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Efficacy and safety of aripiprazole in the treatment of delirium

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Summary

Delirium is a disorder of consciousness and it is caused by acute brain dysfunction in the course of, e.g., severe somatic condition, intoxication or withdrawal syndrome. Delirium management is based on the treatment of the state that caused disturbance in central nervous system. Severe delirium syndromes such as agitation, disorganized behavior or hallucinations require additional pharmacological treatment with antypsychotics. Aripiprazole is used in treatment of schizophrenia, bipolar disorder and Tourette syndrome, but also off-label in delirium. A systematic review of databases was carried out and results were limited to case reports, clinical trials and randomized controlled trials. There is evidence that there is no difference in effectiveness of aripiprazole compared to haloperidol and other atypical neuroleptics. Aripirazole could be a better option in particular groups of patients due to its safer cardiological and metabolic profile as well as better tolerance of treatment. However, data from clinical findings are still insufficient to recommend a routine use of aripiprazole in the treatment of delirium. Therefore, further investigations are necessary to work out new strategy of managing delirium syndrome.

Key words: aripiprazole, delirium, treatment

Delirium is a qualitative disorder of consciousness. In current terminology (compatible with ICD-10), the classification of disorders of consciousness is no longer used and term *delirium* is synonymous with all of qualitative disorders of consciousness [1].

The main symptoms of delirium are: acute cognitive disorders (i.e., attention and memory impairment, disorientation, thinking disorders, disorders of perception), change of psychomotor behavior and disturbances of emotion. The severity of the above symptoms is subject to diurnal fluctuations [1]. The mortality rate for delirium

episodes ranges from 4% to 65%, and the onset of delirium during hospitalization significantly extends hospitalization time [2].

There are three main subtypes of delirium psychomotor profile: hyperactive, hypoactive and mixed [3].

The pathomechanism of delirium is complex [2]. Systemic inflammation causes blood-brain barrier permeability disruption, decreased perfusion in blood vessels of the brain and increased transmission of inflammatory cytokines into the central nervous system (CNS). This state leads to hypoxia and induces neuronal apoptosis. Dysregulation of the hypothalamic-pituitary-adrenal axis may lead to chronic activation of glucocorticoid receptors in the CNS. Additionally, oxidative stress, circadian rhythm dysregulation and neuronal aging can cause disruption of neurotransmission. An increase in activity within the dopaminergic, noradrenergic and glutamatergic neurotransmitter systems as well as a decrease in activity within the cholinergic pathways have been described. In addition, neurotransmission disorders also affect the serotonergic, histamine and GABAergic systems [4].

Risk factors of delirium are: severe somatic condition, age, sensory impairment, and male gender. Except those mentioned above, delirium can be induced by withdrawal syndrome, intoxication with psychoactive substances or other substances, i.e., medicines, organic compounds, phosphates or heavy metals [5].

The prevalence of delirium depends on the profile of the group of patients. In elderly inpatients it reaches 23% [6]. The incidence of delirium among postoperative patients is 18.7% [7] and among acute stroke patients it is 25% [8]. Palliative care patients are a specific group, where delirium prevalence is 4–12% in all patients, 9–57% in hospitalized patients and 6–74% in hospice patients [9]. However, delirium is the most common in intensive care unit (ICU) inpatients. The prevalence in this group of patients is 31.8% and increases to 50–70% in mechanically ventilated patients [10, 11].

There are limited data on the prevalence of delirium due to psychoactive substance use. The prevalence of delirium due to alcohol withdrawal (delirium tremens) is 0.7% in Germany [12] and 0.2% in Finland [13].

Delirium management is based on the treatment of the state that caused disturbance in the central nervous system.

In delirium that developed in the course of withdrawal syndrome, management consists in administering a receptor agonist that was affected by the substance taken by the patient. Management of delirium tremens includes use of benzodiazepines, such as diazepam or lorazepam [14]. However, severe delirium syndromes such as agitation, disorganized behavior or hallucinations require additional pharmacological treatment with antipsychotics [5]. Haloperidol (first generation antipsychotic) is the gold standard in the treatment of delirium symptoms. Based on current reports, sec-

ond generation antipsychotics (specially aripiprazole) can be an alternative to typical antipsychotic drugs.

The aim of the study was to analyze the available data on the use of aripiprazole in the control of delirium symptoms.

A systematic review of databases (PubMed, GoogleScholar and Cochrane Central Register of Controlled Trials) from the period from January 2005 to September 2021 was carried out. Results were limited to case reports, clinical trials and randomized controlled trials. The database search results were obtained using the following key words: "delirium," "aripiprazole," "treatment," and "antipsychotics". Additionally, systematic reviews on the use of aripiprazole in delirium and articles about etiology and pathogenesis of delirium were used.

Aripiprazole – mechanism of action and use

Aripiprazole is a second generation antipsychotic with special mechanism of acting. It has a strong affinity to dopamine receptor D2 as partial agonist. It is also serotonin receptor 5-HT1A partial agonist with antagonist activity at receptor 5-HT2A. Aripiprazole has safe and well tolerated profile, rare side-effects such as QT interval prolongation, extrapyramidal symptoms, sedation and orthostatic hypotension [15].

Aripiprazole is used in the treatment of schizophrenia, bipolar disorder and Tourette syndrome, but also off-label in delirium, treatment-resistant depression as a potentialization of a treatment, psychotic disorder due to dementia, or schizoaffective disorder [16].

Aloa et al. as first reported two cases of delirium treatment with aripiprazole, when a state of patients were improved. The first case was a 65-year-old man with chronic kidney disease, hypertension and diabetes. He developed electrolyte abnormalities resulting from non-compliance with his dialysis. Delirium occurred in the course of his disease. Aripiprazole was used for treatment at a dose of 30mg/day. By the 7th day, the patient was alert and oriented.

The second case was a 37-year-old woman who was hospitalized due to delirium tremens. She was treated with lorazepam and added aripiprazole at a dose of 15mg/day. On day 7, significant reduction of delirium symptoms was observed [17, 18].

In 2006, Starker et al. published a case series of the use of aripiprazole in delirium treatment. Efficacy and occurrence of side effects were evaluated. In the group of 14 patients, evaluated on the 5th day of hospitalization, improvement (defined as over 50% reduction of score in the DRS-R-98) was achieved in 50% of patients. 5–15mg/day (average: 8.9mg/day) dose of aripiprazole was used [19].

In 2011, Boettger and Breitbar estimated effectiveness of aripiprazole in a group of 21 oncological patients with delirium. The Memorial Delirium Assessment Scale (MDAS) was used to estimate severity of symptoms and the period of observation was 7 days. Delirium resolution was defined as MDAS scores <10. It was observed that aripiprazole (dose: 10–30mg/day) reduced delirium symptoms (MDAS <10) in 100% of patients with hypoactive delirium. Slightly worse response was obtained in patients with hyperactive delirium characterized by psychomotor agitation [20].

In 2020, Giovanni Martinotti et al. reported a case series of delirium management with aripiprazole in patients with COVID-19. A group of 16 patients in Italian hospitals was treated with antiviral agents, hydroxychloroquine and tocilizumab. These patients were treated with aripiprazole intramuscular injections to manage psychomotor agitation, disorganized behavior and positive symptoms. Aripiprazole injections rapidly and significantly reduced signs and symptoms of delirium and psychomotor agitation. These symptoms were measured with the Intensive Care Delirium Screening Checklist (ICDS) and the Modified Overt Aggression Scale (MOAS). No drug interaction was reported. Treatment was well tolerated and no side effects were reported, even in intensive care unit (ICU) patients [21].

Only one randomized, double-blind study investigating the efficacy of aripiprazole in delirium was published. Majid Mokhtari et al. prospectively assessed aripiprazole efficacy in preventing delirium among patients after neurosurgery intervention hospitalized in intensive care units. Delirium occurred only in 20% of patients in the study group and in 55% of patients in the control group receiving placebo. The difference in the mean number of days to the onset of delirium and the mean ICU length of stay was not statistically significant between the two groups. Serious adverse reactions related to aripiprazole were not reported [22].

Comparison of efficacy and safety of aripiprazole with other antipsychotics

In most studies comparing aripiprazole with other neuroleptics in treatment of delirium, aripiprazole is compared with haloperidol. The data indicate that there is no significant difference in efficacy between these neuroleptics, while aripiprazole causes extrapyramidal symptoms and hyperprolactinemia less often [23, 24].

In 2009, Jung and Kim published the results of a study comparing aripiprazole with risperidone in terms of delirium treatment. They indicated that aripiprazole seems to be less effective in delirium management. However, the authors emphasized that the study had many limitations, e.g., a small study group [25]. Boettger et al. made broader comparison study estimating efficacy, safety and side effects of aripiprazole, haloperidol, risperidone, and olanzapine. The study group consisted of patients with

cancer and main causes of delirium were drugs (opioids and glucocorticoids), hypoxia, dehydration, and CNS diseases. Since the first psychiatric consultation and the initiation of treatment, patients were evaluated on day 2–3 (T2) and day 4–7 (T3). The average dose of aripiprazole at T3 was 18.3mg/day. In the aripiprazole group, 9.5% of patients showed worsening status of delirium and required modification of pharmacotherapy. No other side effects were reported. The study did not show significant difference in the effectiveness of delirium symptoms control between the compared drugs [26].

Kato et al. made a retrospective study of the use of aripiprazole and other neuroleptics in patients with delirium in emergency units. In both groups, improvement was achieved as assessed by the MDAS scale. There was no significant difference between the two groups in MDAS improvement, however, the aripiprazole-treated group reported fewer side effects, especially sedation [27].

Hatta et al. conducted an observation of the use of neuroleptics in patients with delirium hospitalized in general hospitals. Only 0.9% of treated patients had severe side effects. Most common complications were aspiration pneumonia, cardiovascular diseases and venous thromboembolism. There were no above complications in the aripiprazole group. Extrapyramidal syndrome was the only side effect reported in this group [28].

Based on the existing safety studies, it can be assumed that aripiprazole also has no negative effects on the cardiovascular system [29]. Only one study in this article showed a prolongation of QTc interval (>450ms) during the treatment with aripiprazole [19]. The heart arrhythmia or abnormally low blood pressure were not reported in other studies. It seems that aripiprazole, compared to other neuroleptics, can be a safe option for patients with cardiovascular diseases.

In 2020, recommendations for the treatment of patients with disorders of consciousness in the course of neurocovid were published. The authors emphasized the fact that the patients with COVID-19 have increased risk of QT prolongation and *torsades de pointes*. They showed aripiprazole as one of the treatment option, taking into account its lowest potential for QT prolongation among all neuroleptics [30].

Discussion

Atypical neuroleptics are used in delirium treatment, as an alternative to haloperidol, increasingly more often. Pharmacotherapy with aripiprazole is associated with lower risk of sedation. Therefore, some authors suggested that aripiprazole can be useful in hypoactive delirium [20], which is more common in palliative patients [9]. This group of patients requires long administration of chemotherapy, opioids or

glucocorticoids. The low risk of pharmacokinetic interactions of aripiprazole [29] reduces the risk of serious adverse effects in this group of patients. Due to the fact that delirium is most common in elderly patients, who often take antihypertensive drugs, aripiprazole could be a safe therapeutic option in this group. Using a drug with a relatively low sedative effect, we can minimize the risk of the additive effect of action with cardiovascular drugs. Additionally, excessive sedative effect in the elderly with delirium can lead to increased risk of dizziness, vertigo and falls [31]. Lack of excessive sedation can be favorable in the group of neurological patients (e.g., with stroke) who need early rehabilitation in the ward. Lower risk of extrapyramidal symptoms is also desirable in this group [29].

Administration of aripiprazole also seems advantageous in inpatients with diabetes or dyslipidemia. Aripiprazole has a lower risk of inducing hyperglycemia or hyperlipidemia compared to other atypical neuroleptics [29]. Another important point that supports safety of aripiprazole in delirium treatment is its lack of effect on the cholinergic system [15]. This is associated with a lower risk of side effects such as constipation, urinary retention and blurred vision, but above all with a lower possible risk of deepening cognitive disorders [31]. The use of drugs with low anticholinergic effect will help to avoid increasing, already present in the course of delirium, perturbation in this neurotransmitter pathway [4].

The above-mentioned studies comparing aripiprazole with other neuroleptics may suggest that their effectiveness is similar. However, side effects occurred less often in groups of patients treated with aripiprazole. Unfortunately, the authors of cited studies did not specify which symptoms of delirium were reduced by antipsychotic treatment. Only relying on the study by Giovanni Martinotti et al., we may assume that aripiprazole was effective in reducing psychomotor agitation and aggressive behavior [21]. It is an interesting observation, because aripiprazole has a low sedative effect [29].

Referring to the mechanism of action of aripiprazole, we may hypothetically consider how it impacts the symptoms of delirium. Hyperactivity of the dopaminergic system in delirium [4] can lead to hallucinations and delusions, the incidence of which is as high as 71% and 68% respectively [2]. Their presence can cause psychomotor agitation. Overexcitation of the dopaminergic system in the prefrontal cortex can also lead to impairment of working memory, which is a significant factor in the course of delirium [2]. The excess of dopamine in the accumbens nuclei may result in disruption of attention [2]. The increased level of dopamine may also result in increased excitotoxicity, oxidative stress and apoptosis in the CNS, which is attributable to the pathophysiology of delirium [4]. Aripiprazole may reduce psychotic symptoms and related psychomotor agitation due to its effect on the D2 receptors. By regulating the

dopaminergic system, it may also contribute to the reduction of cognitive dysfunctions and indirectly inhibit the processes that lead to damage in the CNS.

Pre – and postsynaptic 5-HT1A receptors are related to the cognitive functions (including spatial memory), they regulate the activity of cholinergic system. They also have impact on proliferation and neurogenesis of hippocampal cells, as well as on changes in behavior. The activation of 5-HT1A receptor in rats, depending on the agonist's dose, caused both increase and decrease of psychomotor activity [32]. In animal models, it was proved that stereotactic administration of the 5-HT1A antagonist alleviates delirium-like behavior [4]. Using the properties of aripiprazole as a partial agonist of the 5-HT1A receptor may contribute to the improvement in physical activity and orientation in space, which are disrupted in delirium.

Another point concerns the effect of aripiprazole on the 5-HT2A receptor, which plays a role in cognitive functions and psychotic symptoms [33]. By blocking the 5-HT2A receptor, aripiprazole may reduce hallucinations that occur during delirium and thus affect motor agitation. Research on animal models with the use of 5-HT2A antagonists (i.e., ritanserin, risperidone, ketanserin, MDL 11,939) gave inconclusive evidence concerning the improvement or worsening of cognitive functions [33]. Therefore, it is difficult to conclude which of the symptoms, other than psychotic symptoms, may be alleviated by the blocking effect of aripiprazole on the 5-HT2A receptor.

Recapitulation

Based on this review, it seems that aripiprazole could be an effective neuroleptic in the treatment of delirium. It is also worth to notice that aripiprazole may be useful in prevention of qualitative disorders of consciousness. Unfortunately, due to the lack of studies with a sufficiently large group of patients and randomized placebo-controlled trials, we do not have sufficient scientific evidence to create appropriate recommendations. Based on the analyzed research, it is also hard to determine which symptoms in particular are reduced in the course of aripiprazole treatment and what is the mechanism of action in delirium. Aripiprazole can be a preferred neuroleptic in patients with cardiovascular diseases, concomitant lipid and carbohydrate disorders, and those in whom excessive drug sedation may hinder rehabilitation. The above data justify conducting further studies evaluating the efficacy and safety of aripiprazole in the symptomatic treatment of delirium. Collecting as much data as possible will allow to create new management algorithms.

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