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Risperidone And Aripiprazole Playing A Important Role in Pharmacological Therapy of Autism Spectrum Disorders: A Global Overview

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ABSTRACT: Autism spectrum disorder (ASD) is a set of neurological disorders characterized by the presence of deficits in communication as well as a repetitive behavioral pattern. These disorders have a variety of etiologies, ranging from gestational problems, genetic factors and unknown causes. The aim of this study is to present the main drugs used in the treatment of autism and its mechanisms of action. An exhaustive literature search was conducted and the results were compiled and analyzed. Thus, among the classes of drugs used in ASD therapy, atypical antipsychotic drugs were the focus of the study, being risperidone and aripiprazole the ones chosen for review, drugs with more promising results in human research, as well as the main drugs accepted by FDA for the treatment of autism in children and adolescents, risperidone has a blocking effect on dopaminergic D2 receptors and (5-hydroxytryptamine, 5-HT2) serotoninergic receptos, the mechanism of action of aripiprazole is not yet fully understood, but it is known that these drugs generally bind to dopaminergic receptors in the brain, modulating the action of dopamine. Although such therapies era promising, more effective drugs in combat of symptoms such as anxiety and irritability are lacking, as well as reducing symptoms in a broader way without pronounced side effects.

Keywords: Autism Spectrum Disorder, Aripriprazole, Risperidone, Treatment

I. INTRODUCTION

Autism spectrum disorder (ASD) or autism, consists of a range of neurological disorders with common characteristics such as dysfunction in language development in the social sphere, as well as the occurrence of repetitive behaviors and restricted interests [1]. Autism was first referenced in 1911 by the researcher Bleuler, being characterized by the same as, the loss of contact with reality, later in the 40s, Kanner published studies related to the theme, in his reports, he exposed, among other psychopathological characteristics, the Difficulty for autistic children to remember people who were present in their childhood [2].

Regarding of its etiology, autism has several gaps in relation to its causes, starting from this assumption, we have as main known causes the genetic predisposition, as the expression of specific genes that culminate in the appearance of ASD or even rare mutations without previous cases in the family, its etiology is also linked to environmental factors that interfere with the development of the individual, for example possible early lesions that may affect the cerebellum, which may indicate one of the greatest ASD development risks. Serotonin plays a crucial role in autism pathology, since it is a neurotrophic agent during the early stages of human development, so changes in the transport of this neurotransmitter during this stage of life lead to neurological damages that may lead to the development of disorders, such as autism and also epilepsy [3,4,5]. Despite the various hypotheses presented and some scientific confirmations of the pathophysiological characteristics of ASD, its pathogenesis is still controversial and in many points unknown [6,7].

The treatment of autism consists of methods that seek to reduce its symptoms as well as reduce the number of episodes that cause major disorders, such as gene therapies (not yet analyzed in this case), behavioral therapies with the presence of psychologists and psychiatrists, and finally, pharmacological therapies, among them, stimulants, tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIS), mood stabilizers and dopamine antagonists [7,8,9,10]. Administration of atypical antipsychotics is Currently one of the most widely used pharmacological therapies in ASD, its greatest differential in relation to typical or first generation antipsychotics, although it has some advantages, especially in its lower rate of reported side effects such as

tardive dyskinesia and prolactinemia. The analyzed drugs in the present review were Risperidone and Aripiprazole, second-generation drugs, which are reported in the literature as having considerably positive pharmacological effects, such as less aggressive reactions than first generation antipsychotics [11,12,13].

II. MATERIALS AND METHODS

This study constituted in a relevant literature survey on subject, for that the following keywords were related to each other: Autism spectrum Disorder, Treatment, Risperidone, Aripiprazole, considering their appearance in Title, Abstract, and/or text words. Publications were considered in different databases, such as SciELO, LILACS, PubMed, ScienceDirect, and BIREME in the last 15 years. Articles with humans' treatment and animal models were included. After initial survey, Title and Abstract had been read.

III. ATYPICAL ANTIPSYCHOTIC DRUGS

Atypical or second-generation antipsychotic drugs are substances that have a therapeutic effect at doses that do not induce extrapyramidal effects. The main criterion for identifying an atypical antipsychotic is the significant difference between doses required to induce antipsychotic effect and extrapyramidal effects. The action mechanisms of these drugs can be observed in diverse ways, they may be total or partial antagonists of dopaminergic receptors, specifically D2 and D4 receptors associated or not with 5-HT receptors, as well as being antagonists of serotonergic, noradrenergic, histaminergic, cholinergic receptors and also act in the gonadotropic modulation or in the prefrontal cortex [14,15,16]. This class of drugs emerged in the mid-1960s, in Europe, with the discovery of Clozapine. However, it was observed that this drug formed granulocytopenia, which led to its withdrawal from the market. However, in 1988, clozapine was again important as an antipsychotic drug after a clinical study by Herbert Meltzer researchers, who observed improvement of symptoms without extrapyramidal effects [17,18]. Currently there are several atypical drugs, risperidone, aripiprazole, amisulpride, clozapine, paliperidone, olanzapine, quetiapine, ziprasidone, asenapine, iloperidone, lurasidone and cariprazine. Initially, atypical drugs are used in clinical practice for the refractory treatment of schizophrenia. After studies, in 2006, risperidone and aripiprazole were approved by the US Food and Drug Administration (FDA) as a treatment of autism aimed at improving the symptoms of irritability, aggression and self-injury in children and adolescents [19,20].

Risperidone

Risperidone is a second-generation antipsychotic drug that is very used for ASD worldwide. The use of this medication started in 1993 when it was approved by U.S. Food and Drug (FDA), initially for the treatment of schizophrenia in adults. Later, in 2006, the FDA also approves the risperidone use for treating irritability, aggression and hyperactivity related with ASD in adults and children, at least 5 years old. This drug is one of the few antipsychotic medications suitable for pediatric patients [21,22,23]. The risperidone action mechanism is associated with the high affinity for D2 and 5-HTA2 dopamine and serotonin receptors, respectively. However, has also affinity for other receptors, like a1-adrenergic, a2-adrenergic and H1-histaminergic. It is believed that those dopamine and serotonin receptors antagonisms is responsible for the benefits effects in some ASD symptoms and reduced the extra pyramidal symptoms compared with typical antipsychotic [24, 25, 26].

Risperidone use in the ASD treatment is available in oral formulations, like tablets (0.25, 0.5, 1, 2, 3 and 4 mg), oral solution (1 mg/ml) and orally disintegrating tablets (1 mg/ml). The recommendation doses according to FDA depends of the tolerability and response of the patient, in most of the cases the effective dose range is between 0.5 to 3mg per day [24,27,28].The potential efficacy in the irritability and aggressive behavior control was show in various acute studies, one of them was a double-blind study in children and adolescents (5 to 17 years old) who was given daily doses of risperidone for eight weeks when compared with the control group that was receiving placebo. An open-label extension study with patients (5–17 years of age) with risperidone dose based on body weight brings consistent safety findings of the therapy in behavioral disorders with improvement in irritability and related behaviors [29,30,31].

Long-term studies were also developed, one of them with children and adolescents (5-17 years of age) during 21.4 months with placebo and risperidone administration groups, demonstrated that the group with autism and severe irritability that received prolonged risperidone therapy show the improvement in the social skills and reduced irritability [32].However, clinic trials were showing adverse effects associated with use of this medication, like increased appetite, weight gain, hyperprolactinemia, enuresis, somnolence, fatigue, sedation, pyrexia, and upper respiratory tract infection. A recent review about the pharmacotherapies in the ASD treatment emphasizes that this medication administration should be based on the individual patient analysis need, considering the potentials risks and the therapy benefits [33,34,35].

Aripiprazole

Aripiprazole is a second-generation antipsychotic. Second-generation antipsychotics, often called atypical antipsychotics, have a lower propensity to cause TD (tardive dyskinesia) and EPS (extrapyramidal symptoms). Studies have shown that this drug was approved to treat schizophrenia, mixed and manic states of bipolar I disorder (as monotherapy or as an adjunct to either lithium or valproate) and as adjunctive treatment for major depressive disorder (MDD) in adults. Aripiprazole has been evaluated in several open label studies and two large placebo-controlled trials in children with autistic disorder. In these studies, this drug has been found to be effective in the treatment of children and adolescents with irritability associated with autism [36].Recently, aripiprazole has been approved by the FDA for use in children and adolescents aged 6–17 years. It is important to note that the aripiprazole is a partial agonist at the D_2 (dopamine), D_3 and 5-HT_{1A} (serotonin) receptors. The effects, at these kind of receptors, are hypothesized to be the mechanism of action for all indications. Partial agonism at 5-HT_{1A} has anxiolytic effects, and is also hypothesized to be associated with reduced risk of EPS [37,38,39].

Evidence from two randomized controlled trials suggests that aripiprazole can be effective in treating some behavioral aspects of ASD in children. After treatment with aripiprazole, children showed less irritability, hyperactivity, and stereotypies (repetitive, purposeless actions). Moreover, the FDA has approved the use of aripiprazole up to 15 mg/day (initial dose 2 mg/day; recommended dose 10 mg/day) for the children and adolescents in such condition. Aripiprazole is presented in different pharmaceutical and dosage forms, such as tablets (2; 5; 10; 15; 20 and 30 mg), oral solution (up to 25 mg), orally disintegrating tablets (10; 15 mg) and injection solution (5.25; 9.75 and 15 mg). Although aripiprazole has been noted to be safe and generally well tolerated in most of the studies in PDDs (pervasive developmental disorders), some concern remains over its propensity to cause weight gain, EPS and sedation (common one). Moreover, there are also some other side effects, which sometimes may occur, such as change in prolactin and abnormal movements (mild sialorrhea and tremor; muscle stiffness) [39,40].

IV. CONCLUSION

The pharmacological treatment of autism consists of an approach that allows a symptomatic inhibition of the disease, and the second-generation antipsychotics are now more widely used in clinical practice. This class of drugs apparently has few side effects and in most cases they are effective, but in a limited range of symptoms of ASD, it is necessary that other pharmacological and adjuvant therapies be evaluated as a new therapeutic approach in the treatment of ASD.

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