core symptoms include persistent deficits in social interaction and communication and restrictive/repetitive behaviors and interests [1]. In the 1960s, thanks to the studies of Bernard Rimland, it was established that ASD was a psychiatric disorder deriving from the combination of genetic and environmental factors [2].

At the time of publication of the DSM-III, most of the core symptoms of Autistic Disorder were focused on childhood and were generally associated with moderate to severe intellectual impairment and deficits in language development [3]. However, today

up to two thirds of individuals with autism have an average Intelligent Quotient (IQ) and about 75% of the subjects may not present with severe language difficulties [4]. In this scenario High Functioning Autism (HFA) was introduced, even if it is not a term used in the DSM. It identifies patients diagnosed with Autistic Disorder or Pervasive Developmental Disorders Not Otherwise Specified, with average (or above average) intellectual abilities (IQ higher than 70). HFA differs from Low Functioning Autism (IQ lower than 70) in terms of clinical presentation, prognosis and the need for support and assistance in daily life [5].

Nowadays there is a lack of a specific pharmacological treatment for the core symptoms of autism, but some molecules have shown some efficacy in the improvement of behavioral symptoms (such as irritability, hyperactivity, aggressive behaviors) [6,7], anxiety and mood symptoms [8]. In fact, risperidone and aripiprazole are currently the only medications approved by the FDA for autism spectrum disorder-associated symptoms, targeting the irritability [9].

There are several risk factors for ASD, such as environmental and genetic factors. The first one includes factors that occur during the pre-perinatal period such as parental age, asphyxia-related birth complications, maternal obesity and gestational diabetes [10]. In addition, the risk developing ASD can be increased by fever, viral infections (like rubella or flu) or pharmacological therapies like thalidomide and valproate taken during pregnancy [11,12]. Genetic factors (i.e., DNA methylation, de novo mutation, rare genetic variations, copy number variation) can also contribute to autism [13]. Other factors like the dysfunction of the dopaminergic signaling system in certain brain areas, especially in the dopamine (DA) mesocorticolimbic signaling pathway, are considered to be the basic pathogenetic processes involved in autism [14]. The alterations include the reduction in DA release in the prefrontal cortical area, diminished responsiveness of the nucleus accumbens [15] and hypoactivation of the reward system [16]. In addition, by altering dopamine transmission, genetic variants and mutations of dopamine transporters can lead to ASD-like behavior patterns [17]. Moreover, dopamine is one of the main neurotransmitters involved in social behavior, social cognition and the control of movement. D2 receptors (DRD2) might be connected to stereotypy and repetitive behaviors and language impairment in ASD. This is why the use of D2 partial agonists like aripiprazole, cariprazine and brexpiprazole has been approved in autism [18].

There is also some evidence, albeit limited, of the role of TMS in autism through an increase in dopamine release [19]. Initial research has suggested that TMS may have a positive impact on some cognitive and behavioral functions in certain individuals with Autism Spectrum Disorder (ASD) [20–22].

Given the scarce literature and the few treatment options for autism, we reported here a case of possible therapeutic choice with cariprazine after the failure of the first-choice treatment with aripiprazole.

2. Treatment of HFA with "Third" Generation Antipsychotics: An Overview of the Current Literature

Research into the current literature on PubMed, using the keywords "High Functioning Autism, Autism Spectrum Disorder, Cariprazine, Aripiprazole, Partial agonist antipsychotic, DRD2/DRD3", was conducted in June 2023. This research was a focused, narrative and non-systematic review.

Among antipsychotic drugs, aripiprazole and risperidone (a D2 and 5-HT2A receptor antagonist, respectively) have already been approved by the FDA for the treatment of irritability, hyperactivity and stereotypical behavior in ADS children [23]. No major differences between these two drugs seem to be present in terms of efficacy and tolerability, despite some side effects like weight gain or sedation [24]. This aspect was highlighted in the review by Sochocky and coll. [25], where the beneficial effects on behavioural symptoms associated with AD/HFA were observed after treatment with aripiprazole, risperidone, olanzapine and quetiapine. Risperidone trials provide slightly higher confidence, but this review cannot endorse one SGA over another.

A recent review [26] provided a brief description of the role of D2 partial agonists and their potential use in ASD. According to this, impairment in social interactions and repetitive and stereotyped behaviors may be related to D2 and D3 receptors [26].

D2/D3 partial agonists exhibit varying degrees of D2 and D3 intrinsic activity, making each molecule unique in terms of clinical efficacy and safety. Brexpiprazole had the highest affinity for the dopamine D2 receptor among the third generation antipsychotics, followed by aripiprazole and cariprazine [27]. Their activity on D3 receptors, on the other hand, showed a substantial difference. Specifically, whereas aripiprazole has a delayed, monophasic dissociation, cariprazine has biphasic binding characteristics. This implies that it can respond quickly to changes in dopamine levels [28].

According to a 2018 meta-analysis [29], aripiprazole seems to be most effective in the acute treatment of irritability, hyperactivity/noncompliance, improper speech and stereotyped behavior in children and adolescents with ASD. Currently, second generation antipsychotics (SGAs) are still used, primarily to target the related symptoms of AD/HFA rather than the primary symptomatology. A systematic review and meta-analysis from 2013 [25] confirms that SGAs have a significant positive impact on associated behaviors in the youngest AD/HFA population.

A piece of work by Mattila and coll. [30] reported a 74% prevalence of at least one psychiatric comorbidity in their AD/HFA participants. In particular, the three most frequent comorbid diseases were behavioral disorders (44%), anxiety disorders (42%) and tic disorders (26%) [30], and all of these could be treated well with an SGA. The Clinical Global Impression (CGI) scale was largely used to evaluate symptoms related to HFA. Stigler and coll. highlighted a considerable improvement in the irritability dimension using the CGI-I, with 22 (88%) of 25 individuals being scored as much or very much improved [31]. Additionally, in this work, an improvement in irritability symptoms, evaluated with the Aberrant Behavior Checklist scale, was detected in most of the participants. Besides the effects on the irritability and hyperactivity dimensions, some studies have also investigated the impact of SGAs on social and communication impairments, as well as on repetitive interests and activities [29]. Moreover, a reduction in related symptoms such as irritability may allow study subjects to be more susceptible to adaptive behaviors [31].

Another aspect that has to be considered is the nosology and diagnosis, with ongoing debate over whether AD can be reliably distinguished from HFA and a proposal to include HFA in the DSM-5 diagnostic category of ASD [3]. Given the diagnostic ambiguity, rigorous therapy research has been delayed.

Finally, there is a lack of studies investigating the optimal dose impact on outcome measures. All trials employed low-to-medium dose ranges, such as aripiprazole 2.5–15 mg/day, quetiapine 25–150 mg/day, risperidone 0.5–3.5 mg/day and olanzapine 2.5–15 mg/day. Pharmacological studies are weak in rigor, and there are few trials including psychosocial therapy [25].

3. Clinical Case

A 25-year-old patient entered the Mental Health Center of Chieti with a diagnosis of "High functioning autism, delusional ideation, Obsessive-Compulsive Disorder, Mild Depressive Episode". The diagnosis of High Functioning Autism was given in his adulthood, in 2019, by the local Child Neuropsychiatry Services, through the use of psychometric scales such as RAADS (Ritvo Autism Asperger's Diagnostic Scale-Revised) = 94, ADI-R (Autism Diagnostic Interview-Revised) and ADOS2 (Autism Diagnostic Observation Schedule Second Edition) module 4. In this period, after obtaining a high school diploma with difficulty, the patient changed their degree course three times due to poor concentration. The patient's interests were narrow and pervasive and often the ideation on such obsessive topics was tinged with abnormal or delusional aspects. He exhibited a pronounced focus on several aspects: aesthetics (expressing an interest in facial bone reconstruction methods, deeming facial perfection as a crucial factor for an enhanced quality of life), safety (particularly in the construction of earthquake-resistant buildings and bank vaults) and

the classification of human sciences (he categorized websites on the internet). Over a span of several years, he grappled with uncontrolled or explosive behaviors such as outbursts and restlessness. These behaviors led to conflicting experiences of relief and guilt. He appeared disheartened concerning his own mental state and future prospects, often relying on parental support in situations involving responsibility and decision-making. Starting from a young age, he irregularly took medications that included serotonin regulators, mood stabilizers, and third-generation antipsychotics. In November 2021, he sought assistance at the Mental Health Center in Chieti after independently modifying and reducing the therapy prescribed in 2019 (which included lithium, aripiprazole and sertraline) due to perceived ineffectiveness. During his first visit, we recommended a dosage of 100 mg of sertraline and a gradual discontinuation of aripiprazole, to be replaced by cariprazine. Consequently, cariprazine was prescribed at a dose of 1.5 mg, and following the cessation of aripiprazole, the cariprazine dosage was gradually increased to 3 mg per day, with no reported adverse effects. Within a week, both the patient and his parents reported a reduction in anxiety and improvements in obsessive and impulsive behaviors. In January 2022, carbolithium was reintroduced alongside an increase in the cariprazine dosage to 4.5 mg per day. By March, there were signs of improvement in his psychopathological conditions, marked by fewer crises, better impulse control and a return to academic pursuits, albeit with some difficulty in maintaining consistency. The patient exhibited a more responsive mood, reduced feelings of guilt and increased mental relaxation. Recently, he has started a romantic relationship with a young woman.

In order to evaluate the diagnostic framework and treatment efficacy, psychometric scales were administered to the patient at admission to the Mental Health Centre (T0) in April 2022 (T1) with the following findings (see Table 1):

- Q-LES-Q-SF (Quality of Life Enjoyment and Satisfaction Questionnaire—Short Form) is a recovery-oriented, self-report measure with an uncertain underlying factor structure, variously reported in the literature to consist of either one or two domains [32].

  T0 = 30, T1 = 42.

- BIS11 (Barratt Impulsiveness Scale) is the most frequently used measure among various self-report questionnaires of impulsivity, exploring 30 items in order to increase construct validity and to improve psychometric characteristics [33].

  T0 = 76, T1 = 62.

- BPRS 4.0 (Brief Psychiatric Rating Scale Vers 4.0) enables the rater to measure psychopathology severity and it is characterized by 24 items [34].

  T0 = 51, T1 = 35.

- RAADS-R (Ritvo Autism Asperger's Diagnostic Scale-Revised) is a valid and reliable instrument to assist in the diagnosis of ASD in adults. It includes 80 items whose 16 questions describing non symptomatic (normative) behaviors [35].

  T1 = 75 (2019 score was 95).

Table 1. Psychometric scales in patient at admission to the Mental Health Centre (T0) and in April 2022 (T1).

Psychometric Scales	T0	T1
Q-LES-Q-SF	30	42
BIS11	76	62
BPRS 4.0	51	35

4. Discussion

To the best of our knowledge this is the first case report on pharmacological treatment of HFA with cariprazine. This drug is a third-generation antipsychotic characterized by partial agonism of DRD2 and the D3 receptor (DRD3), but with a lower ability to activate DRD2 than other third-generation antipsychotics, such as aripiprazole. The main peculiarity of cariprazine is its high affinity for DRD3, greater than dopamine itself or other antipsychotics [36].

In the current literature third-generation antipsychotics, such as aripiprazole, have been associated with impulse dysregulation probably induced by their partial agonistic effect on DRD2, together with their effect on the 5-HT1A, 5-HT2A, 5-HT2B and 5-HT7 receptors, which has been also associated with an increase in addictive behaviors such as gambling and the prevention of relapse in psychoactive drug addiction [37,38]. This aspect could be explained by the polymophism of DRD2 (DRD2Taq1A) that could lead to a different sensitization of DRD2 [39]. The evidence suggests that the behavioral manifestations and symptom response following treatment with third-generation antipsychotics may have multiple causes and explanations.

In our report we observed a significant reduction in impulsivity and aggressiveness after switching to cariprazine, probably due to its unique receptor profile. This molecule, in fact, is characterized primarily by DRD3 partial agonism and serotonin 5-HT1A partial agonism, while aripiprazole is more selective for DRD2 than DRD3 [40]. There is also a potential drug–drug interaction between carbolithium and cariprazine: while impulsivity has traditionally been linked to the dysregulation of serotoninergic and dopaminergic systems, some authors have suggested that lithium may reduce impulsivity levels through its ability to regulate these neurotransmitter systems [41].

DRD3, almost completely localized in limbic structures thanks to dopamine binding, contributes to limiting dopamine release, especially at the cortical level [42]. Therefore, the partial DRD3 agonism would facilitate dopamine release, leading to a reduction in anhedonia and motivation loss [43] or a decrease in dopamine activity, increasing, in this way, the acetylcholine release at the cortical level, contributing to the precognitive effects of cariprazine [44]. The antidepressant effect and cognitive improvement are also supported by cariprazine agonism on the 5-HT1A serotoninergic receptor [45]. Some functional analyses of DRD3 agonists and antagonists suggest that this receptor could be involved in locomotor inhibition [46,47].

Finally, in our report, cariprazine also seems to have been effective on obsessive symptoms. To investigate the implication of D2 and D3 receptor stimulation on obsessive symptoms, some preclinical studies showed that quinpirole, a dopamine D2/D3 receptor agonist, can produce long-term changes in some compulsive behaviors, like checking [48]. Therefore, cariprazine could also be effective in other neuropsychiatric conditions that share the same dopaminergic pattern. In support of this hypothesis, some studies have reported that Ser9Gly dopamine DRD3 polymorphism was associated with the symptoms and also the development of obsessive compulsive personality disorder (OCPD), with a particular association between the DRD3 Gly/Gly genotype and OCPD [49]. The glycine allele is associated with greater reward-related DA release which supported by an in vitro study showing that Ser9Gly D3 autoreceptors have a higher affinity for DA in both G-protein-coupled and uncoupled receptor states [50].

5. Conclusions

In this report we observed a reduction in aggressiveness and impulsivity, and in particular, cognitive improvement and a reduction in obsessive symptoms, making cariprazine a new possible pharmacological choice for the treatment of HFA thanks to its unique receptor profile.

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Informed Consent Statement: Written informed consent was obtained from the patient and his parents for the publication of this case report and the accompanying data. All patient data were treated confidentially and anonymously.

Data Availability Statement: Data are contained within the article.

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