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Lurasidone in the Management of Autism Spectrum Disorder: A Review

Ricardo Vieira Nasser[1*], Bárbara Modesto[1], Arthur Lopes Ribeiro Penido[1], Sônia Maria Motta Palma[2]

[1]Serviço de Psiquiatria da Faculdade de Medicina da Universidade de Santo Amaro (UNISA), São Paulo, SP, Brasil. [2]Ambulatório de Psiquiatria da Infância e Adolescência da Faculdade de Medicina da Universidade de Santo Amaro (UNISA), São Paulo, SP, Brasil.

ABSTRACT

OBJECTIVE

To demonstrate that lurasidone can be an alternative for adolescents with Autistic Spectrum Disorder (ASD), especially if the patient has a history of adverse metabolic effects and/or ineffectiveness or intolerance to the use of Aripiprazole or Risperidone.

METHODS

Systematic review of articles from the PubMed platform, with only articles in Portuguese and English being selected, with no period limitation. Inclusion criteria for the study: studies that address the treatment of ASD; studies that address treatment focusing on the use of Lurasidone; works that bring clear methodology.

RESULTS

Lurasidone has shown promise, given its low profile of adverse effects, such as lower weight gain, hyperlipidemia, hyperglycemia, and insulin resistance. In addition to the potential benefits of Lurasidone for the treatment of irritability in children with ASD, there may also be a potential antidepressant effect, which may influence the symptom profile. It is currently approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia in adolescents from the age of thirteen and on monotherapy for bipolar depression from the age of ten. However, there are studies of tolerance in children and adolescents from the age of six with doses <120 mg / day.

CONCLUSIONS

Given the risk of long-term adverse metabolic effects of most atypical antipsychotics, Lurasidone can serve as an alternative. However, to date, no evidence has been found consistent with the use of lurasidone for patients with ASD who exhibit irritability, aggressiveness, and impulsivity as associated symptoms.

DESCRIPTORS

Lurasidone Hydrochloride, Autistic Disorder, Therapeutics.

Corresponding author:
Sonia Maria Motta Palma. Ambulatório de Psiquiatria da Infância e Adolescência da Faculdade de Medicina da Universidade de Santo Amaro (UNISA). Rua Professor Enéas de Siqueira Neto, 340 – Jardim das Imbuias, São Paulo, SP, Brasil.
Email: soniammpalma@hotmail.com
ORCID ID: https://orcid.org/0000-0003-3152-4758

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INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, social interaction and the presence of restricted resources, repetitive patterns of behavior, interests, or activities. Symptoms appear during initial development and may occur with or without intellectual and/or language disabilities[1].

ASD can be associated with a wide range of challenging behaviors. Moderate to severe symptoms of irritability (broadly defined to include tantrums, aggression, self-regression, and rapid changes in mood) were observed in about a quarter of the subjects in several studies. These maladaptive behaviors can interfere with daily activities, substantial caregiver stress, and can have an impact on long-term prognosis. In addition, aggressiveness or self-injurious behavior is associated with an increased risk of psychiatric hospitalization among children with ASD[1].

The Center for Disease Control estimates that 1 in 59 children has been diagnosed with this disorder in the United States, with incidents occurring in all socioeconomic, ethnic, and racial groups. A systematic review of ASD studies estimates a prevalence of 20 per 10,000 (95% confidence interval [CI]: 4.9-82.1)[2].

The atypical antipsychotics Risperidone and Aripiprazole are currently the only drugs approved by the United States Food and Drug Administration (FDA) for the treatment of irritability associated with ASD. The use of antipsychotic drugs was reported in 10% of children with ASD in South London and the Maudsley NHS Foundation Trust, with Risperidone and Aripiprazole comprising 55% and 32% of the interventions used, respectively. Self-flagellating behaviors, aggression, reduced adaptive function and parental concerns were significantly related to the use of antipsychotics in these children[2].

The use of Lurasidone is currently approved by the FDA for the treatment of schizophrenia in adolescents from the age of thirteen and as monotherapy for bipolar depression from the age of ten[3].

However, there are studies of tolerance in children and adolescents from the age of six with doses <120 mg / day. Therefore, doses vary from 20 to 120 mg / day, being metabolized mainly by cytochrome P-450 (CYP) 3A4, with the advantage of not inducing or inhibiting any CYP enzymes, in addition to an elimination half-life of approximately 18 hours4.

The aim of this study is, through a literature review, to verify that Lurasidone can be a viable alternative in adolescents with ASD, especially if the patient has a history of adverse metabolic effects and/or ineffectiveness or intolerance to the use of Aripiprazole or Risperidone.

METHODS

The present study is a systematic review of articles on the PubMed platform, accessed through the keywords: *Lurasidone; Autism Spectrum Disorder* using the Boolean AND operator. Only articles in Portuguese and English were selected, with no period limitation. The inclusion criteria for our study were: studies that addressed the treatment of Autism Spectrum Disorder; studies that addressed the treatment focusing on the use of Lurasidone; Works that brought clear methodology; works with quantitative and qualitative methodology were included.

From the articles selected in the digital search, we checked the bibliographic references regarding the inclusion criteria. After the selection of the eligible articles, a critical reading of them was made, aiming at the extraction of the results that were in accordance with our objective and then a narrative synthesis of the results obtained was performed.

RESULTS

In our digital search strategy, we found nine articles on PubMed, no articles were found with these specifiers on the Scielo platform. Dated from 2014 to 2018. Of which seven met the inclusion criteria. There are two systematic reviews of the literature, a meta-analysis, three clinical trials and a case report (Figure 1).

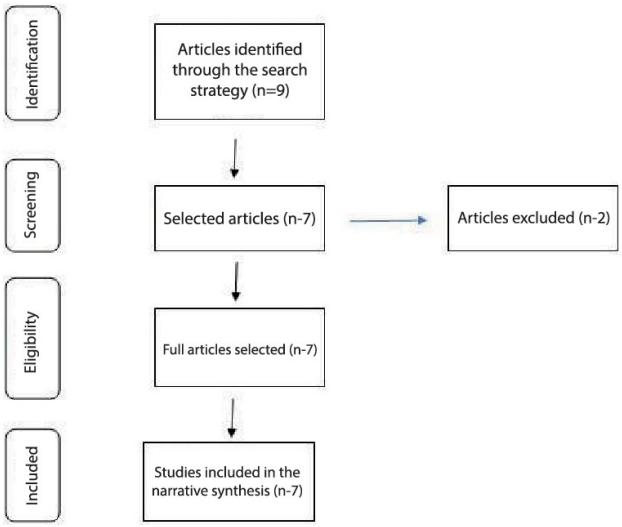

Figure 1. Search strategy according to Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) 20.

The review "A Focused Review on the Treatment of Pediatric Patients with Atypical Antipsychotics" demonstrates that there is more empirical data on the acute, long-term efficacy and tolerability for several of the antipsychotic drugs considered. They have also been used as an adjunctive treatment for disruptive behavior disorders with aggression, which have not responded to treatment with stimulants[5].

The studies in "Atypical Antipsychotics for Irritability in Pediatric Autism: A Systematic Review and Network Meta-analysis" used the Irritability Behavior Checklist (ABC-I) to measure the effectiveness of atypical antipsychotic monotherapy. Eight studies comparing four interventions - Risperidone, Aripiprazole, Lurasidone and placebo in 878 patients were included[2].

A total of 150 participants in the "Lurasidone for the Treatment of Irritability Associated with Autistic Disorder" study, aged 6 to 17 years, were randomized to 6 weeks of double-blind treatment, of which 149 received the study drug (Lurasidone or placebo). The 6-week treatment completion rates were 76% for the placebo group, 88% for the lurasidone 20 mg/day group and 92% for the lurasidone 60 mg/day group. Efficacy measures included the Aberrant Behavior Checklist Irritability subscale (ABC-I) and the Clinical Global Impressions, Improvement (CGI-I) scale, and were analyzed using a mixed likelihood model for repeated measures[1].

Based on the clinical outcome of the case report "Lurasidone Treatment in a Child with Autism Spectrum Disorder with Irritability and Aggression", Lurasidone can be a reasonable alternative, especially if the patient has a history of adverse metabolic effects. However, as there are no published studies on the efficacy of Lurasidone in children with ASD, future research is needed[6].

The study "Lurasidone in Children and Adolescents: Systematic Review and Case Report" showed that Lurasidone is significantly more effective than placebo, with moderate effect sizes and is well tolerated for bipolar depression and schizophrenia in young people. Studies published in youth, in general, used doses of up to 80 mg/day[7].

Lurasidone can be considered comparable to other atypical antipsychotics, such as Ziprasidone, Risperidone or Aripiprazole in chemical structure or affinity with D2 and 5-HT2a receptors. Thus, the work "Lurasidone for the treatment of irritability and anger in autism spectrum disorders" demonstrates that there are no data to suggest that Lurasidone is effective and tolerable in the treatment of irritability in children with ASD[8].

Exposure to Lurasidone, after administration of multiple doses to the population of children and adolescents, was like exposure observed at steady state in adults. Adverse events were qualitatively similar to those reported in adults. Disruptions due to adverse events were dose-related, with the dose of 120 mg / day being better tolerated than higher doses, especially in younger children, as shown in the "Pharmacokinetics and Tolerability of Lurasidone in Children and Adolescents with Psychiatric Disorders"[4].

DISCUSSION

About Lurasidone, an atypical antipsychotic with dopamine D2 and 5HT2A receptor antagonism, in addition to the binding affinity to the 5HT7, 5HT1A and norepinephrine α1c receptor, and minimal or no affinity for the H1 and M1[1] receptors. When compared to Risperidone, it has more potent affinity for the 5-HT1A receptor and as for the D2 antagonism, it is complete just like Risperidone, while Aripiprazole is a partial agonist of it. Such pharmacological properties are important to mention because they justify the findings in the improvement of symptoms.

Antipsychotics are believed to affect aggressive and impulsive behavior through dopamine and serotonin regulation and the benefits of mood and decreased depression, and irritability are estimated to be associated with 5HT7 and α2 receptor antagonism and properties partial 5HT1A agonists[3].

In a review of double blind randomized clinical trials, Lurasidone was used as a treatment for irritability associated with ASD in children between 6 and 17 years of age. It was investigated by Loebel et al (2016) that, after 6 weeks of treatment with fixed doses, once a day, of lurasidone (20 or 60 mg/day) or corresponding placebo, found no difference in irritability at the end point, as measured by ABCI subscale scores[5].

In a case report, Lurasidone was started with 10 mg per day for a patient with ASD, showing irritability, perseverance, and aggression. After 2 weeks it increased to 20 mg a day. One month later, there was an improvement in irritability and aggressive behaviors[6].

CONCLUSION

The evidence regarding the effectiveness and tolerability of antipsychotic drugs for mental disorders in children and adolescents has expanded exponentially in recent years. It is to be expected that in additional long-term studies these drugs will continue to inform evidence-based practice in clinical settings[5].

Given the risk of long-term adverse metabolic effects of most atypical antipsychotics, lurasidone can serve as an alternative, as it has been shown to have fewer effects on weight gain, dyslipidemia, hyperglycemia, and insulin resistance in adults[6]. However, to date, no evidence has been found consistent with the use of Lurasidone for patients with ASD who exhibit irritability, aggressiveness, and impulsivity as associated symptoms.

REFERÊNCIAS

1. Loebel A, Brams M, Goldman RS, Silva R, Hernandez D, Deng L, Findling RL. (2016). Lurasidone for the Treatment of Irritability Associated with Autistic Disorder. J Autism Dev Disord. 2016; 46: 1153–1163.
2. Fallah MS, Shaikh MR, Neupane B, Rusiecki D, Bennett TA, Beyene J. Atypical antipsychotics for irritability in pediatric autism: A systematic review and network meta-analysis. J. Child. Adolesc. Psychopharmacol. 2019 Apr;29(3):168-180.
3. Stahl SM. Stahl's Essential Psychopharmacology Prescriber's Guide: Children and Adolescents. 1ª Ed. New York US: Sheridan Books; 2019.
4. Findling RL, Goldman R, Chiu YY, Silva R, Jin F, Pikalov A, Loebel A. Pharmacokinetics and tolerability of lurasidone in children and adolescents with psychiatric disorders. Clin Ther. 2015 Dec 1;37(12):2788-97.
5. Lee ES, Vidal C, Findling RL. (2018) A focused review on the treatment of pediatric patients with atypical antipsychotics. J Child Adolesc Psychopharmacol 28(9):582–605.
6. Millard PH, McLaren JL, Coffey DB. (2014). Lurasidone treatment in a child with autism spectrum disorder with irritability and aggression. J Child Adolesc Psychopharmacol. 2014 Aug;24(6):354-6.
7. Channing J, Mitchell M, Cortese S. Lurasidone in Children and Adolescents: Systematic Review and Case Report. J Child Adolesc Psychopharmacol. 2018 Sep;28(7):428-436.
8. McClellan L, Dominick KC, Pedapati EV, Wink LK, Erickson CA. (2017): Lurasidone for the treatment of irritability and anger in autism spectrum disorders. Expert Opin Investig Drugs. 2017 Aug;26(8):985-989.