Residência RP Pediátrica
Publicação Oficial da Sociedade Brasileira de Pediatria
ISSN-Online: 2236-6814

Submitted on: 03/12/2021
Approved on: 08/29/2021

ORIGINAL PAPER

Use of antipsychotic agents in children and adolescents

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Keywords:
Antipsychotic Agents, pediatrics, neurology, child Adolescent.

Abstract

OBJECTIVE: To describe the profile of pediatric patients undergoing regular treatment with antipsychotics agents. **METHODS:** Descriptive study of a case series with cross-sectional data collection of patients' files using antipsychotics agents, under 14 years of age treated at a Neuropediatric service from April to July 2020. For statistical analysis, we used the Fisher exact test and the Pearson's Chi-square test with a 5% significance level.**RESULTS:** We assessed 98 patients, and 74 (75.5%) were males, the median age in the evaluation period was 8.5 (2.5 to 14 years). The main diagnosis was Autism Spectrum Disorder (53%) and Intellectual Deficit (46.9%). The most frequent prescription indications were aggressiveness (76.5%) and restlessness (43.8%). The main drugs prescribed were Risperidone (85.7%) and Periciazine (6.1%). The most evident adverse effects were weight gain (15.3%) and increased appetite (10.2%). The MOAS (Modified Overt Aggression Scale) showed changes in 71 patients (72.4%). Clinical evolution was reported as favorable by parents for 95 patients (96.94%). **CONCLUSIONS:** The use of antipsychotics in pediatrics is constantly expanding, but studies on the effects on this population are still lacking and with that the off-label use becomes commonplace. Further studies on the use of antipsychotics in the pediatric age group are expected to be developed.

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INTRODUCTION

Antipsychotics are essential in the treatment of several neurological and psychiatric conditions of children and adolescents, such as Autistic Spectrum Disorder (ASD), Intellectual Deficit (ID), Disruptive Associative Mood Disorder associated with Attention Deficit/Hyperactivity Disorder (ADHD), Oppositional Defiant Disorder (ODD) among others. Initially, antipsychotics were used in children and adolescents only to treat schizophrenia and bipolar disorder[1]. Its use is authorized by ANVISA for children over 4 years of age. Despite this, its use in children from certain age groups is not recommended by regulatory agencies.

Many marketed antipsychotics do not have label approval for specific use in the pediatric population. In the US, the Food and Drug Administration (FDA) approved only two medications from the atypical antipsychotic class for the treatment of irritability in ASD from 5 years of age: Risperidone and Aripiprazole[2].

Even though data on the safety of Risperidone in the pediatric setting is limited, off-label use is increasingly common. The term "off label" refers to drugs prescribed outside their licensed indications with respect to dosage, age, indication or route of administration. The purpose of off-label use is to benefit an individual patient[3,4].

Although Risperidone has not been approved for use in Associative Disruptive Mood Disorder, it is often used off--label for this purpose, as well as for aggression, Obsessive Compulsive Disorder (OCD), Post Traumatic Stress Disorder, Personality Disorders , ADHD and TOD.[3,5]

Antipsychotics produce adverse events in most patients, regardless of indication, which may include weight gain, arrhythmias, tardive and withdrawal dyskinesia, diabetes mellitus, hyperlipidemia and anemia, which have been well documented in adults[3]. In children, the effects are similar, but there are no data available to document the effect. profile of use in children and adolescents are limited and there is a possibility that adverse effects in this population are more severe than in adults[5].

The use of this drug class in pediatric prescriptions is constantly expanding. The lack of studies in this population makes off-label use commonplace. For this reason, this study seeks to improve understanding of the profile of patients who receive antipsychotic treatment in childhood and adolescence and to contribute to increasing the safety of prescribing these drugs in the pediatric age group. The aim of this study is to profile and understand the clinical characteristics of pediatric patients who are regularly treated with antipsychotics.

METHODS

This is a descriptive study of a series of cases, with cross-sectional data collection. Data were collected through the evaluation of the medical records of patients who were followed up for 3 months. All patients younger than 14 years old who used antipsychotic drugs during the study period and who were treated at the service's general Pediatric Neurology outpatient clinic were included.

The variables evaluated were gender, age, diagnoses, data regarding the medication (type, dose, age when prescribed, prescription indication, adverse effects and duration of use), clinical evolution and score on the MOAS scale (Modified Overt Aggression Scale) which objectively and quantitatively assesses aggressiveness symptoms. In this scale, the severity of four types of aggression is analyzed: verbal aggression, physical aggression against property, self-aggression and hetero aggression. Each type of aggression is rated on a four-point scale with pre-specified weights; the most severe aggressive event within each category is multiplied by the assigned weight factor and then summed to generate a total aggression score of up to 100 points.

Statistical analysis was performed according to the nature of the variables, number of study groups and types of analyzes required using the Statistical program by Statsoft®. Fisher's exact test and Pearson's chi-square test were used with a significance level of 5%.

RESULTS

General features

All 98 patients who used antipsychotics while attending the outpatient clinic were included.

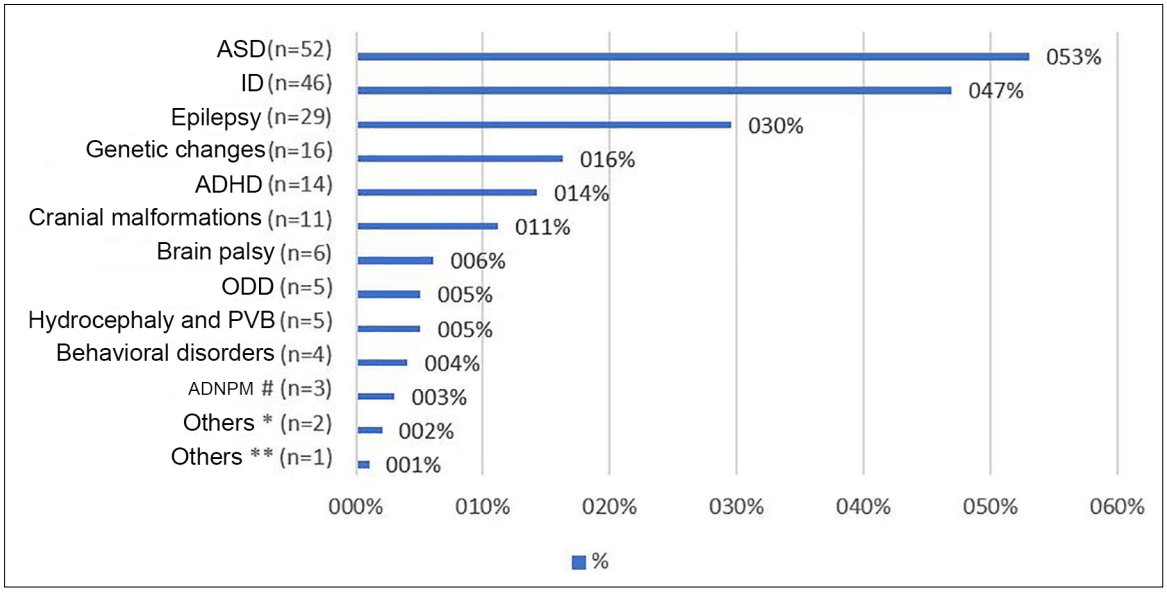
It consisted of 98 children and adolescents, of whom 74 (75.5%) were males. The median age in the evaluation period was 8.5 years (2.5 to 14 years). The main diagnosis among the evaluated patients was ASD (53%), followed by DI (46.9%). Patients could have more than one diagnosis simultaneously (Graph 1).

ASD (Autistic Spectrum Disorder); ID (Intellectual Deficit); ADHD (Attention Deficit Hyperactivity Disorder); ODD (Oppositional Defiant Disorder); PVD (Peritoneal Ventricular Bypass).

TREATMENT FEATURES

The median age of initiation of antipsychotic prescription was 5 years (1 to 14 years). Regarding the time of medication use, we found a median of 2.2 years (1 month to 8.4 years). Treatment with antipsychotics had already occurred for at least one year in 62.24% of patients. The most frequent prescription indications were aggressiveness (76.53%) and psychomotor restlessness (43.87%) (Table 1).

The main drugs prescribed were Risperidone (85.71%), with an average dose of 0.04±0.02 mg/kg/day; and Periciazine (6.12%) at an average dose of 0.26±0.18mg /kg/day. Forty-four patients (44.98%) were undergoing polytherapy, 33 patients (33.67%) using antiepileptic drugs (AED), 8 patients (8.16%) using methylphenidate, 4 patients (4, 08%) using serotonin reuptake inhibitors and 3 patients (3.06%) using tricyclic antidepressants. The same patient could be using more than one drug class and the concomitant use of multiple antipsychotics occurred in 2 patients (2.04%).



Graphic 1. Diagnoses found.* Myelomeningocele, environmental disorders, immune disorders (the same frequencies were observed for each of the items) ** Tic disorder and psychosis (same frequencies observed for each of the items.

Table 1. General characteristics.

Characteristic	n(%)	Characteristic	n(%)
Medication		Indication	
Risperidone	84 (85)	Aggressiveness	75 (76)
Periciazine	6 (6)	Restlessness	43 (43)
Aripiprazole	3 (3)	Self-aggression	17 (17)
Amplyctil	2 (2)	Hetero aggression	10 (10)
Haloperidol	1 (1)	Sleep disorder	4 (4)
Olanzapine	1 (1)	Irritability	2 (2)
Quetiapine	1 (1)	Psychosis	2 (2)
Patients in polytherapy	44 (44)	Tics	1 (1)
		Hyperactivity	1 (1)
		Behavioral change	1 (1)
Adverse effects			
Weight gain	15 (15)		
Appetite increase	10 (10)		
Sleep disorder	9 (9)		
Prolactin increase	1 (1)		
GI disorder	1 (1)		
None	67 (68)		

Adverse effects.

Regarding gender, 32.43% of males and 29.17% of females had some type of adverse effect, the most evident of which were weight gain (15.30%) and increased appetite (10 .20%) (Table 1).

Among the patients who used antipsychotics for more than one year (n=61), 21 (34.43%) had adverse effects, while those who used them for less than one year (n=37) 10 (27.03 %) showed adverse effects. There was no difference in the occurrence of adverse effects when compared with each of the studied variables.

Most of the patients in the study used Risperidone; therefore, some analyzes were performed only with these patients, aiming to standardize the cases, in the same way with the ASD and ID diagnoses.

The adverse effects found for those diagnosed with ASD or ID and prescribed Risperidone (n=81) are shown in table 2.

Children younger than 5 years with an off-label prescription of Risperidone (n=13) did not have more adverse effects than those older than 5 years (p>0.05).

Table 2. Patients using Risperidone diagnosed with ASD and ID.

Diagnosis		ASD n (%) 48(59,26)	ID n (%) 33 (40,74)	*p*
Sex	Male	36 (75)	25 (75)	0,52**
	Female	12 (25)	8 (24,2)	0,52**
MOAS scale	Changed	40 (83,3)	21 (63,6)	0,04**
	Verbal aggression	23 (47,9)	16 (48,4)	0,95*
	Aggression against assets	21 (43,7)	14 (42,4)	0,90*
	Self-aggression	25 (52,0)	11 (33,3)	0,09**
	Hetero aggression	28 (58,3)	18 (54,5)	0,73*
	Occurrence	18 (37,5)	11 (33,3)	0,70*
Adverse effect	Weight gain	10 (20,8)	5 (15,1)	0,36**
	Appetite increase	7 (14,5)	3 (9,0)	0,35**
	Sleep disorder	3 (6,6)	4 (12,1)	0,29**
	Prolactin increase	1 (2,0)	0	0,59**
	Gastrointestinal disorder	1 (2,0)	0	0,59**
Development	Improvement	48 (100)	31 (93,9)	0,16**
	No improvement	0	2 (6,0)	0,16**

*p obtained by Pearson's chi-square test. **p obtained by Fisher's exact test.

MOAS SCALE

The MOAS scale showed alterations in 71 patients (72.44%). The total score ranged from 1 to 65 with a total mean of 12.03 ± 6.36 for all diagnoses, 12.38 ± 6.36 for patients with ASD and 6.5 ± 2.12 for patients with ID (p >0.05). In the separation of criteria, we found verbal aggression in 48 patients (48.97%), with a mean score of 1.02 (±1.42), aggression against property in 38 patients (38.77%) with a mean score of 2.12 (± 3.41), self-harm in 41 patients (41.83%) with a mean of 2.84 (± 4.04), hetero aggression in 53 patients (54.08%) with a mean of 5.95 (± 6.65). There was no difference between genders for each component of the MOAS scale.

Considering the use of Risperidone, patients diagnosed with ASD showed more changes in the MOAS scale than patients with ID (p=0.04). There was no statistical difference regarding the scores on the individual scale criteria. (Table 2).

CLINICAL DEVELOPMENT

Parents subjectively reported their perception of improvement in the patient's behavior after starting medication in 95 patients (96.94%).

According to the parents' perception, among the patients diagnosed with ASD (n=52), all showed improvement with the therapy, and among those diagnosed with ID (n=46), improvement occurred in 34 patients (73.91 %) (p>0.05). There was no difference in symptomatic improvement regarding the duration of medication use (p>0.05).

Among the patients using Risperidone, there was a report of perception of clinical improvement in 97.53% of them. For those with initial off-label prescription (n=13) the perception of improvement occurred in 100%; and there was no statistical difference in relation to patients with prescription over 5 years (p=0.35).

DISCUSSION

The prescription of antipsychotics in the pediatric age group is still a challenge due to the lack of clinical, randomized and controlled studies. The present study exposes characteristics of a series of cases of children and adolescents using antipsychotics in a neuropediatric clinic.

The use of antipsychotics was more frequent among males, as observed by Kaguelidou et al.[6], in which the prescription for males was higher for all age groups. Possibly correlated to the fact that the main diagnoses found in this series of cases are more prevalent in males. In the same study, the prescription was null in patients under 4 years of age for some countries evaluated. In the present study, the median age observed during the evaluation period was 8.5 years (2.5 to 14 years). Thus, there were patients in whom the prescription of antipsychotics occurred at an age younger than

the recommended age, considering the main antipsychotics prescribed in the study, Risperidone and Periciazine, which are indicated above 5 and 3 years of age, respectively. Possibly due to treated symptoms, such as restlessness and aggressiveness, commonly appearing at younger ages than those for which the prescription is recommended.

The increase in the use of antipsychotics probably reflects off-label prescription in non-psychotic disorders, such as ADHD, restlessness, and in children younger than the approved age groups[7]. In the present study, we found that the main prescription indications were aggressiveness and restlessness. For Dinnissen et al.[8] in a study with 436 children and adolescents in the Netherlands, the main target symptoms were inattention/hyperactivity (25%), aggressiveness (24%) and other disturbing behaviors (41%). Concomitant use of multiple antipsychotics occurred in 3.2% of patients, while in this study it occurred in 2.04% of patients.

We showed that the most frequent diagnoses among the evaluated patients were ASD and ID. There were also cases of ADHD, behavior disorder and tic disorders, diagnoses that also benefit from the use of antipsychotics. In a study of 116 patients carried out by Cicala et al.(9) the most frequent pathologies found were ADHD (n=36), ASD (n=35), behavioral disorder (n=20) and tic disorders (n= 19), thus demonstrating a similarity in diagnoses in the pediatric age group using antipsychotics.

Risperidone is the most frequently prescribed antipsychotic in all European countries [6]. In 1993, Borre et al.(10) described a double-blind study with adolescents and adults in which the results indicated that it was significantly effective in the treatment of behavioral disorders in patients with ID versus placebo. These studies corroborate the results found in our study, in which Risperidone was the antipsychotic prescribed for 85.71% of patients with relevant efficacy.

A follow-up study of 107 children aged 5 to 12 years with below-average intelligence (IQ ≥ 36 and ≤84) who received 0.02 to 0.06 mg/kg/day of Risperidone suggested that this antipsychotic is generally well-tolerated at doses of up to 0.06 mg/kg/day and effective in the long term[11]. In the present study, we found that Risperidone was prescribed with a mean dose of 0.04±0.02 mg/kg/day, effective in 97.53% of patients without statistical correlation with use duration.

Adverse effect profiles are not the same for each antipsychotic agent, but may include weight gain, development of diabetes, sedation, extrapyramidal symptoms, increased prolactin levels, dystonia, and increased QT interval[8,12].The Adverse events did not occur in all patients in the study, the most evident were weight gain and increased appetite, sleep disorders, increased prolactin and gastrointestinal disorders were also found. Children are more vulnerable than adults to developing often harmful adverse effects[6,13]. No serious adverse effects were found in the present study.

The use of antipsychotics in pediatrics is often long-term. This chronic exposure during development can lead to dysfunctional changes in metabolic and neurological processes, for example, prolonged hyperprolactinemia can cause a delay in pubertal maturation, menstrual disorders, gynecomastia and sexual dysfunction - occurrences that are even more distressing for an adolescent than for an adult[9]. In a study carried out in Italy in 2020 with 116 pediatric patients, the increase in serum prolactin with Risperidone (n=17) was mostly asymptomatic[9].In the current study, only one patient had an increase in serum prolactin with Risperidone, being asymptomatic. Unfortunately, as this is a retrospective study, this data cannot be measured, as it is not routinely collected. The results of the Italian study confirmed that Risperidone and Aripiprazole are relatively well-tolerated therapeutic options for the treatment of a variety of disorders, even after one year of therapy.

One of the most challenging conditions of antipsychotic use is the potential to trigger epileptic seizures. In the available literature, Risperidone-related seizures are very rare[12].Thus, Risperidone has often been suggested as a candidate agent for the treatment of behavioral problems in children with epilepsy. In this study almost 30% of the patients had epilepsy, but there were no occurrences of epileptic seizures as an adverse event. Seizures triggered by antipsychotics have been considered to be a dose-dependent adverse effect. Slow dose titration and close follow-up are of vital importance[12].

Of the behavioral problems of patients with ASD, aggressiveness is quite common. Parents report that up to 68% of children and adolescents with ASD demonstrate hetero aggression[14]. In addition, the occurrence of self-aggression varies from 33 to 71% of cases[15]. By applying the MOAS scale to assess aggression, we found that there were changes in 71 patients (72.44%). And among patients using Risperidone with a diagnosis of ASD, there was a greater change in the scale, with statistical significance and a tendency towards greater occurrence of aggressiveness in the self-aggression item in relation to patients with ID. Social skills are a challenge in ASD, applied behavior analysis studies suggest that self-harm acts as a functional operant behavior[16]. Thus, it is plausible that self-harm is more likely to become socially conserved in individuals with lower levels of social skills, in which alternative communication strategies are limited.

A study with 490 children with ASD developed by Chen C et al.[17] found a total score on the MOAS scale with a mean of 3.47 ± 5.63. In the present study, we found a mean total score of 12.03 ± 6.36 for all diagnoses, 12.38 ± 6.36 for patients with ASD and 6.5 ± 2.12 for patients with ID. The MOAS scale was a useful tool in objectively understanding the aggressiveness of the evaluated patients; and thus, supported by data from the literature that states that aggressiveness, whether hetero--aggression or self-aggression, is a frequent behavior among patients with ASD. The MOAS scale can be a useful tool in assessing aggressiveness during antipsychotic treatment.

In conclusion, children under five years of age with an off-label prescription of Risperidone did not have more adverse effects when compared to children older than five years of age. The off-label use must be carefully monitored since the safety profile in relation to the risks during the prescription of this drug class still remains uncertain. It is expected that

more comprehensive studies on the use of antipsychotics in the pediatric age group will be developed.

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