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**\*Corresponding author:** NA Aliyev, Department of psychiatry and Addiction, Azerbaijan State Advanced Training Institute, Baku, Azerbaijan,  
E-mail: [aliyevnadir@yahoo.com](mailto:aliyevnadir@yahoo.com)

**ORCID:** <https://orcid.org/0000-0003-4825-7270>

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## Research Article

# Cariprazine in therapy of visual hallucinations. Randomized, double-blind placebo-controlled study

NA Aliyev<sup>1\*</sup> and ZN Aliyev<sup>2</sup>

<sup>1</sup>Department of psychiatry and Addiction, Azerbaijan State Advanced Training Institute, Baku, Azerbaijan

<sup>2</sup>Department of psychiatry, Azerbaijan Medical University, Baku, Azerbaijan

## Abstract

**Objective:** We studied cariprazine in therapy of visual hallucinations with a therapeutic resistance due to traumatic brain injury randomized, double-blind placebo-controlled study manner.

**Methods:** To traumatic brain injury hundred patients (100 all men) whom we studied were under observation in Mental Health Center of the Ministry of Health of the Republic of Azerbaijan from January 2020 to June 2021. The method of randomization was given by lottery []. Each patient was randomized to receive either in agreement of the instruction cariprazine (50 patients) over 5 day in dose 6 mg one times per os in morning after meet for 12 weeks or matched placebo (50 patients) in a double-blind manner. A structured clinical interview, for DSM-5Axis I Disorder, Patient Edition, was used to diagnose according to DSM-5 major or mild neurocognitive disorder due to traumatic brain injury.

**Results:** All patients (50) treated with cariprazine treated participants responded by 12 weeks, versus two of the 50 placebo-treated participants ( $p < 0.001$ ). The most common and problematic side effect in the cariprazine group was not.

**Conclusions:** The authors believe this to be the first double-blind placebo-controlled randomization study to test the efficacy of a cariprazine in the management of in therapy of visual hallucinations with a therapeutic resistance due to traumatic brain injury randomized, double-blind placebo-controlled study manner. They need to be replicated in a larger study group.

## Introduction

Cariprazine (vraylar, reaqilq) is an antipsychotic of the new generation, which is a partial agonist of dopamine receptors. The drug differs from other antipsychotics with high affinity to D<sub>3</sub>-dopamine receptors, which is about 10 times higher than other drugs. It is believed that D<sub>3</sub>-receptors play an important role in the modulation of cognitive processes and emotional regulation. These pharmacological properties of the drug determine the intended clinical targets in patients with schizophrenia. The obtained data demonstrate the predominance of cariprazine in the dominant clinical picture with negative symptoms and simultaneous favorable tolerance profile [1-3].

The prevalence of traumatic brain injury in the United

States, 1.7 million cases occur each year, resulting in 1.4 million emergency department visits, 275,000 hospitalizations, and 52,000 deaths. About 2% of the population lives with TBI-related disabilities. In the United States, 59% of TBI cases are in men. The most common causes of TBI in the United States are falls, car accidents and headaches. Collisions and head blows during contact sports are increasingly recognized as a source of mild TBIs, as recurrent mild TBIs can lead to cumulative long-term consequences [4].

## Materials and methods

This was a double-blind, placebo-controlled trial for patients diagnosed with DSM-5 for visual hallucinations with a therapeutic resistance due to traumatic brain injury. The patients gave their informed, written consent to participate. In accordance with the Helsinki Declaration of the World



Medical Association “Recommendations for doctors engaged in biomedical research involving people”, adopted by the 18th World Medical Assembly (Finland, 1964, revised in Japan in 1975, Italy - 1983, Hong Kong - 1989, the South African Republic - 1996, Edinburgh - 2000); The Constitution of the Republic of Azerbaijan, the Law “On Psychiatric Assistance” (adopted on 12.06.2001, with amendments and additions - 11.11.2011, Decisions of the Cabinet of Ministers of the Republic of Azerbaijan No. 83, dated April 30, 2010 “On Approval of the Rules for Conducting Scientific, Preclinical and Clinical studies of medicines” are established. The conditions of the conducted researches corresponded to the generally accepted norms of morality, the requirements of ethical and legal norms, as well as the rights, interests and personal dignity of the participants of the studies were observed.

The study periods: from January 2020 to June 2021. Patients were observed at the Mental Health Center of the Ministry of Health of the Republic of Azerbaijan. This was a double-blind, placebo-controlled trial for patients diagnosed with DSM-5 for Visual hallucinations with a therapeutic resistance due to traumatic brain injury.

Hundred patients (100 all men) whom we studied were under observation in Mental Health Center of the Azerbaijan Republic from January 2020 to June 2021. The method of randomization was given by lottery. Each patient was randomized to receive either in agreement of the instruction cariprazine (50 patients) over 5 day in dose 6 mg one times per os in morning after meet for 12 weeks or matched placebo (50 patients) in a double-blind manner. A structured clinical interview, for DSM-5 Axis I Disorder, Patient Edition, was used to diagnose according to DSM-5 major or mild neurocognitive disorder due to traumatic brain injury. Eligible participants were required to be between 18 and 65 years of age.

Analysis of response refers to the last observation carried forward for all subjects who had valuable efficacy at baseline and with treatment. The responder analysis was conducted by using the chi-square ( $\chi^2$ ) and analysis of variance (ANOVA) according to Glantz [5].

## Results

Characteristics of the patients randomly assigned to the two treatments are shown in Table 1

Statistical differences between the two groups are not significantly [5]. The results of treatment are shown in Table 2. Response was defined as a 100% reduction in the symptoms of Visual hallucinations with a therapeutic resistance due to traumatic brain injury. The responder was conducted by  $\chi^2$  demonstrated superior for than for placebo (Table 2). Cariprazine was generally well tolerated by the patients in the study. The two common side effects leading to discontinuation in the cariprazine group were allergic reaction and drowsiness, sweating a frequent complaint during placebo treatment occurred in two of 50 men. From Cariprazine group patients improvement observed in 48 while in the placebo group, improvement was noted in only 2 patients.

**Table 1:** Sociodemographic characteristics of patients.

Characteristic	Cariprazine n = 50	Placebo n = 50
	Mean SD	Mean SD
Age (years)	38.5 ± 9.1	38.7 ± 9.0
Duration of illness in month	6,0±0,6	5,9±0,7
Education:		
– primary school	28 (56%)	30 (60%)
– secondary school	22 (44%)	20 (40%)
Marital status:		
– never married	10 (20%)	10 (20%)
– married	30 (60%)	28 (56%)
– divorced or separated	10 (20%)	12 (24%)
Employment status		
– unemployed	18 (36%)	22 (44%)
– employed	32 (64%)	28 (56%)

Note: differences between groups are not significant

**Table 2:** The results of the square analysis.

Treatment Groups	Observed number	Expected number	chi-square ( $\chi^2$ )
	Yes improvement*	Not improvement*	Total
Placebo	2 (12.43)	48 (11.57)	50
Cariprazine	48 (13.56)	2(8,0.43)	50
Total	50	50	100

Note: Expected numbers indication in the brackets  $\% \chi^2 = 22.68$ ,  $df = 1$ ,  $p < 0.001$ .

## Discussion

### Hallucinations

Hallucinations are perception-like experiences that occur without an external stimulus [DSM-5].

They are bright and clear, with full force and the impact of normal perception and are not under voluntary control. They can occur in any sensory modality, but auditory hallucinations are most common in schizophrenia and related disorders. Auditory hallucinations are usually perceived as voices, familiar or unfamiliar, as opposed to the person's own thoughts. Hallucinations must take place in the context of a clear sensorium; those that occur on falling asleep (hypnagogic) or on awakening (hypnopompic) are considered to be within the normal experience. Hallucinations can occur from any sensory input (eg, visual, olfactory, gustatory, tactile, or auditory), but certain etiological factors can cause certain hallucinatory phenomena. Olfactory hallucinations indicate temporal lobe epilepsy. Hallucinations can range from simple and unformed to very complex and organized, depending on etiological and environmental factors. A psychotic disorder caused by another medical condition is usually not diagnosed if the person performs a reality check for hallucinations and realizes that they are the result of the disease. Visual hallucinations can have a variety of themes, including somatic, grandiose, religious, and most commonly, persecution. In general, however, the relationship between visual hallucinations and certain illnesses is less specific than in the case of hallucinations.

Cariprazine is an antipsychotic of the new generation, which is a partial agonist of dopamine receptors. The drug differs from other antipsychotics with high affinity to D3-dopamine receptors, which is about 10 times higher than other drugs. It is believed that D3-receptors play an important role in the modulation of cognitive processes and emotional regulation.



These pharmacological properties of the drug determine the intended clinical targets in patients with schizophrenia. The obtained data demonstrate the predominance of cariprazine in the dominant clinical picture with negative symptoms and simultaneous favorable tolerance profile [ 1– 3].

As you know, antipsychotics are the main pharmacological agent used in schizophrenia. Their obligatory property is the ability to reduce psychotic symptoms, as well as psychomotor agitation. At the same time, various clinical manifestations of schizophrenia determine the need to influence also other groups of symptoms, primarily negative, affective disorders and cognitive impairments. Apparently, such a multimodal action of the antipsychotic drug at the stage of long-term therapy is necessary, but with active and continued therapy, it is also desirable.

With the traditional and current classification of drugs by clinical action, sedatives, incisive and de-inhibiting antipsychotics are distinguished. In the practical work of a psychiatrist, this taxonomy is still often fundamental in the adoption of a rational choice of an antipsychotic in various clinical situations. At the same time, however, there are costs of such “excess” commitment. In particular, the use of drugs with disinhibitory activity in patients with psychotic symptoms is limited, where they may also be effective. In addition, the classification does not consider drugs with a broad multi-receptor mechanism of action and universal clinical activity.

Kariprazine is a registered drug under the name reagila in various dosages in Azerbaijan. As provided by the instructions for this antipsychotic drug, it is intended for the treatment of schizophrenia and is recommended for use at the stages of active, continued and long-term therapy. The advantage of cariprazine over other antipsychotics is its proven efficacy in dominant negative symptoms. The presented work proved that cariprazine in therapy of auditory hallucinations in a patient with a therapeutic resistance due to traumatic brain injury is very effective.

Kariprazine has a 6–8-fold greater affinity for D3 receptors than for D2 receptors, with a specificity for the D3 receptor, which is 3–10 times higher than the specificity of aripiprazole for this receptor [6]. Aripiprazole binds more efficiently than cariprazine to human and rat 5-HT<sub>2A</sub>, 5-HT<sub>2C</sub> and adrenergic receptors. In contrast, cariprazine has lower affinity for human and rat hippocampal 5-HT<sub>1A</sub> receptors (and exhibits low intrinsic efficacy), low affinity for human 5-HT<sub>2A</sub> receptors, moderate or low affinity for histamine H<sub>1</sub> and 5-HT<sub>2C</sub> receptors, and negligible affinity for cholinergic or adrenergic receptors, all of which indicate a decrease in the propensity for side effects, are associated with these receptors.

## Conclusion

Problems of pharmacological treatment of visual

hallucinations with a therapeutic resistance due to traumatic brain injury very problematic. Because classical and atypical antipsychotics cause serious extrapyramidal side effects. This is the first study on the use of cariperzine in therapy of visual hallucinations with a therapeutic resistance due to traumatic brain injury, randomized, double-blind placebo-controlled study. All patients (50) treated with cariprazine treated participants responded by 12 weeks, versus two of the 50 placebo-treated participants ( $p < 0.001$ ). The most common and problematic side effect in the cariprazine group was not.

## Limitation of the study

First, our small study group and we recommend that these results be replicated in a larger group so that effect sizes can be more precisely estimated. Second, it is necessary study of possibility generalizability these data to women. Notwithstanding these limitations, this study suggests that, cariperzine are efficacious and well tolerated in the treatment of visual hallucinations with a therapeutic resistance due to traumatic brain injury very.

## Author disclosure information

The authors declare that the article is submitted on behalf of all authors. Authors declare no financial and personal relationship with other people or organizations that could inappropriately influence this work. The authors declare no conflicts of interest. No sponsor provided funding for this study.

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