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Antipsicóticos atípicos no tratamento da irritabilidade severa em crianças e adolescentes com Perturbação do Espectro do Autismo: Uma Revisão

Atypical antipsychotics for severe irritability in children and adolescents with Autism Spectrum Disorder: A Review

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Dedico este trabalho a todos os que me ajudaram a concretizá-lo:

À minha mãe, pelo apoio incondicional durante o meu percurso académico.

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Atypical antipsychotics for severe irritability in children and adolescents with Autism Spectrum Disorder: A Review

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Abstract

Autism spectrum disorder is a brain-based neurodevelopmental disorder characterized by impairments in social communication and by the presence of restricted, repetitive patterns of behaviour and interests. It has its onset in early childhood and significantly impacts the children and the family lives. Irritability and aggression are common co-occurring psychiatric conditions in autism spectrum disorder (25%) and the usage of atypical antipsychotics might be considered. The goal of the present review is to analyse the short and long-term efficacy and safety of risperidone, aripiprazole and paliperidone in the treatment of irritability in children and adolescents with autism spectrum disorder. A literature review was performed, searching PubMed and Cochrane Database of Systemic Reviews, using the Medical Subject Headings. The studies considered in this review show their efficacy in the short and long-term treatment. Although atypical antipsychotics have a safer profile than typical antipsychotics, they are associated with a significant weight gain and metabolic complications that shouldn't be overlooked. During antipsychotic treatment, it would be prudent to conduct a metabolic screening and implement preventive measures such as a calorically appropriated diet and physical exercise to reduce weight gain. In conclusion, the use of antipsychotics should be reserved for severe and enduring cases of irritability, when behavioural interventions have been tried and failed and when harm to self and others imminently exceeds the risk of harm from medication.

Keywords: Aripiprazole; Atypical antipsychotics; Autism spectrum disorder; Paediatric irritability; Paliperidone; Risperidone.

Introduction

Autism spectrum disorder (ASD) is a brain-based neurodevelopmental disorder. It's defined as a spectrum that can range from very mild to severe, according to the fifth revision of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 criteria, which changed ASD diagnostic criteria and created an umbrella diagnosis, in 2013.[1-3] Subtypes such as autistic disorder, Asperger's disorder, childhood disintegrative disorder and Pervasive Developmental Disorder Not Otherwise Specified are now included in the diagnosis of ASD.[3] Despite interindividual differences, the disorder is characterized by core symptoms in two domains: 1) social communication and 2) restricted, repetitive patterns of behaviour and interests.[2,4] Diagnosis is clinical, since there are no reliable biomarkers. To be diagnosed with ASD, individuals must have or have had struggle in three social communication subdomains and must have or have had difficulty in two of the four restricted, repetitive pattern sensory-motor behaviours, and symptoms must be a burden, causing clinically significant impairment in social, occupational, family and school environment.[1] Diagnosis of ASD can be made early, in children, as onset of ASD symptoms typically occurs below the age of 3, although symptoms may not fully manifest until school age or later.[2] Experts recommend the use of a validated screening tool at 18 and 24-month children.[5] Current population prevalence is estimated to be 1.5% in developed countries around the world.[2,6,7] ASD risk is 3-4 times higher in boys than girls.[1,4]

Youth with ASD, particularly those lacking a functional communication system, may exhibit behavioural disturbances as a manifestation of frustration or as a means of communication, which are more common in ASD (20-25%) than in those without

ASD.[1,3,8] Serious behavioural disturbances include irritability, which may manifest as aggression, self-injury and severe tantrums.[8] Frequently, the presence of irritability disrupts school environment, jeopardizing their education and it limits their inclusion in the family, relationships and social activities, causing significant parent and caregiver stress.[3,7] Secondary irritability causes such as sinusitis, headaches, gastrointestinal disorders can mimic or increase behavioural symptoms common to ASD and so they should be ruled out, before initiating targeted therapy.[3] In the case of severe irritability that is acutely or imminently unsafe, targeted psychopharmacotherapy should be considered.[3] Antipsychotics are not a cure for autism, they will only help to improve irritability in youth with ASD, not core symptoms, when intensive behavioural therapy has not been effective.[5] Therefore, antipsychotics should be used as part of a multimodal treatment plan, involving behavioural and educational therapy.[5]

The aim of this review is to discuss the short and long-term efficacy and safety of risperidone, aripiprazole and paliperidone in the treatment of irritability in children and adolescents with ASD.

Data sources

Studies were identified from PubMed and Cochrane Database of Systemic Reviews. A MEDLINE/PubMed literature search was conducted applying the Medical Subject Headings (Mesh) and keywords of "Aripiprazole"; “Atypical antipsychotics”; “Autism spectrum disorder”; “Paediatric irritability”; “Paliperidone”; “Risperidone”, which resulted in 179 references. A total of seventeen studies were included in this review. We

selected both open-label and double-blind randomised controlled trial (RCT), review articles and one case-report published since 2002 until 2019, written in English.

The primary outcome was reduction in irritability, measured by the reduction in the Aberrant Behavioural Checklist-Irritability (ABC-I) score in the atypical antipsychotic group, as compared with placebo, in RCT, in children and adolescents aged between 5 to 17 years, with a diagnosis of ASD. The adverse events (i.e. weight gain and metabolic parameters) were also assessed in this review. The ABC-I subscale includes questions about aggression, self-injury, tantrums, agitation, and unstable mood on a scale of 0 to 45, with higher scores indicating greater severity.

Atypical antipsychotics

Risperidone and aripiprazole are the only medications approved by the US Food and Drug Administration (FDA) for ASD-associated irritability.[9,10] Due to a lack of scientific evidence of efficacy and safety and due to difficulties in including young children in trials, antipsychotics aren't approved for children younger than 5 years old.[11] Paliperidone is not FDA-approved, nonetheless, is being regarded as a potential new treatment of resistant irritability in youth with ASD.

RISPERIDONE

Risperidone is an atypical antipsychotic (AAP), a selective antagonist with a high affinity for 5-HT2A and D2 receptors. This agent has also a relative high affinity for histamine H1 and α1-adrenoreceptors.[12,13] Furthermore, it has low to moderate affinity for 5-HT1A, 5-HT1C and 5-HT1D receptors. It's broadly metabolized by cytochrome P450 in

two enantiomers of 9-hydroxyrisperidone.[13] The total clinical effect is owned by the combined effect of risperidone and 9-hydrorisperidone.[9,13] Elimination of risperidone is manly, 70%, through urine and 14% in the feces.[9,14]

Risperidone was the first drug approved by the FDA for the treatment of serious dysfunctional behaviours in youth aged 5-17 years with ASD in 2006.[15,16]

Regarding risperidone, 4 double-blind RCT assessing short-term efficacy and safety, and 4 open-label studies assessing long-term efficacy and safety were included in this review.

Efficacy of short-term risperidone treatment on irritability

In 2007, the Cochrane collaboration published a systematic review and meta-analysis[17], which included two 8-week RCT exploring the short-term effects of risperidone treatment on irritability, in children/ adolescents aged between 5-17 years with ASD, that are comprised in this review.[18,19] Results showed more than 50% statistically significant reduction on the ABC-I subscale, concluding that risperidone is effective in treating acute irritability in youth with ASD.[11,16] According to another double-blind RCT, which enrolled 55 children aged between 5-12 years, 8-week treatment with risperidone also resulted in significantly greater reduction in irritability (ABC-I: -13.4 vs -7.2, $p<0.05$).[20] Furthermore, a 6-week, double-blind RCT assessed the efficacy of risperidone at a lower dose than the minimum dose currently recommended, which is 0.5-3.5 mg/day.[21] Patients (N= 96; aged 5-17 years) received two risperidone dose levels: risperidone low dose (RLD), 0.125 to 0.175 mg/day (based on weight) or risperidone high dose (RHD), 1.25 to 1.75 mg/day (based on weight).[21] RHD was effective in the treatment of irritability in youth with ASD. Mean reduction in ABC-I was significantly

greater in the high-dose compared to placebo (PBO), respectively -12.4 vs -3.5, p<0.001.[21] Nevertheless, RLD didn't demonstrated significant efficacy in the treatment of irritability in ASD children and adolescents, respectively -7.4 vs -3.5, p=0.164.[21]

Acute adverse drug reactions related to risperidone

Adverse drug reactions (ADR) associated with short-term risperidone treatment in ASD are common but are frequently mild to moderate.[11,18,19] The most frequently reported ADR is weight gain.[14] An average weight gain of 2.7 kg was reported in both 8-week studies.[13,17] Somnolence, upper respiratory tract infections (URTI), fatigue and increased appetite are also statistically significant and are commonly associated with short-term risperidone treatment.[13,22] Risperidone induced somnolence and drowsiness occurred in 49% vs 72.5% and increased appetite occurred in 73% vs 22.5%, comparing, respectively, McCracken et al. to Shea et al., and URTI occurred in 37.5% according to Shea et al.[8] Extrapyramidal symptoms (EPS) were associated with risperidone in 27.5% children, mostly tremor and hypokinesia.[19,22] In McCracken et al. weekly neurologic evaluation showed no EPS.[18] In Pandina et al., although weight gain was not statistically significant (2.4 kg vs 1.1 kg, p=0.276), the most common ADR were consistent with the results of the above mentioned studies: somnolence (74%), URTI (41%), rhinitis (26%), fever (26%), increased saliva (15%), coughing (15%), vomiting (11%), increased appetite (11%) and anorexia (11%).[20] In Kent et al., the incidence of ADR was higher in the RHD (87%) than in the RLD (60%).[21] In the RLD, children gained 1.2 kg, while in the RHD, they gained 2.4 kg.[21] EPS were most frequent in the RHD (16%), mostly akathisia (13%). No incidence of tardive dyskinesia was reported during the study. Mean change from baseline in serum prolactin levels (SPL) was greater in the RHD (20.23 ng/ml) than in the

RLD (2.58 ng/ml) or PBO (1.27 ng/ml).[21] One potentially prolactin-related ADR of oligomenorrhea was reported in one patient in the RHD group. No clinically meaningful change in fasting glucose, cholesterol, LDL or HDL levels was reported during 6 weeks.[21] Nevertheless, insulin levels and insulin resistance increased with increasing risperidone dose.[21]

Efficacy and safety of long-term risperidone treatment on irritability

A study conducted by RUPP[23], an open label extension (OLE) study which enrolled 63 of 101 subjects allocated to a 8-week RCT[18], showed maintained 59% reduction of the ABC-I subscale ($p<0.001$) over 16 weeks. Additionally, those who discontinued risperidone after 6 months had a significantly higher relapse rate of irritability and took less time to relapse compared to those remaining on risperidone, 62.5% (34 days) vs 12.5% (57 days) respectively.[23] Troost et al. confirms these findings.[24] After 6 months of risperidone, the ABC-I score significantly decreased compared to PBO, ($p\leq0.05$).[24] During the discontinuation phase, 67% subjects, randomized to PBO, relapsed compared to 25% who continued risperidone and, respectively, suffered a 60% vs 14% increased of ABC-I score.[24] Those who discontinued risperidone, not only had a significantly higher relapse rate of irritability, but also took less time to relapse compared to those remaining on risperidone.[24] A long-term OLE study[25], which enrolled 84 of the 101 subjects allocated to the 8-week RCT[18], showed continued decreased on ABC-I subscale for up to 21.4 months. Kent et al. conducted a 6-month OLE study, in which the improvement in ABC-I subscale, observed in the 6-week RCT, continued in the OLE for all treatment groups.[26] The ABC-I score improved from 41% to 76% in the PBO, 52% to 79% in the RLD, whereas

for RHD, the improvement in ABC-I was maintained at 83%.[26] These findings suggest that long-term treatment may be necessary to maintain improvements in irritability.[16]

Regarding ADR, both studies reported weight gain: 5.1 kg vs 5.7 kg vs 4.3-5.5 kg, respectively, according to RUPP, Troost et al. and Kent et al. [23,24,26] The most common ADR reported by Kent et al. were: increased appetite (11%), increased weight (9%), vomiting (9%), sedation (8%), pyrexia (8%), URTI (8%), somnolence (5%) and fatigue (5%).[26] None of these events were rated as severe and there was minimal to no change in EPS scores, with a similar frequency (7-8%) across all groups and with no reports of tardive dyskinesia.[26] In this study, no clinically meaningful increases occurred in mean fasting glucose or LDL-cholesterol levels with risperidone treatment. Nonetheless, slight increases in triglycerides were observed in the RHD group.[26] Mean changes from baseline in SPL were greater in the RHD (13.51 ng/ml) and RLD (13.74 ng/ml) than in PBO (12.36 ng/ml). One potentially prolactin-related ADR of irregular menstruation was reported in one patient, in the RLD group.[26]

Long-term risperidone treatment is associated with increased risk of hyperprolactinemia within 1-2 months of treatment, after which SPL tend to diminish as treatment continues.[27-30] Elevation of SPL is associated with risperidone D2-receptor blockade action in the tuberoinfundibular pathway.[31-33] Hyperprolactinemia can have clinical implications such as galactorrhoea, gynecomastia, sexual and reproductive dysfunction, and osteoporosis.[34,35]Nevertheless, there's still some uncertainty regarding the consequencies of hyperprolactinemia in youth compared to adults, due to difficulties in identifying sexual side effects in developmentally delayed children.[27-29]

ARIPIPRAZOLE

Aripiprazole has a distinct mechanism of action.[36] It's a partial dopamine D2 receptor agonist with double action, depending whether it's in a hyperdopaminergic or a hypodopaminergic state, acting as an antagonist or an agonist respectively.[7,37] It's also an antagonist for 5-HT2A, resulting in increased dopamine release which reduces EPS by diminishing excessive dopaminergic blockade.[7,38] Additionally, it's a partial agonist of 5-HT1A, which exerts an anxiolytic effect, and has a strong affinity for D3 receptors and a moderate affinity for dopamine D4, serotonin 5-HT2C and 5-HT7, and a low affinity for alpha 1-adrenergic, muscarinic M1 receptors and histamine H1 receptors.[36-39]. Activity is mostly due to the parent drug, aripiprazole, and in lesser extent, to its metabolite dehydro-aripiprazole.[7] Elimination of aripiprazole is mainly through hepatic metabolism by CYP2D6 and CYP3A4.[13]

Aripiprazole was FDA approved, in 2009, for the treatment of irritability in paediatric patients, aged 6 to 17 years, with ASD.[16]

Regarding aripiprazole, 3 double-blind RCT assessing short-term efficacy and safety, and 3 open-label studies assessing long-term efficacy and safety were included in this review.

Efficacy of short-term aripiprazole treatment on irritability

In 2012, the Cochrane collaboration published a systematic review and meta-analysis, which included two 8-week RCT exploring the short-term effects of aripiprazole treatment on irritability, in children/ adolescents aged between 6-17 years with ASD, that are comprised in this review.[40-42]Results showed that all groups receiving

aripiprazole demonstrated significantly greater improvement in mean ABC-I score compared with PBO ($p \leq 0.05$).[42] In Marcus et al., the mean decreases in the ABC-I score for the three fixed dosage groups of aripiprazole (5, 10 or 15 mg/day) were, respectively, 12.4, 13.2, 14.4.[40] Owen et al. found similar improvements in the ABC-I score.[41] Ninety-eight patients aged 6-17 years were enrolled in the study and those randomized to aripiprazole were treated with flexible doses (5,10 or 15 mg/day).[41] The mean decrease in the ABC-I subscale was 12.9 in the aripiprazole group vs 5.0 in the PBO ($p \leq 0.001$).[41] Furthermore, Ichikawa et al. conducted an 8-week double-blind RCT which demonstrated that flexible-dose aripiprazole can be effective in reducing irritability in Japanese children and adolescents with ASD, as shown by the statistically significant reduction in the ABC-I score compared to PBO (-11.4 vs -7.5, $p \leq 0.05$).[43] These results were consistent with those from previous RCT conducted in the US.[40,41]

Acute adverse drug reactions related to aripiprazole

Aripiprazole seems to be a safe AAP in young patients with ASD.[38]ADR associated with short-term aripiprazole treatment in ASD are commonly mild to moderate when they occur.[37,40,41] The most common ADR include sedation, fatigue, somnolence, vomiting, drooling, increased appetite, weight gain, and tremor. Aripiprazole induced sedation and drooling occurred, respectively, in 23.6% and in 9% of the children, according to Marcus et al.[40] Aripiprazole induced fatigue occurred in 15.2% vs 21.3%, somnolence occurred in 8.5% vs 17%, vomiting occurred in 13% vs 14.9% and increased appetite occurred in 12% vs 14.9%, comparing, respectively Marcus et al to Owen et al.[40,41] Marcus et al. recorded a mean weight gain of 1.3 kg in the aripiprazole group compared with 0.3 kg in the PBO ($p \leq 0.05$).[40] Owen et al. recorded a mean weight gain of 2.0 kg in

the aripiprazole group compared with 0.8 kg in the PBO (p ≤0.005).[41] Regarding EPS, tremor is the most frequent and is more likely to occur in the aripiprazole group.[13,40,41] According to Ichikawa et al., the mean change in weight wasn't significantly different between aripiprazole and PBO (1.24 vs 0.58 kg; p=0.085).[43] Somnolence was the most commonly reported ADR in the aripiprazole group (51.1%), and the frequency was higher than that in previous US studies.[40,41] Nausea (6.4%), vomiting (6.4%), fatigue (6.4%) and increased appetite (4.3%) were also described ADR in this study.[43] The incidence of EPS (6.4%) is lower than in previous US studies.[40,41] Mean SPL significantly decreased in the aripiprazole group compared to PBO from baseline to week 8 (-13.8 vs -2 ng/mL; p<0.001).[43] No patient in the aripiprazole group experienced an increase in SPL.[43]

Efficacy and safety of long-term aripiprazole treatment on irritability

A 52-week OLE study enrolled 330 children with ASD, who had previously been enrolled in the above 8-week RCT or who were enrolled as *de novo* subjects.[44] Results demonstrated aripiprazole significantly diminishing the ABC-I score in *de novo* subjects The ABC-I score achieved in the prior study remained constant over the 52 weeks in the prior aripiprazole subjects.[16,44] Another double-blind RCT enrolled 157 patients of which 85 showed a ≥25% improvement of the ABC-I score over 13-26 weeks.[45]Additionally, those who discontinued aripiprazole had a non-statistically significant higher relapse rate of irritability and took less days to relapse compared to those who maintained aripiprazole up to 16 weeks, 52% (29 days) vs 35% (56 days), (p=0.097), respectively.[13,45] Nevertheless, the NNT was 6, suggesting that some children may benefit from long-term aripiprazole treatment.[16] An OLE study in Japan, which enrolled prior PBO and prior

aripiprazole groups who had completed a previous 8-week RCT, assigned all of them to aripiprazole treatment.[46] Symptoms of irritability were improved early in the course of treatment, in patients receiving aripiprazole for the first time during this study (ABC-I: -6.3). For patients who had previously received 8-week aripiprazole treatment, improvements in ABC-I score (ABC-I: -2.6) were maintained. [46] These findings support previous US long-term studies and suggest that youth with ASD may benefit from long-term aripiprazole treatment in reducing irritability.[37,44,45]

Regarding ADR, in both studies the most common ADR was weight gain, with Findling et al. reporting a 3.2 kg increase in phase 1 and a 2.2 kg increase in phase 2.[13,37] Ichikawa et al. reported a total weight gain of 5.2 kg in 48 weeks.[46] According to Marcus et al., in addition to weight gain, common ADR included: vomiting (19%), nasopharyngitis (13%), increased appetite (13%), pyrexia (12%), URTI (12%), insomnia (10%) and EPS (14.5%), most commonly tremor (3.0%).[44]Findling et al. showed that the most common ADR were somnolence (14.8%), vomiting (14.2%) and EPS (17.4%), most commonly tremor (6.5%), in the first phase, and URTI (10.3%), constipation (5.1%), movement disorder (5.1%) and EPS (7.7%), in the second phase. [45] Ichikawa et al, besides supporting previous US long-term studies, showed a decrease in SPL in prior PBO (-11.5 ng/mL), with aripiprazole treatment, within 48 weeks.[41,44,46] There were no other clinically relevant metabolic findings.[46]

PALIPERIDONE

Paliperidone, 9-hydroxyrisperidone, is the active metabolite of the high-potency risperidone.[47] It's an AAP, a 5-HT2A and a D2 antagonist.[48] Although paliperidone and risperidone have similar receptor binding profiles in vitro, paliperidone might offer

several advantages over its parent risperidone.[49] Namely, fewer CYP2D6 interactions which leads to almost 60% of it being excreted unchanged in the urine, preferable in patients with hepatic problems.[49,50] It's the only drug in its class to have a osmotic-controlled oral delivery system for up to 24h, facilitating once-daily dosing.[47,48] Moreover, paliperidone shows a faster dissociation on D2 receptors and greater efficiency in intracellular signal transmission processes than risperidone, which might explain why subjects with a prior ineffective trial of risperidone responded to paliperidone.[49,50]

Paliperidone is FDA approved for schizophrenia in adolescents, aged 12 to 17 years.[49] Nevertheless, it's, occasionally, as the majority of AAP, used off-label and it's being regarded as a potential new treatment of resistant irritability in youth with ASD.[50]

Efficacy and safety of short-term paliperidone treatment on irritability

Regarding paliperidone, only two studies from 2011-2012 were found up to date, January 2020, and both are mentioned in this review.

A small 8-week open-label study[49], which enrolled 25 young patients with ASD, showed 84% responders to paliperidone treatment, which was associated with significant improvement in irritability, ≥25% improvement of the ABC-I subscale ($p \leq 0.001$). Likewise, Kowalski et al. have reported on the successful use of paliperidone for the treatment of severe irritability in a 5-year-old child with ASD who was unable to tolerate oral medications and so it had to be used paliperidone palmitate, the IM formulation of paliperidone.[51] Three months following initiation of paliperidone palmitate, it was demonstrated a notable 62% improvement in his ABC-I score and his aggression and tantrums had diminished in frequency and severity.[51] Regarding ADR, paliperidone

palmitate was well tolerated and an increase in appetite was the only noteworthy adverse effect.[51] Stigler et al.[49] also investigated the occurrence of ADR. The most common ADR were mild and included excessive appetite (36%), weight gain (2.2 kg, p≤0.001), tiredness (28%) and rhinitis (32%). Mild to moderate EPS , for instance sialorrhea, tremor and akathisia, were recorded in four of twenty-five subjects.[49] SPL increased significantly from 5.3 to 41.4 ng/ml (p≤0.0001).[49]

However, this area is under-researched and larger scale RCT are necessary to study the efficacy and tolerability of paliperidone for paediatric population with ASD.[49,50]

Metabolic monitoring. Prevention and treatment of weight gain associated with antipsychotic treatment

Metabolic monitoring should include a baseline assessment of blood pressure, height, waist circumference, weight, fasting lipid profile and fasting plasma glucose. Personal and family history of obesity, diabetes, dyslipidaemia, hypertension and cardiovascular diseases should also be documented.[16,22] Metabolic monitoring should be assessed not only prior to initiation of treatment but also repeated periodically thereafter.[52] More detailed information is presented in **Table 1**. Treatment with either risperidone or aripiprazole holds a significant weight gain risk, which predisposes children/adolescents to later metabolic complications.[53]Regarding weight gain, a calorically appropriated diet and physical exercise are essential and may be the most effective measures for weight gain prevention.[12] AAP-induced weight gain may be reversible but stopping AAP treatment often leads to relapse of irritability.[54] As a pharmacologic management of

overweight, metformin, a biguanide drug FDA-approved for treatment of type 2 diabetes, has been shown to be effective in diminishing weight gain or stabilizing pre-AAP weight in youth with ASD, even in the absence of diabetes, while being safe.[54-56] Nevertheless, metformin is associated with gastrointestinal side effects such as nausea, vomiting and diarrhea.[16,54]

Metabolic Parameters	Frequency of monitoring			Observations
	1 month	2 months	3 months	
Blood pressure	-	-	YES	Monitor once a year
Fasting lipid profile	-	-	YES	Monitor in 5 years
Fasting plasma glucose	-	-	YES	Monitor once a year
Weight	YES	YES	YES	Monitor closely every 3 months

Table 1: Metabolic monitoring for youth with ASD whilst antipsychotic treatment.

Conclusion

Concerns regarding EPS of typical antipsychotics triggered the development of AAP. Antagonism at the 5-HT2A receptor may be responsible for the reduced EPS of AAP by decreasing excessive dopaminergic blockade.[12] Due to their safe profile, AAP are a very interesting choice for treating severe irritability in ASD children. Nevertheless, weight gain can limit their use.[52,57] The risk of severe weight gain is higher in youth than in adults and weight gain during development is a particularly significant medical concern, as it could predict adult obesity, metabolic syndrome, cardiovascular morbidity and malignancy.[12,24,57-59] There are many factors that influence the propensity for weight gain such as: appetite increase, histamine H1 and 5-HT2C receptors.[12] Weight gain promotes not only adipose tissue accumulation which potentially results in insulin

resistance/diabetes but also hypertriglyceridemia, an independent risk factor for cardiovascular diseases.[12,59] Although awareness of weight gain and possible treatment with metformin is increasing, monitoring of metabolic effects other than weight gain is commonly overlooked.[7] Thus, metabolic screening should be offered for those receiving AAP.[16,60]

Risperidone and aripiprazole are the only FDA-approved in youth, remaining the mainstays of ASD irritability treatment. Only one head-to-head study of aripiprazole versus risperidone in youth with ASD exists.[61] There's an opinion that aripiprazole is safer than risperidone. However, comparison of risperidone and aripiprazole has yielded no significant difference in efficacy or safety, in this study.[62] Risperidone and aripiprazole are significantly and similarly effective for the treatment of irritability in paediatric ASD patients, and both are associated with significant and similar weight gain.[61] There is a propensity for rapid, early weight gain with risperidone versus slower but consistent weight gain with aripiprazole.[7] Therefore, in order to choose the best pharmacological option, a clinical equipoise considering the patient's clinical profile may be necessary.[37] Risperidone is given twice daily in youth with ASD, while aripiprazole, due to its longer half-life ought to be given once-daily, which might constitute a relative advantage.[7] Furthermore, risperidone is associated with hyperprolactinemia, whilst aripiprazole is associated with an absence of prolactin elevation or, sometimes, its decline.[63] Nonetheless, in patients experiencing tolerability problems such as clinical signs of hyperprolactinemia, it may be beneficial to replace risperidone with aripiprazole, since aripiprazole maintains the efficacy of risperidone treatment, but without a prolactin elevation.[62,64] Therefore, risperidone and aripiprazole are both effective and safe options for the treatment of short and long-term treatment of irritability in children with

ASD. Paliperidone might offer several advantages over its parent risperidone such as being given once-daily and greater efficiency in intracellular-signalling pathways, which might explain why subjects with a prior ineffective trial of risperidone responded to paliperidone.[47-50] Paliperidone seems to be a potential new treatment of resistant irritability in youth with ASD, which explains the increasing off-label usage, since it's not approved by the FDA yet.[50] However, larger-scale RCT are necessary to study it's efficacy and tolerability in youth with ASD.[49,50]

In conclusion, AAP should be reserved for severe and enduring cases of irritability, when behavioural interventions have been tried and failed and when harm to self and others imminently exceeds the risk of harm from medication.[13,22,65] Behavioural interventions should always be offered as first-line treatment since, unlike medication, they're not "biologically intrusive".[11] Psychopharmacotherapies ought only to be considered after excluding reversable medical conditions, ideally in combination with behaviour therapy.[65] Long-term safety is essential for youth treated with AAP, mainly given the established need for ongoing treatment in ASD.

Conflicts of Interest:

The authors declare no conflict of interest in conducting this work.

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Supplementary Materials

Reference	Design	Duration	N (age)	Dose	Outcomes measures	Results: Antipsychotic vs placebo	Adverse effects
RISPERIDONE							
McCracken et al., 2002	RCT	8 weeks	101 (5-17 y)	0.5-3.5 mg/day	ABC-irritability CGI	ABC-I: 56.9% vs 14.1% reduction (p≤0.001) CGI: 69% vs 12% improved (p≤0.001)	Weight gain 2.7 kg vs 0.8 kg (p≤0.001) Increased appetite (73%), fatigue (59%), drowsiness (49%), dizziness (16%), drooling (27%) (p≤0.05)
Shea et al., 2004	RCT	8 weeks	79 (5-12 y)	0.01-0.06 mg/kg/day	ABC-irritability CGI	ABC-I: 64% vs 31% improvement CGI: 87.2% vs 39.5% improved (p≤0.05)	Weight gain 2.7 kg vs 1.0 kg (p≤0.001) Somnolence (72.5%), upper respiratory tract infections (37.5%), rhinitis (27.5%), increased appetite (22.5%)
Pandina et al., 2007	RCT	8 weeks	55 (5-12y)	0.01-0.06 mg/kg/day	ABC-Irritability CGI	ABC-I: -13.4 vs -7.2 (p<0.05) CGI: 58% VS 21.4% (P<0.05)	Weight gain 2.4 kg vs 1.1 kg (p=0.276) Somnolence (74%), upper respiratory infection (41%), rhinitis (26%), fever (26%), increased saliva (15%), coughing (15%), vomiting (11%), increased appetite (11%), anorexia (11%), influenza-like symptoms (11%).
Kent et al., 2013	RCT	6 weeks	96 (5-17y)	Low dose 0.125 or 0.175 mg/day (based on weight) High dose 1.25 or 1.75 mg/day (based on weight)	ABC-irritability CGI	RLD: ABC-I: -7.4 Vs -3.5, p=0.164 (NNS) CGI: much/very much improved 17% vs 15%, p=0.985 (NNS) RHD: ABC-I: -12.4 Vs -3.5, p<0.001 CGI: much/very much improved 63% vs 15%, p<0.001	Weight gain RLD: 1.2 kg vs 0.7 kg Weigh gain RHD: 2.4 kg vs 0.7 kg The most common ADR in the combined RLD and RHD were: Increased appetite (26%), sedation (15%), somnolence (11%) and weight gain (11%), EPS most frequent in the RHD (16%): mostly akathisia (13%); Mean change from baseline in serum prolactin levels was greater in the RHD(20.23 ng/ml) vs RLD(2.58 ng/ml) vs placebo(1.27 ng/ml).

Network RUoppa, 2005 (extension of McCracken, 2002)	Open label RDT	Part I: 4 months Part II: 8 weeks	63 (5-17 y) 32 (5-17 y)	0.5-4.5 mg/day	ABC-irritability CGI Relapse rate Time to relapse	ABC-I: 59% reduction (p≤0.001) CGI: 82.5% improved Relapse rate: 12.5% vs 62.5% (p≤0.01) Time to relapse: 57 days vs 34 days	Weight gain: 5.1 kg (p≤0.001) Increased appetite (7.9%), drowsiness (3.2%), tiredness (1.6%)
Troost et al., 2005	Open label RDT	Part I: 6 months Part II: 8 weeks	26 (5-17 y) 24 (5-17 y)	0.5-3.5 mg/day	ABC-irritability CGI Relapse rate Time to relapse	ABC-I: -11.1 (p≤0.05) CGI: 69% much/very much improved Relapse rate: 25% vs 67% (p≤0.05) Time to relapse: 7 weeks vs 6 weeks	Weight gain: 5.7kg, p<0.0001 Increased appetite (61.5%), anxiety (38.5%), fatigue (34.62%).
Kent et al., 2013 (extension of 6 week-RCT of Kent et al., 2013)	Open label	6 months	79 (5-17y)	Flexibly dosed up to a maximum dose of: 1.25 or 1.75 mg/day (based on weight)	ABC-irritability CGI	ABC-I: NNS among the three groups, p=0.800) RHD: -13.0 RLD: -13.2 Placebo: -11.8 CGI: much/very much improved RHD vs RLD vs placebo, p=0.684 (NNS)	Weight gain: 4.3-5.5 kg. Increased appetite (11%), increased weight (9%), vomiting (9%), sedation (8%), pyrexia (8%), upper respiratory tract infection (8%), nasopharyngitis (6%), somnolence (5%), fatigue (5%). EPS (8%). Mean change from baseline in serum prolactin levels was greater in the RHD (13.51 ng/ml) and RLD (13.74 ng/ml) vs placebo (12.36 ng/ml).
Aman et al., 2015 (extension of McCracken, 2002)	Open label	21 months	84 (5-17 y)	Mean 2.47 +-1.29 mg/day	ABC-irritability CGI	ABC-I p≤0.025: score decrease of -12.4 vs -5.66 CGI: NSS	Weight gain (p≤0.05) Increased appetite (42.1%) Enuresis (19.6%)

ARIPIPRAZOLE							
Marcus et al., 2009	RCT	8 weeks	218 (6-17y)	5,10 or 15 mg/day (fixed dose)	ABC-irritability CGI	ABC-I: score decreased of -8.4 for placebo to -12.4 for 5 mg/day, to -13.2 for 10mg/day, to -14.4 for 15 mg/day (p≤0.05) CGI: p≤0.05 all doses	Weight gain: 1.3-1.5 kg vs 0.3 kg (p≤0.05) Sedation (23.6%), fatigue (15.2%), vomiting (13%), increased appetite (12%), drooling (9%), somnolence (8.5%), EPS (22.4%): tremor is the most frequent (10.3%).
Owen et al., 2009	RCT	8 weeks	98 (6-17y)	5,10 or 15 mg/day (flexible dose)	ABC-irritability CGI	ABC-I: score decreased of -12.9 vs -5.0 (p≤0.001) Mean CGI: 2.2. vs 3.6 (p≤0.001)	Weight gain: 2.0 kg vs 0.8 kg (p≤0.005) Fatigue (21.3%), Somnolence (17%), vomiting (14.9%), increased appetite (14.9), EPS (14.9%): tremor is the most frequent (8.5%).
Ichikawa et al., 2017	RCT	8 weeks	92 (6-17y)	1-15 mg/day (flexible dose)	ABC-irritability CGI	ABC-I: -11.4 vs -7.5 (p≤0.05) CGI: -1.4 vs -0.7 (p≤0.05)	Weight gain: 1.24 kg vs 0.58 kg, p=0.085. Somnolence (51.1%), nausea (6.4%), vomiting (6.4%), fatigue (6.4%), increased appetite (4.3%). EPS (6.4%): salivary hypersecretion (4.3%), akathisia (2.1%), gait disturbance (2.1%), bradykinesia (2.1%), tremor (2.1%). Mean serum prolactin concentrations significantly decreased in the aripiprazole group compared to placebo from baseline to week 8 (-13.8 vs -2 ng/mL; p<0.001).
Marcus et al., 2011 (extension of Marcus, 2009 and Owen,2009 studies)	Open label	52 weeks	330 (6-17y)	5,10 or 15 mg/day (flexible dose)	ABC-irritability CGI	ABC-I: score significantly decreased of -8.0 vs -6.1 CGI: significant improvement, with 58% scoring 1(very much improved) or 2 (much improved)	Weight increase (23%), vomiting (19%), nasopharyngitis (13%), increased appetite (13%), pyrexia (12%), upper respiratory tract infection (12%), insomnia (10%), EPS (14.5%)-most commonly tremor (3.0%).
Findling et al., 2014	RCT RDT	Phase 1: 13-26 weeks Phase 2: 16 weeks	157 (6-17y) 85 (6-17y)	2-15 mg/day	ABC-irritability CGI Relapse rate Time to relapse	ABC-I: ≥25% improvement (85/157) CGI: ≤2 (85/157) Relapse rate: NSS (35% vs 52%; p=0.097) Time to relapse: NSS (56 days vs 29 days; P=0.097)	Phase 1: Weight gain: 3.2 kg vs 2.6 kg Somnolence (14.8%) and vomiting (14.2%). EPS (17.4%)-most commonly tremor (6.5%). Phase 2: Weight gain: 2.2 kg vs 0.6 kg. Upper respiratory tract infection (10.3%), constipation (5.1%), movement disorder (5.1%). EPS (7.7%)

Ichikawa et al., 2018 (extension of 8-week RCT of Ichikawa et al., 2017)	Open label	48 weeks	86 (6-17y)	1-15 mg/day (flexible dose)	ABC-irritability CGI	ABC-irritability: -6.3 (prior placebo) -2.6 (prior aripiprazole) CGI -0.9 (prior placebo) -0.5 (prior aripiprazole)	Total weight gain: 5.2 kg. Nasopharyngitis (61.6%), somnolence (32.6%), influenza (29.1%), and increased weight (24.4%), vomiting (14%), increased appetite (11.6%), upper respiratory tract inflammation (10.5%). EPS (12.8%): mostly salivary hypersecretion (7%) and akathisia (4.7%). A decrease in serum prolactin levels occurred in prior placebo patients (-11.5 ng/mL).
Risperidone vs Aripiprazole							
Ghanizadeh et al., 2014	RCT	2 months	59 (4-18y)	Risperidone mean dose: 1.12 mg/day. Aripiprazole mean dose: 5.5 mg/day.	ABC-irritability CGI	ABC-irritability: Risperidone: -9 vs Aripiprazole: -11.6, p=0.5 (NNS) CGI: ''much improved'' Risperidone: 5/29 vs Aripiprazole: 9/27, p=0.3 (NNS)	ADR RISPERIDONE VS ARIPIPRAZOLE: Increased appetite: (40% vs 34.5%, p=0.7); Drooling: (40% vs 31%, p=0.5); Drowsiness: (16.7% vs 20.7%, p=0.7); fatigue: (13.3 vs 13.8, p=1.0)
PALIPERIDONE							
Stigler et al., 2012	Open label	8 weeks	25 (12-21y)	3-12 mg/day	ABC-irritability CGI	ABC-I: ≥25% improvement (p≤0.001) CGI: 84% improved (p≤0.001)	Weight gain: 2.2 kg (p≤0.001) Increased appetite (36%), tiredness (28%) and rhinitis (32%). Mild to moderate EPS, for instance sialorrhea, tremor and akathisia (four of twenty-five subjects) Serum prolactin elevation (p≤0.0001)
Kowalski et al., 2011	Case report	3 months	1 (5 y)	39 mg/ 0.25 mL IM monthly	ABC-irritability CGI	ABC-I: 62% reduction CGI: 1 = ''very much improved''	Weight gain and increased appetite.

Table 2: Characteristics of included studies of risperidone, paliperidone and aripiprazole for irritability in youth with autism spectrum disorder. Legend: ABC-I: Aberrant Behaviour Checklist – Irritability; CGI: Clinical global impression; RCT: Randomized controlled trial; RDT: Randomized discontinuation trial; RHD: Risperidone high dose; RLD: Risperidone low dose; IM: Intramuscular; NSS: Not statistically significant

Abbreviations
AAP: Atypical antipsychotics
ABC-I: Aberrant Behaviour Checklist - Irritability
ADR: Adverse drug reactions
ASD: Autism spectrum disorder
EPS: Extrapyramidal symptoms
FDA: Food and Drug Administration
RCT: Randomized controlled trial
RDT: Randomized discontinuation trial
RHD: Risperidone high dose
RLD: Risperidone low dose
SPL: Serum prolactin levels
NNT: Number needed to treat
NSS: Not statistically significant
OLE: Open label extension
PBO: Placebo
URTI: Upper respiratory tract infection

ANEXOS:

Anexo I. Agradecimentos

Anexo II. Normas de escrita e submissão à revista Portuguese Journal of Pediatrics

ANEXO I.

Agradecimentos

“It does not matter how slowly you go as long as you do not stop.”
—*Confucius*

Ao se aproximar o fim de mais uma etapa no meu percurso académico, talvez uma das mais importantes, já que me ensinou o poder da autonomia e me permitiu afinar a capacidade de tomar decisões, não poderia deixar de agradecer a todos os que me ajudaram a concretizar este projeto.

Ao meu orientador, Doutor Daniel José Dias Gonçalves, por ter aceitado nortear este projeto e consequentemente pela paciência e pela disponibilidade prestadas.

À Faculdade de Medicina da Universidade do Porto, a minha segunda casa, que me fez crescer como pessoa, ao expor-me diariamente a novos desafios, que me fizeram ‘’lutar com garra pelos meus objetivos’’ e me ensinaram a ser humilde.

A todos os meus colegas de curso, que tal como eu experienciaram momentos de verdadeira ansiedade e que ainda assim nunca me voltaram as costas e me fizeram sorrir.

À minha família que nunca deixou de acreditar em mim e nas minhas capacidades e que sempre me facilitou o percurso académico.

PORTUGUESE JOURNAL OF PEDIATRICS
Official journal of Portuguese Society of Pediatrics

INSTRUCTIONS FOR AUTHORS

Manuscript text

Original articles

Original articles should include the following sections: Introduction, Methods, Results and Discussion. At the end of the discussion five short bullets must be presented, highlighting "What is new in this study". Acknowledgements (if applicable), References, Tables and Figures.
Original articles should not exceed 4000 words (excluding references and captions of illustrations), up to six illustrations (tables, figures) and up to 60 references. A structured abstract of the main text with a maximum of 250 words.

Review articles

Review articles are comprehensive articles that synthesize old ideas and suggest new ones. They cover large fields. They can be of clinical or basic science research. Although usually by the invitation of the Editor-in-Chief, the journal occasionally accepts unsolicited review articles about important issues or recent advances. Before you submit a review, please send a brief outline (no more than 500 words) to the Editor-in-Chief indicating the importance and novelty of the subject, and why you are qualified to write it. A submission invitation does not guarantee acceptance.
Review articles should not exceed 4000 words (excluding abstract, references and captions of illustrations), up to six illustrations (tables, figures) and up to 75 references. An unstructured abstract of the main texts with a maximum of 350 words.

Systematic reviews and meta-analyses

The text should not exceed ,000 words, excluding a structured abstract (of up to 350 words). It cannot include more than 80 references, and up to six illustrations (tables, figures).
Systematic reviews may or may not use statistical methods (meta-analysis) to analyze and summarize the results of the included studies.
Systematic Reviews should be presented in the following format: Introduction, Methods, Results, Discussion. The subject must be clearly defined. The purpose of a systematic review should be to produce a conclusion based on evidence. Methods must provide a clear indication of the literature search strategy, data mining, classification of evidence and analysis. PRISMA guidelines (http://www.prisma-statement.org/) must be followed.
We recommend that all systematic reviews are registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/).

Case reports

Case reports should include the following sections: Introduction, Case Report and Discussion. At the end of the discussion five short bullets should be presented, highlighting "What this report shows".
The text must not exceed 2000 words (excluding abstract, references and captions of illustrations), four illustrations (tables, figures) and 25 references. It must include an unstructured abstract not exceeding 150 words. It should not have more than five authors and all authors must have had a substantial individual contribution to the writing of the manuscript and not only be involved in the patient care. Those who were only involved in patient care should be listed in
The acknowledgements.
CARE guidelines (http://www.care-statement.org/) must be followed.

Case series
These are articles that describe sets of cases, in a perspective of reflection on a particular experience of diagnosis, treatment or prognosis. The text must include the following sections: Introduction, Methods, Results, Discussion. At the end of the discussion five short bullets should be presented, highlighting "What is new in this study". It should not exceed 4000 words (excluding abstract, references and captions of illustrations), up to six illustrations (tables, figures) and up to 60 references. The abstract should not exceed 250 words and should be structured in the same way as the main text.

Editorials
Editorials are the responsibility of the Editorial Board or by invitation of the Editor-in-Chief and comment on current topics or on articles published in the journal. They should not exceed 1200 words (excluding references and captions of illustrations), 15 references and may contain an illustration (table or figure). They have no abstract.

Letters to the Editor
Letters to the Editor are critical comments about an article published in the journal or a short note about a given topic or clinical case. Letters to the Editor should not exceed 600 words (excluding references and captions of illustrations), 10 references and may include a figure or table. They have no abstract.
If it includes a critical comment about an article, the following general structure must be followed: identify the article (reference 1); justify your writing; provide evidence (from the literature or from personal experience); provide a summary; cite references. The author answers must comply with the same structure. The timing of the Letters to the Editor is related to the probability of acceptance (submission until four weeks after the publication of the article in question).

Images in Pediatrics
Images in Pediatrics are an important contribution to clinical learning and practice. This section is intended for the publication of clinical, radiological, histological and surgical images, among others.
The title should not have more than eight words. Authors must be at most four. Images must be of high quality and educational value.
Up to 4 figures are allowed. Captions should be brief and informative. Arrows or other symbols should be included as necessary to facilitate understanding of the images. The text should not exceed 300 words, up to five references, and should include a brief medical history and relevant data of the physical examination, laboratory and clinical follow-up, as appropriate. They have no abstract.

Perspective
This type of manuscript is submitted at the invitation of the Editorial Board, although unsolicited proposals and submissions can be accepted (and, thus, encouraged). It can cover a wide variety of themes in health care, including: current or emerging problems, controversies in the field of pediatrics, management and health policy, medical education, history of medicine, society issues and epidemiology, among others. An author wishing to propose an article in this category should send the respective abstract by e-mail to the Editor-in-Chief, an indication of the authors (no more than three authors are recommended) and the title of the article for evaluation. Upon acceptance of the proposal, the final article must contain a maximum of 1200 words (excluding references and captions of illustrations), two illustrations (table, figure) and up to 10 references. An abstract is not mandatory.

Guidelines

The submission of consensus and guidelines of the Portuguese Pediatric Society (SPP) or other societies should be made by its respective Presidents or their representatives by contact of the Editorial Board. The authorship is attributed to the Section or Society in question, and the date of approval of the document, the names of the authors involved and their institutional affiliation must appear at the end of the text.

Clinical practice guidelines should not exceed 4000 words, up to 6 illustrations (tables or figures) and up to 100 references. An abstract is not mandatory.

Cochrane Corner

Manuscripts that consist on a selected recent Cochrane Review, particularly relevant, with the following scope: a) are intended to present a summary of the results of a systematic review or an overview of Cochrane Collaboration reviews, complemented by an original comment of the authors; b) must address a systematic review or an overview included in the Cochrane Database of Systematic Reviews and/or in the Evidence-Based Child Health: a Cochrane Review Journal already published in initial or updated version, is "active" (not removed) and is not "empty" (with no studies included); c) the theme should be pediatric in scope and at least some of the included studies must have pediatric subjects. This type of manuscript is to be submitted at the invitation of the team responsible for the Cochrane Corner, although it can be derived of external requests. Its structure must include a title that includes "Cochrane Corner:" and the subject, Introduction, Abstract of the Cochrane review (divided into Objectives, Methods, Results and Conclusion) and a Commentary to contextualize the evidence, any limitations, applicability and implications for clinical practice and research. It should not exceed 1200 words (excluding references and captions of illustrations) and can be complemented by an illustration (table, figure). In the case of a full copy of a figure or table being present, the appropriate publication authorization must be secured by the authors. Up to 10 references are permitted. An abstract is not mandatory.

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Manuscript word-limit

Article type	Abstract	Keywords	Main text structure	Max. words	Tables/figures	References
Original article	Max. 250 words; structured (Introduction and Objectives, Methods, Results and Discussion)	Up to 6	Introduction; Methods; Results; Discussion; Summary; Acknowledgments; if any; References; and figure legends, if any	4000	Total up to 6	Up to 60
Review article	Max. 350 words; unstructured	Up to 6	Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 75
Systematic review	Max. 350 words; structured	Up to 6	PRISMA	4000	Total up to 6	Up to 80
Case report	Max. 150 words; unstructured	Up to 6	Introduction; Case report; Discussion; Conclusion(s) (optional); References; and figure legends, if any	2000	Total up to 4	Up to 25
Case series	Max. 250 words; structured (Introduction and Objectives, Methods, Results and Discussion)		Introduction; Methods; Results; Discussion with Conclusion(s); Summary, Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 60
Editorial	None	None	Unstructured	1200	Total up to 1	Up to 15
Letter to the Editor	None	Up to 6	Unstructured	600	Total up to 1	Up to 10
Images in Pediatrics	None	Up to 6	Unstructured	300	Total up to 4	Up to 5
Perspective	None	Up to 6	Unstructured	1200	Total up to 2	Up to 10
Guidelines	None	Up to 6	Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 100
Cochrane Corner	None	Up to 6	Introduction, Objective, Methods, Results, Conclusion and Commentary; References; and figure legends, if any	1200	1	Up to 10

Guidelines on the contents of the different sections

Introduction

The introduction should essentially contain the scientific arguments that contextualize the subject matter, substantiate the realization of the study and justify its objectives. This section should only contain the necessary references for these purposes.

Methods

In this section the author should describe:

a) Study sample or population (specifying its definition and means of identification, recruiting and selection);
b) Study location in time and space;
c) Study design;
d) Data collection methods;
e) Data analysis methods. Statistical methods should be described with sufficient detail. The computer program (and its version) used for data analysis should be mentioned, as well as its manufacturer.

Ethical considerations should be stated at the end of this section, including the approval of ethics committees and the obtaining of informed consent, if applicable.

Results

The results must be presented in the text and can be complemented by illustrations (tables, figures), following a logical sequence. Authors should mention only the main observations of the illustrations and redundant information (in duplicate in the text and illustrations) should not be provided.

Discussion

The discussion should not include repeated information contained in the other sections of the article. It should focus on possible limitations of the study; relation of the results with findings by other studies; innovative aspects of the study and the conclusions that result from them. Only the indispensable references to discuss the results of the study should be included. The conclusion is included at the end of the discussion, and it is important that it is in accordance with the objectives of the study. Authors must avoid statements and conclusions that are not fully supported by the results of the research carried out.

Style guides

Use of word-processing software

It is important that the file is saved in the native format of the word processor. The text should be in a single-column format. Keep the text layout as simple as possible.
To avoid unnecessary errors, you are strongly advised to use the grammar and spelling checking functions of your word processor.

General requirements

All articles submitted to the journal must comply with these instructions. Failure to do so will result in the return of the manuscript and possible delay in publication.

- Manuscripts should be sent in DOC, DOCX or RTF format, and should not be blocked or protected.
- The text of the manuscript should be typed double-spaced. Do not format the text in multiple columns.

- All margins should be at least 30 mm.
- All pages should be numbered consecutively in the top right-hand corner, beginning in the title page.
- Specify any special characters used to represent characters that are not on the keyboard.

References Citations

in the text

Superscript Arabic numerals are used in the text. Authors may be identified, but the reference number must always be given.

References to unpublished data and personal communications should be made directly in the text and should not be numbered. Citation of a reference as "in press" implies that it has been accepted for publication.

Format of the reference list

Make sure that all the references mentioned in the Reference List are cited in the text, and vice versa. References should be listed using Arabic numerals in the order in which they are cited in the text. The reference list should be added as part of the text, not as a footnote. Reference software specific reference codes are not allowed.

Make sure that the data provided in the references are correct. When copying references, be careful as they may contain errors.

References to published articles should include the name of the first author followed by the names of the other authors, article title, journal name and the year of publication, volume and pages. Journal names should be abbreviated according to the Medline style.

A detailed description of the formats of different reference types can be found in "Uniform Requirements for Manuscripts Submitted¬ to Biomedical Journals" (http://www.nlm.nih.gov/bsd/uniform_requirements.html). List all the authors if there are six or fewer. Et al. should be added if there are more than six authors.

It is mandatory to indicate the DOI (Digital Object Identifier) in all references that have it.

Examples

Published article

Wallace IF, Berkman ND, Watson LR, Coyne-Beasley T, Wood CT, Cullen K, et al. Screening for speech and language delay in children 5 years old and younger: a systematic review. Pediatrics 2015;136:448-62. doi: 10.1542/peds.2014-3889

Article in press

Hunter G, Blankenburg R, Andrews J, Stevenson T. An unusual case of abdominal pain and hyponatremia in a 16-year-old girl with disordered eating. Pediatrics 2017 (in press) doi: 10.1542/peds.2017-0291.

Book

Murray PR, Rosenthal KS, Pfaller MA, Kobayashi GS. Medical microbiology. 4th ed. St. Louis: Mosby; 2002.

Book chapter

Castellano Barca G, Hidalgo Vicario M, Ortega Molina M. Transtorno del comportamento alimentário. In: Castellano Barca G, Hidalgo Vicario M, Redondo Romero A, editores. Medicina de la adolescência – atención integral. Madrid: Ergon; 2004. p.415-29.

Thesis
Borkowski MM. Infant sleep and feeding: a telephone survey of Hispanic Americans [thesis]. Mount Pleasant: Central Michigan University; 2002.

Web page
At a minimum, the full URL and the date on which the document was consulted must be given. Any other information, if known (author name, date, reference to a publication of origin, etc.), must also be given.
Programa nacional de luta contra a tuberculose. Sistema de vigilância (SVIG-TB). Direção-Geral da Saúde – Divisão de Doenças Transmissíveis [retrieved March 2005]. Available at: http://www.dgsaude.pt/upload/membro.id/ficheiros/i006875.pdf.

Footnotes

Footnotes should be avoided. When necessary, they must be numbered consecutively and appear at the bottom of the appropriate page.

Acknowledgements (optional)

Collate acknowledgements in a separate section at the end of the article before the references; in order to thank all of those who contributed to the study but have no weight of authorship. In this section, you can thank all of the sources of support, whether financial, technological or consulting, as well as individual contributions.

Funding sources

The author should mention all funding sources, as well as their influence on the manuscript's conception or decision to submit for publishing.

Awards and previous presentations

The author should mention any award attributed to the study, as well as any presentation of its content prior to the manuscript's submission.

Abbreviations

Do not use abbreviations or acronyms in the title and in the abstract. Non-standard abbreviations should be defined on first use, in full, soon followed by the abbreviation in parentheses, then use the abbreviation only. This is not needed if the abbreviation is a standard unit of measure. Excessive and unnecessary use of acronyms and abbreviations should be avoided. They should be used only when they facilitate readability, reducing the repetition of long technical terms.

Study location

The institutional affiliation of the authors must be mentioned on the front page. The identification of the institution where the study took place should not be explicit in the abstract nor in the abstract place in order to maintain the double anonymity of the review process. In case the location may be important for the understanding of the manuscript, it must be done in terms of generic characterization of the level of differentiation and geographical location of the institution (e.g. "level III university hospital " or "health center in a rural area").

Numbers

Numbers one through nine must be written in length, except when they have decimals or if followed by units of measure. Numbers greater than nine are written in digits, except at

the beginning of a sentence. The point is to be used as a decimal separator. A thousands separator should not be used. Numeric ranges must be separated by "–" (for example, 25-30). A space between a value and the respective unit of measure should be used (for example, 25 -30 mg), except for percentages (for example, 3%) and temperature values (for example, 5ºC), which must be presented without a space.

Units of Measure

Units of measure in the International System of Units should be used. Measures of length, height, weight and volume should be expressed in metric units (meter, kilogram, or liter) or their decimal multiples. Temperatures should be written in degrees Celsius (° C), blood pressure in millimeters of mercury (mmHg), and hemoglobin in g/dL. All measurements should be referred to in the biochemical or hematological metric system according to the International System of Units (SI).

Names of diseases

The names of diseases should be written with lowercase initial letter, except for those that contain toponyms or anthroponyms.

Trade names

Precisely identify all the drugs and products with their generic (international non-proprietary name) name. Use of drug trade names is not recommend, but when the use is unavoidable, the product name must come after the generic name, in parentheses, in lower case, followed by the trademark symbol, in superscript (®).

Species names

The author should write species names in italics (e.g. *Homo sapiens*). The genus and species must be written in detail, both in the title of the manuscript and the first mention in the manuscript. After the first mention, the first letter of the name of the genus followed by the specific name of the species may be used (e.g. *H. sapiens*).

Names of instruments and equipment

Instruments of measurement, diagnosis or computer programs used in the study and mentioned in the manuscript should be presented in a general manner and by its commercial description, followed by the symbol ® and the name of the manufacturer, in parentheses.

Genes, mutations, genotypes and alleles

They must be written in italics. The recommended name should be consulted in a genetic nomenclature database (e.g. HUGO for human genes). Sometimes, it is advisable to indicate the gene synonyms the first time that it appears in the text. Gene prefixes such as those used for oncogenes or cellular localization should be shown in italics (e.g. *v-fes*, *c-MYC*).

Tables and figures

Tables and figures should be numbered in the order in which they are cited in the text with Arabic numerals and identified as a Figure or Table. Each Figure and Table included in the manuscript must be referred to in the text; e.g. An abnormal immune response can be at the source of the symptoms of the disease (Fig. 2). It is associated with the other two lesions (Table 1). Figure: When referred to in the text is abbreviated as Fig., while Table is not abbreviated. In captions, both words are written unabbreviated.

Each Table and Figure should be accompanied by a corresponding succinct and clear caption. Captions should be self-explanatory (without the need to resort to the text).
Graphics should be clear as to whether the information includes individual values, averages or medians, if there is representation of the standard deviation and confidence intervals and sample size (n).
Photographs must include identifiers (arrows and asterisks). Color photographs may be published, if considered essential.
Each Table should be used to show the results, showing individual lists or summarizing data, but it must not constitute a duplication of the results described in the text. It must be accompanied by a short but clear and informative title. The units of measurement used should be indicated (in parentheses below the heading of each category) and the numbers must be reduced to decimals of clinical significance.
Footnotes should contain information relevant to specific cells of the table; use the following symbols in order, as needed: *, †, ‡, §, ||, ¶, **, ††, ‡‡.
If patient photographs are used, they must not be identifiable, or their pictures must be accompanied by written permission for use.
The color illustrations are reproduced at no extra cost.
General principles:

- Number the illustrations according to their sequence in the text.
- Provide the captions of illustrations separately.
- Scale the illustrations to near the desired dimensions of the published version.
- Send each illustration in a separate file.

Inclusion of the previously published figures and/or tables requires the authorization of the copyright holder (author or editor).
The submission must be made separately from the text in accordance with the instructions in the platform.
The figure files must be provided in high resolution, 800 dpi for graphics and 300 dpi for photographs. The color illustrations are published at no extra cost.
Image files should be delivered in one of the following formats:

- JPEG (.jpg)
- Portable Document Format (.pdf)
- PowerPoint (.ppt)
- TIFF (.tif)
- Excel (.pptx)

Multimedia Files

The multimedia files must be sent in a separate file with the manuscript. The multimedia material must follow the quality standards of production for publication with no need of any modification or editing. Acceptable files include: MPEG, AVI or QuickTime formats.

Appendices

Appendices should be used to submit long or detailed surveys, extensive mathematical calculations and/or item lists. They should be placed after the reference list, if necessary, with captions. Long appendices, such as algorithms, protocols and research will be published online only; the URL will be provided in the printed manuscript where the attachment is quoted.
If more than one appendix is present, they should be identified as A, B, etc. Formulas and equations in appendices must be numbered separately: Eq. (A.1), Eq. (A.2), etc.; the next appendix should be named, Eq. (B.1) and so on. Similarly, for tables and figures, they should be named: Table A. 1; Fig. A. 1, etc.

Style

The APP follows AMA Manual of Style (10th Edition).