SYSTEMATIC REVIEW ARTICLE

Effects of Risperidone in Autistic Children and Young Adults: A Systematic Review and Meta-Analysis

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Abstract: There are several studies investigating the effects of risperidone on autism, but many of these studies are contradictory or inconclusive. This systematic review and meta-analysis investigated the effects of risperidone on five domains of the Aberrant Behaviour Checklist (ABC) scale on Autism Spectrum Disorder (ASD), as well as weight gain and waist circumference. The protocol for the present systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO). For this study, we analysed articles (2,459), selecting them according to the PICOS strategy (Population, Intervention, Comparison, Outcome, Study design). Although risperidone is effective for the treatment of lethargy and inadequate speech, concerns about the association between weight gain, waist circumference and risperidone require a need for evaluation of the risk-benefit ratio in its use. There was a significant association between weight gain, waist circumference and risperidone. In conclusion, it was possible to suggest the efficacy of risperidone for the treatment of lethargy and inadequate speech. Finally, we emphasize that the risk-benefit in its use should be evaluated (Protocol number CRD42019122316).

1. INTRODUCTION

Characterised as a neuronal disorder that appears in early childhood, Autism Spectrum Disorder (ASD) compromises some aspects of the development of sociability and language in children and adolescents. To these, we can add restricted and repetitive patterns of behaviour [1, 2], as well as they can be associated with other comorbidities, including anxiety, intellectual disability, epilepsy, aggression, sleep disorders and gastrointestinal problems [3]. According to the current Diagnostic and Statistical Manual of Mental Disorders (DSM-5) definition, the term ASD encompasses all previous classifications of autism [Autistic Disorder, Asperger Syndrome, Disintegrative Childhood Disorder and Invasive Developmental Disorder - Not Otherwise Specified (PDD-NOS)] [4].

ASD has complex aetiology, which is associated with genetics, environment and neurobiology. Several diagnoses were prescribed with the help of questionnaires that describe clinical pictures of patients with particular characteristics.

Behaviour can be assessed by behavioural scales such as the Aberrant Behaviour Checklist (ABC scale) [5, 6]. ABC scale was originally developed to evaluate the efficacy of the psychotropic medication and has been used in behavioural and psychiatric research on children and adults because of its high reliability and validity. The ABC scale is sensitive to both pharmacological and psychosocial treatment effects, and can differentiate between behavioral phenotypes in people with neurodevelopmental disorders [7].

Although little is known about the multiple factors involved in the treatment of ASD, the drugs used are always directed at symptomatic treatment. Several classes are prescribed, especially antipsychotics; however, there are still ongoing discussions about their effectiveness and side effects in ASD [8].

Risperidone is a Second Generation Antipsychotics (SGA), which was initially developed for the treatment of schizophrenia. Since 2006, its use has been approved by the Food and Drug Administration (FDA) for the treatment of irritability associated with autistic disorder. Risperidone is intended to reduce symptoms, such as aggression, and rapid mood swings. Studies report a significant improvement in symptoms associated with autism when risperidone is ad-

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ministered as compared to a placebo. It was possible to observe an improvement of 43% in the mean change in irritability [9-11].

After more than a decade, the adverse effects of risperidone in patients with ASD are still unclear. Its association with the weight gain and development of metabolic syndrome has been well discussed in the scientific world, leading to a fear of its use [12]. Obesity is a common disorder and is associated with several medical complications that may manifest in insulin resistance and metabolic syndrome [12-14]. In addition, inadequate weight gain and metabolic disturbances may lead to Type 2 Diabetes Mellitus [15-17].

There are several studies investigating the efficacy of risperidone, which constitutes a considerable body of evidence to determine its effectiveness in ASD. However, many of these studies are contradictory or inconclusive, especially regarding its efficacy in the treatment of inadequate speech and lethargy [6, 10]. To answer these questions, some authors have performed systematic reviews and meta-analyses. Sharma and Shaw [2] addressed the efficacy of risperidone in treating maladjusted behaviours, such as irritability and aggressiveness. Almandil *et al*., [18] evaluated weight gain and other metabolic effects of Second General Antipsychotics (SGAs), and the authors observed significant weight gain due to the use of SGAs. However, there were limitations regarding the number and duration of studies. Sochocky and Milin [19] estimated the efficacy of SGAs, without drug-isolated sub-analysis, and showed no real efficacy of risperidone in the treatment of Asperger's syndrome. Fung *et al*., [20] conducted a systematic review and meta-analysis of the use of antipsychotics in the treatment of autism, especially aggressiveness and irritability, not performing medication meta-analysis alone. Furthermore, this study used only the ABC scale total score [20]. Thus, a better understanding of the effects of risperidone on the individual with ASD is necessary, such as a joint evaluation of different outcomes and a review of the quality of existing literature. Some of these studies did not describe the quality analysis of the studies used or showed only poor quality. There was also no analysis of the risk of bias.

In this context, the objectives of this study were to perform a systematic review and meta-analysis of the efficacy of risperidone on ASD assessed by the ABC scale and on weight gain and waist circumference and also evaluate the quality and the risk of bias of the publications by means of standardised tools.

2. METHODS

2.1. Search Strategy

The protocol for the present systematic review and meta-analysis was registered on the International Prospective Register of Systematic Reviews (PROSPERO; https://www.crd.york.ac.uk/PROSPERO, protocol number CRD42019122316). This study was conducted and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. We conducted a search for articles that evaluated the treatment of risperidone in individuals diagnosed with ASD using the databases Scopus, PubMed and Web of Science without any restrictions of date, type of document or language. The dates of the search and the search criteria by databases are described in Supplementary Table **1**. The last search was completed on 04 January 2019. All supplementary materials have been published on Mendeley Data (http://dx.doi.org/10.17632/ktjcf4m58t.2).

2.2. Selection of Relevant Articles

For the study selection, we used the PICOS strategy (Population, Intervention, Comparison, Outcome and Study design):

Population: Individuals with ASD, according to the current DSM-5 definition [4], including males and females of 2 to 17 years old.

Intervention: risperidone therapy.

Comparison: Baseline values were compared with those after risperidone treatment, and/or compared to the placebo group.

Outcome: Risperidone's effect in each or all domains of ASD (irritability, inappropriate speech, hyperactivity, lethargy and stereotypical behaviour), was evaluated by the ABC scale, as well as for weight gain and waist circumference; and *study design*: before-and-after studies regardless of the existence of comparison groups. All reviews, case reports, editorials and studies published in summary form and articles that were inaccessible, even after attempts to contact the corresponding author, were excluded.

2.3. Selection of Studies and Data Extraction

Duplicate studies were excluded using reference managers (Mendeley® and JabRef). The eligibility process was conducted in two separate stages. First, three researchers (AMP, BJMS and BCA) independently screened all non-duplicate articles and excluded non-relevant articles based on the title or abstract. A final list was agreed upon, with discrepancies resolved by a fourth researcher (JMDA). Second, full-text versions of the studies selected from stage 1 screening were downloaded and independently assessed for eligibility by the two researchers. Any discrepancies were resolved by a third researcher.

2.4. Risk of Bias of Included Studies

The quality of the studies was evaluated using the Jadad scale [21]. Articles with a Jadad score lower than 3 were classified as low quality, while those higher than 3 were classified as high quality [21]. In addition, the risk of bias for each reference included in the meta-analysis was assessed using the Cochrane Risk of Bias Tool [22]. Risk of bias domains included selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other biases. The overall bias risk score was the lowest score for any of the criteria

(if any item was scored as high risk of bias, the whole study was scored as high risk of bias; if all items were scored as low risk, the whole study was classified as low risk).

2.5. Statistical Analyses

Analyses were conducted as per protocol data [23]. All analyses were performed with Comprehensive Meta-analysis software, version 2.0.057 (Biostat, Englewood, NJ, USA).

Independent meta-analyses were performed for each one of the five sub-scales of the ABC scale, as well as for weight gain and waist circumference. The results of each of the primary studies were described by subtracting the mean after the treatment from the mean before treatment. Differences in the means of individual studies were pooled to produce the Standard Paired mean difference. In addition, in comparison group studies, differences between pre and post treatment means in the intervention and placebo groups were combined to produce the standardised mean difference. In both cases, the random effects model was applied; except when the number of studies was less than four, in which case the fixed effects model was employed. For each variable submitted to meta-analysis, the studies were separated according to the follow-up time of participants, into short (up to 8 weeks) and long-term follow-up (more than 8 weeks). Evaluations were performed separately for each group.

The heterogeneity in the primary results was analysed using the Q test and the I^2 statistic, which describes the percentage of real dispersion in effect-sizes which is not due to the random error. The possibility of the occurrence of publication bias was analysed through Egger's tests. In all procedures, the significance level was 5%.

3. RESULTS

3.1. Search Strategy

The initial research identified 2,459 articles and 41 were included in the meta-analysis. Fig. **1** reports the PRISMA flowchart detailing the screening process, and Supplementary Table **2** reports the studies discarded after reading the full text, together with the specific reasons for exclusion.

3.2. Characteristics of Studies Included in the Meta-Analysis

Of the 41 studies included in the meta-analysis, only two were recorded on ClinicalTrials.gov [24, 25]. Twenty-four had an open-label design, 2 were cross-sectional, 1 was performed by chart review and the other studies (fourteen – 14) were experimental double-blind studies. In most of the studies, the follow-up time ranged from 8 to 24 weeks, but one study had a follow up time of 72 weeks [26] and another, 84 weeks (Aman *et al*. 2015). The dosage used was established by weight ranges (mg/day) or dose by weight (mg/Kg/day). For all studies, the ABC scale (baseline and endpoint or mean change), weight gain and waist circumference (baseline and endpoint or mean change) were available. The percentage of males in our meta-analysis was 78.28%. The mean age in years was 8.13±2.68 and the range age was 2 to 17 years. The characteristics of the studies are described in Table **1**.

3.3. Results of the Meta-Analysis

3.3.1. Effects of Risperidone on Autistic Behaviour

In this study, the studies were grouped into short- (up to 8 weeks) and long- (after 8 weeks) times of use. As shown in Fig. **2**, risperidone was effective in improving the overall clinical condition of ABC scale of the autistic individual both for short and long-term uses. This was also demonstrated for treating irritability, although in this case the reduction was greater with long-term use (Fig. **3**). In addition, the use of risperidone over short time period reduced irritability, with a large effect over placebo (Fig. **3C**).

Short-term risperidone treatment decreased hyperactivity, inappropriate speech, lethargy and stereotypic behaviour from ASD individuals as compared to baseline values (Figs. **4A**, **5A**, **6A** and **7A**) or to placebo use (Figs. **4C**, **5C**, **6C** and **7C**). Similar results were found for long-term risperidone treatment (Figs. **4B**, **5B**, **6B** and **7B**). The short-term treatment was more effective in reducing inappropriate speech and lethargy than the long-term treatment. On the other hand, for stereotypic behaviour, the greatest effect was achieved in upto eight-week risperidone treatment.

3.3.2. Effects on Weight Gain

The effects of risperidone on weight gain in autistic individuals are described in Fig. **8**. In the meta-analysis of weight gain for long-term risperidone use, contradictory data was observed among the studies found in the literature, since the value was very close to zero. It can be observed that regardless of the time of risperidone use, there was an increase in patients' weight compared to baseline values (Fig. **8A** and **8B**). Similar results were found when the effect of short- and long-term treatment with risperidone on the weight of patients was compared to placebo (Fig. **8C** and **8D**). In addition, it was possible to associate weight gain with an increased waist circumference over long periods of use (Fig. **9**).

3.3.3. Quality of the Reports (Jadad Score)

The score of the quality of evidence for the 41 articles used in this study is presented in Table **1**, with individual analysis by Jadad. The criteria used in the evaluation of these articles were mainly about randomisation and double-blind studies using the Jadad scale, and the data are presented in Supplementary Table **3**. One article [24] had the lowest score (-1) in the Jadad score and 4 presented with a score of zero (0), while 12 presented with the maximum score (5). Among the included studies, 19 presented with high quality, because their Jadad scores were greater than 3 [21].

3.3.4. Risk of Bias

As shown in Table **1**, 19 studies were, overall, considered to have a high risk of bias, while 7 presented an unclear risk. The individual analysis by the Cochrane Risk of Bias Tool is shown in Supplementary Fig. **1**. All articles that were at
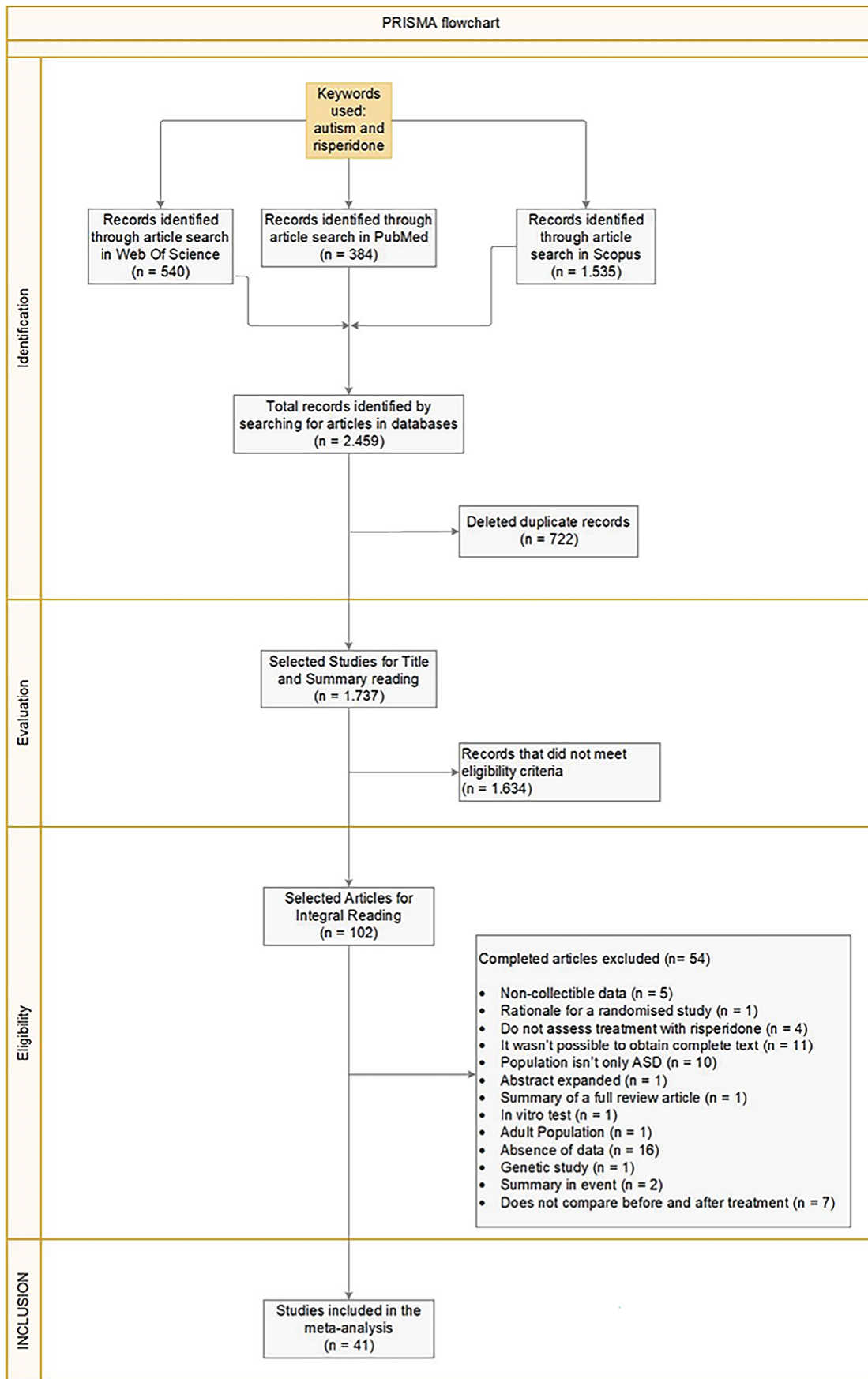
Fig. (1). PRISMA Flowchart reporting the study screening process. ABC Scale: Aberrant Behaviour Checklist scale.

Table 1. **Characteristics of the studies included in this systematic review and meta-analysis.**

Study	Length (Weeks)	Diagnostic Criteria	Population Size	Sample Size	Age[1] (Mean±SD)	Age Range[1]	Men (%)	Quality[2]	Risk of Bias[3]
Rezaei *et al.*, 2018 [28]	12 and 24	DSM-5	34	17	12.41±2.45	—	65	High	Low
Firouzabadi *et al.*, 2017 [29]	8	DSM-5	56	56	6.9±1.1	2.5 a 14	71.4	Low	Some Concerns
Nikvarz *et al.*, 2017 [30]	4 and 8	DSM-IV	34	16	6.56±3.51	4 a 17	66.7	High	Some Concerns
Lamberti *et al.*, 2016 [31]	12 and 24	DSM-5	44	22	7.9±2.3	6 a 13	79.54	Low	High
Scahill *et al.*, 2016 [12]	8, 16 and 24	DSM-IV	97	41	6.9±2.35	4 a 13	84.67	Low	Low
Yoon *et al.*, 2016 [32]	—	—	202	59	8.88±3.70	2 a 20	83.05	High	High
Aman *et al.*, 2015 [27]	21	DSM-IV	84	55	8.82±2.69	—	79.8	High	High
Calarge *et al.*, 2015 [25]	24	DSM-IV	124	49	7.7±2.4	4 a 13	85	High	Some Concerns
	72	DSM-IV	96	96	13.2±2.7	7 a 17	92		
Boon-Yasidhi *et al.*, 2014 [29]	—	DSM-IV	45	45	8.15±2.98	2 a 15	77.77	High	Some Concerns
Choi *et al.*, 2014 [33]	8	DSM-IV	45	45	9.5±4.38	3 a 15	77.77	Low	High
Ghaeli *et al.*, 2014 [34]	8	DSM-IV	15	15	6.5±3.5	4 a 15	66.66	Low	High
Ghanizadeh *et al.*, 2014 [24]	4 and 8	DSM-IV	59	30	9.5±4.6	5 a 15	76.7	High	Low
Wink *et al.*, 2014 [35]	—	DSM-IV	142	72	—	6 a 15	81.69	High	High
Kent *et al.*, 2013 [36]	6	ADI-R	77	50	9±3.1	5 a 17	88	High	Low
Kent *et al.*, 2013[37]	24	DSM-IV ADI-R	56	56	9.2±3.1	5 a 17	89	High	Some Concerns
Arnold *et al.*, 2012 [26]	24 and 72	—	87	36	7.54±2.33	4 a 13	83	High	High
Wei *et al.*, 2011 [38]	8	—	40	40	—	5 a 12	92.5	High	Low
Correia *et al.*, 2010 [39]	1, 3, 6, 12	ADI-R e ADOS	45	45	8.67±4.30	até 18	75.6	High	High
Desousa, 2010 [40]	16	ADI-R e ADOS	40	20	—	5 a 16	—	Low	Some Concerns
Hoekstra *et al.*, 2010 [41]	8	ADI-R	32	32	8.74±2.83	5 a 16	87.5	High	High
Capone *et al.*, 2008 [42]	240	DSM-IV	23	23	7.8±2.6	3 a 13	86.95	Low	High
Gencer *et al.*, 2008 [43]	24	DSM-IV	28	13	10.2±2.8	7 a 17	32.14	High	Some Concerns
Miral *et al.*, 2008 [44]	12	DSM-IV	30	15	10.0±2.7	7 a 17	80	High	Low
Anderson *et al.*, 2007 [45]	8, 6 e 88	DSM-IV	101	49	8.8±2.7	5 a 17	81.18	High	High
Pandina *et al.*, 2007 [46]	8	DSM-IV	55	27	7.4±2.4	5 a 12	78.78	High	Low
Canitano, 2006 [47]	24	DSM-IV	11	11	8.7±2.2	—	63.63	Low	High
Lindsay *et al.*, 2006 [48]	8	DSM-IV	20	20	—	—	—	Low	Low
Luby *et al.*, 2006 [49]	24	DSM-IV	23	11	4.1±0.90	2.5 a 6.0	73.91	Low	Low
Nagaraj *et al.*, 2006 [50]	24	DSM-IV	39	19	5.03±1.70	2 a 9	87.17	Low	Low
Aman *et al.*, 2005 [51]	4, 8, 12 and 16	DSM-IV	101	49	8.8±2.7	5 a 17	81.18	High	High
McCracken, 2005 [52]	16	DSM-IV	63	63	8.6±2.8	5 a 17	77.8	Low	Low
Troost *et al.*, 2005 [53]	24	DSM-IV	24	12	4±3.4	5 a 17	91.6	Low	Low
Gagliano *et al.*, 2004 [54]	12 and 24	DSM-IV	20	20	6.0±2.4	3 a 10	70	High	High
Martín *et al.*, 2004 [55]	24	—	63	63	8.6±2.9	5 a 17	—	Low	High
Shea *et al.*, 2004 [56]	8	DSM-IV	79	25]	7.6±2.3	5 a 12	77.21	High	Low
Arnold *et al.*, 2003 [57]	4 and 8	—	87	44	8.8	5 a 17	—	High	High
McCracken *et al.*, 2002 [58]	8	DSM IV	101	49	8.8±2.7	5 a 17	81.18	High	Low
Masi *et al.*, 2001 [59]	16	—	24	24	4.6±0.66	3.6 a 6.6	87.5	Low	High
Masi *et al.*, 2001 [60]	16	DSM-IV	10	10	4.9±0.8	3.9 a 6.5	70	Low	High
Zuddas *et al.*, 2000 [61]	1, 3 and 6	DSM-IV	11	11	12.3±3.8	7 a 17	72.72	Low	High
Nicolson *et al.*, 1998 [62]	12	DSM-IV	10	10	—	4.5 a 10.8	—	Low	High

DSM – Diagnostic and Statistical Manual of Mental Disorders; ADI-R – Autistic Diagnostic Interview Revised; ADOS – Autism Diagnostic Observation Schedule. [1]Age in years. [2]The Quality of study was evaluated with Jadad Score. [3]Risk of Bias was evaluated by Cochrane Risk of Bias Tool.
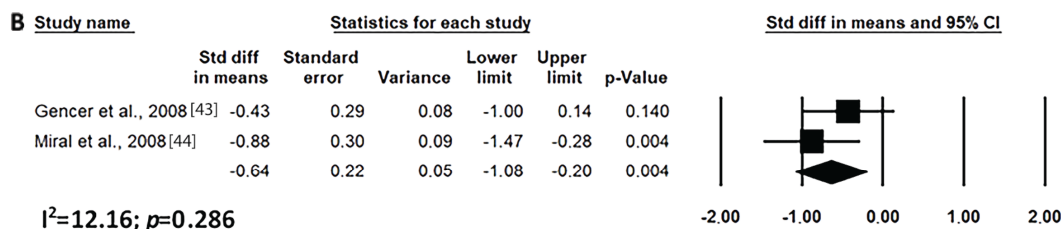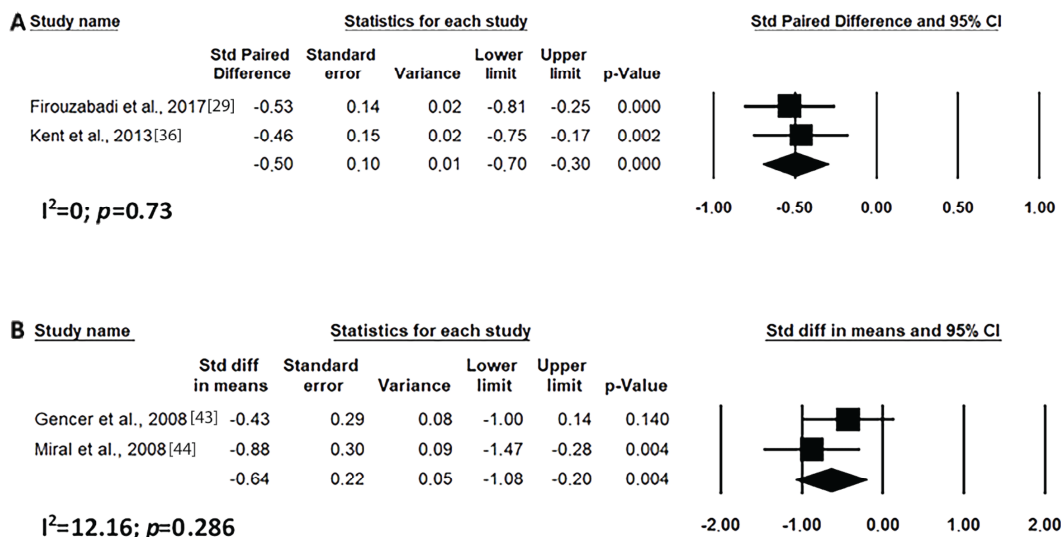
Fig. (2). Results of the meta-analysis of the evaluation of ABC scale total score on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks). Confidence Interval (CI), Heterogeneity (I^2) and heterogeneity's *p*-value (*p*).
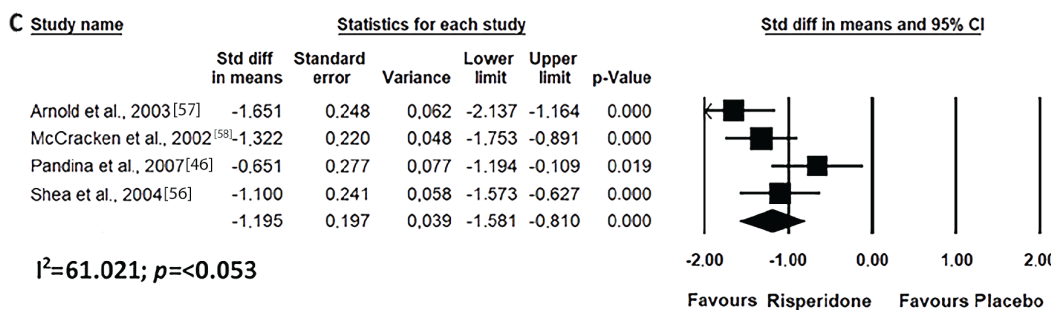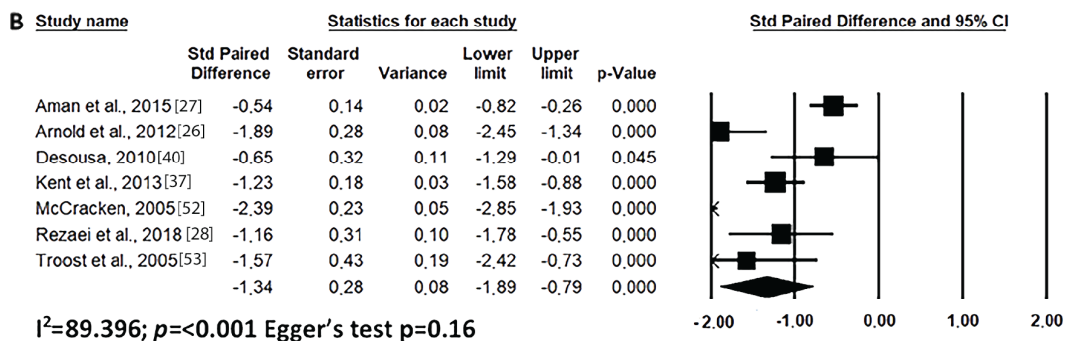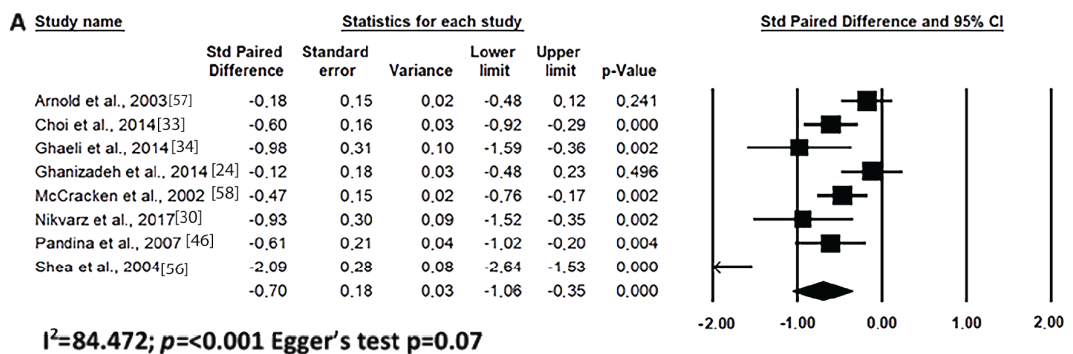

Fig. (3). Results of the meta-analysis of the evaluation of irritability in the ABC scale on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo. Confidence Interval (CI), Heterogeneity (I^2) and heterogeneity's *p*-value (*p*).
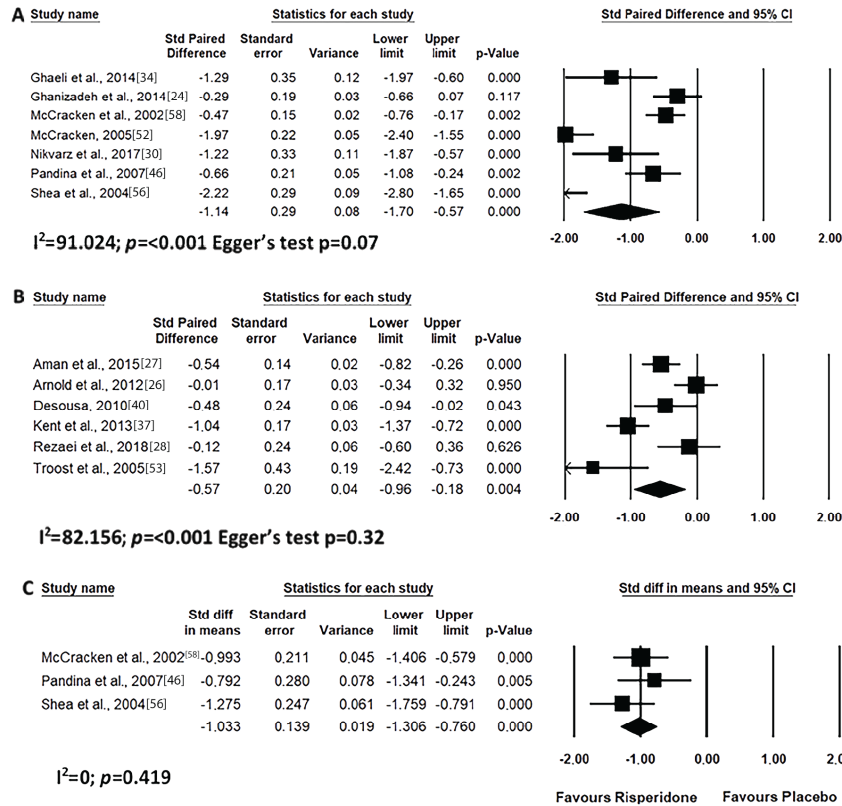
Fig. (4). Results of the meta-analysis of the evaluation of hyperactivity in the ABC scale on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo. Confidence Interval (CI), Heterogeneity (I2) and heterogeneity's p-value (p).
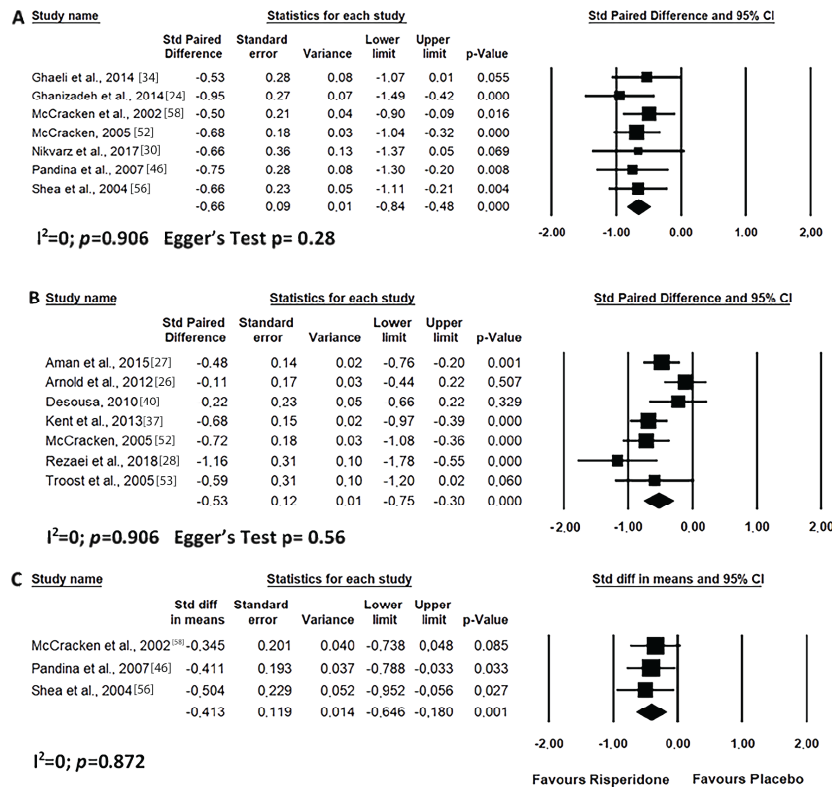

Fig. (5). Results of the meta-analysis of the evaluation of inappropriate speech in the ABC scale on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo. Confidence Interval (CI), Heterogeneity (I2) and heterogeneity's p-value (p).
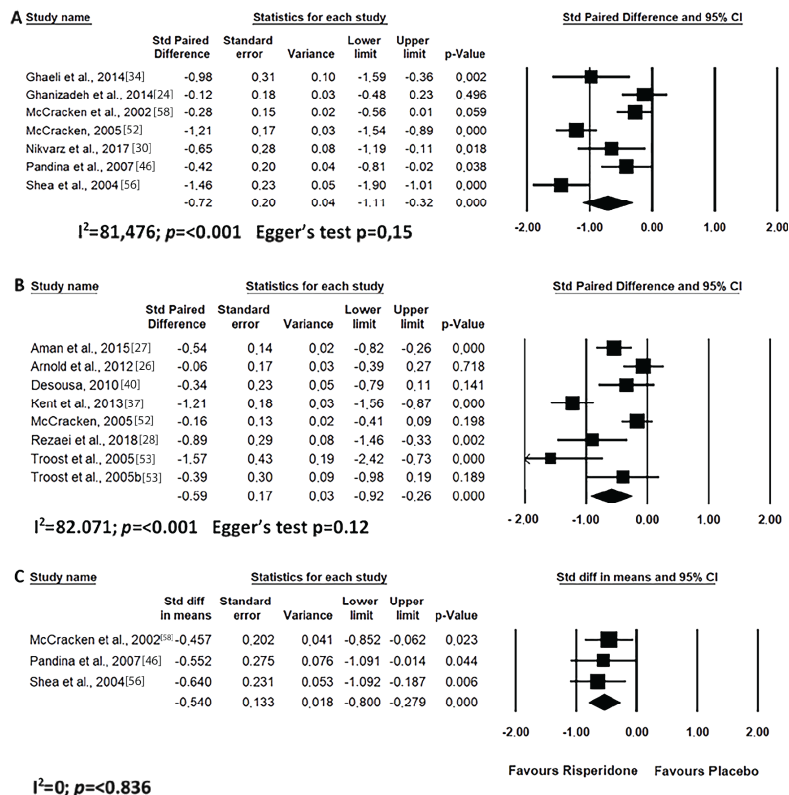
Fig. (6). Results of the meta-analysis of the evaluation of lethargy (social withdrawal) in the ABC scale on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo. Confidence Interval (CI), Heterogeneity (I2) and heterogeneity's p-value (p).
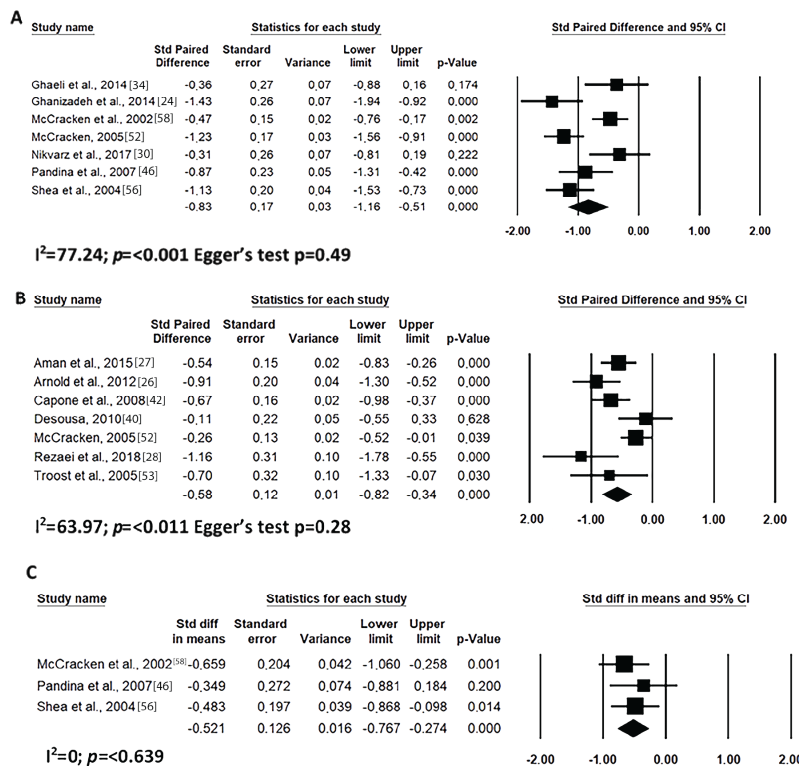

Fig. (7). Results of the meta-analysis of the evaluation of stereotypic behaviour in the ABC scale on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo. Confidence Interval (CI), Heterogeneity (I^2) and heterogeneity's *p*-value (*p*).
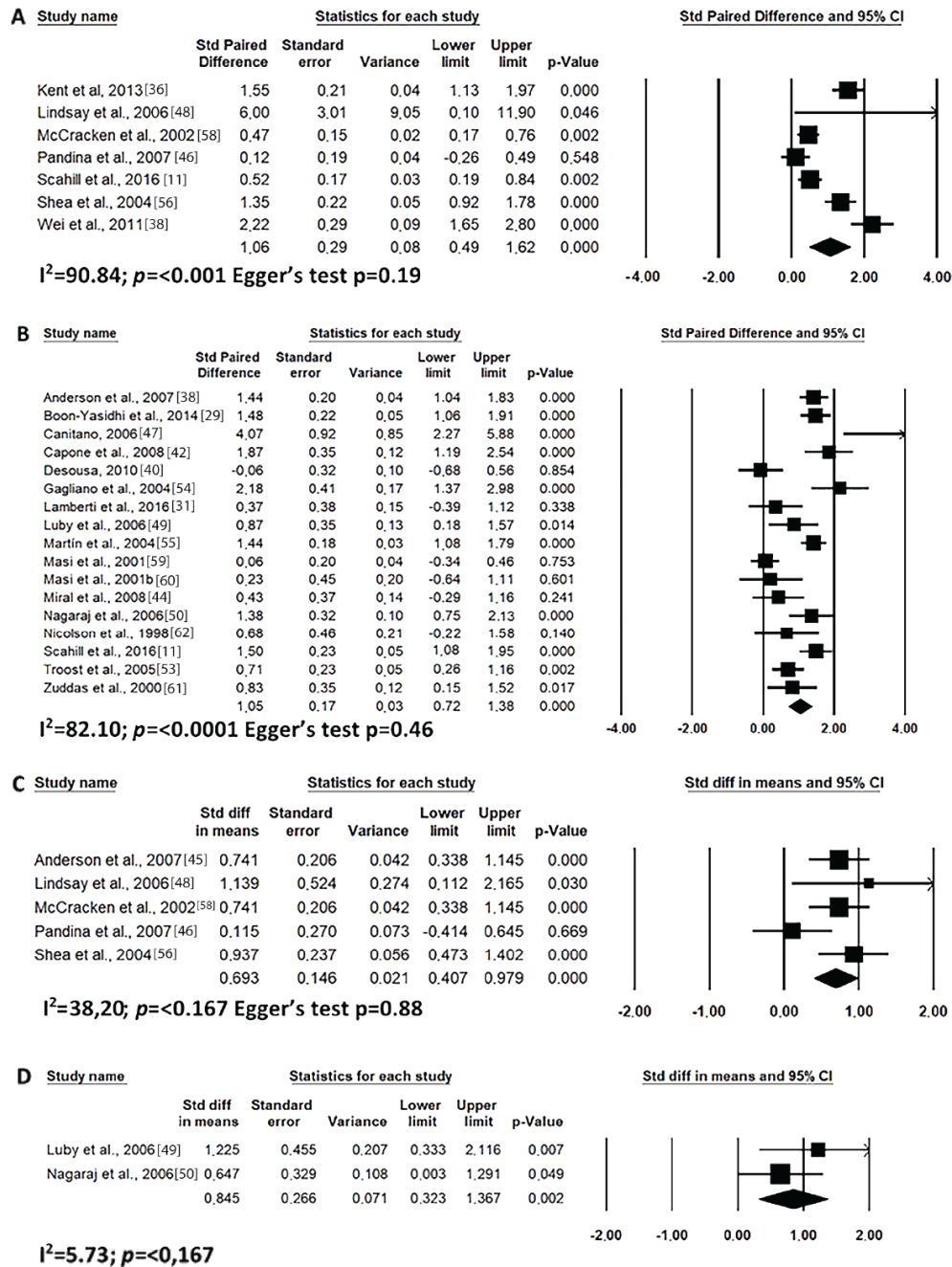
Fig. (8). Results of the meta-analysis of the evaluation of weight gain on treatment with risperidone: (**A**) short-term (until up 8 weeks); (**B**) long-term (after 8 weeks); (**C**) versus placebo in short-term (until up 8 weeks); (**D**) versus placebo in long-term (after 8 weeks). Confidence Interval (CI), Heterogeneity (I^2) and heterogeneity's *p*-value (*p*).
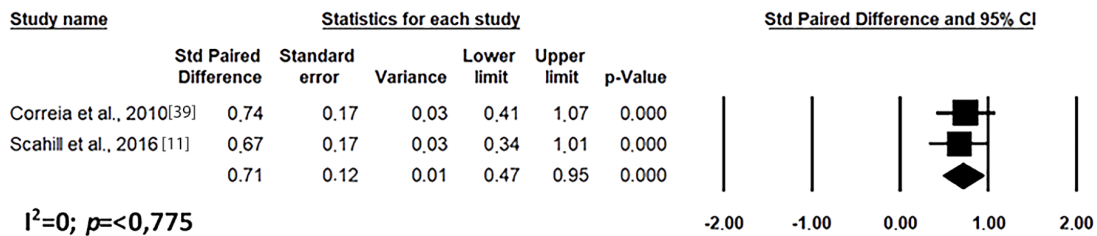

Fig. (9). Results of the meta-analysis of the evaluation of waist circumference on treatment with risperidone in long-term (after 8 weeks). Confidence Interval (CI), Heterogeneity (I^2) and heterogeneity's *p*-value (*p*).

a high risk of bias were due to the randomisation process (Supplementary Fig. **2**). The quantitative evaluation of publication bias, as measured by Egger's intercept (Egger's test), was not significant in any meta-analysis performed.

4. DISCUSSION

The mechanism of action of risperidone is related to its affinity with dopamine D_2 receptor and the 5-HT_2A serotonin receptor, in addition to binding to α_1 e α_2 adrenergic and to H_1-histaminergic receptors. Risperidone binds by blocking D_2 e 5-HT_2A receptors and is also an antagonist of adrenergic α_1 e α_2 and histamine H_1 receptors. The active metabolite of risperidone, 9-OH-risperidone (called paliperidone), has the advantage of binding to a lesser extent to H_1 histaminergic receptors. These dopamine and serotonin receptors antagonisms are believed to be responsible for the beneficial effects on ASD and for reducing extrapyramidal symptoms. The effects of risperidone on aggression, irritability stereotypes, tantrums and restlessness can be attributed to dopamine antagonism. The effects on communication skills, restricted activity patterns and the ability to respond emotionally and socially (such as detachment, inattention, relationships or eye contact) can be considered as a result of serotonin antagonism [50, 63-65].

Although it has been suggested that appetite stimulation is probably the main mechanism of body weight gain induced by antipsychotic drugs [66], female juvenile rats treated with risperidone also have a decrease in the locomotor activity, in addition to increase in the food intake and body weight gain [67]. These effects are accompanied by elevated mRNA expression of hypothalamic H1 receptor, neuropeptide Y (NPY) and agouti-related peptide (AgRP), without affecting the hypothalamic proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART) mRNA expression [67]. Therefore, these results suggested that risperidone increases the appetite and body weight gain in juveniles *via* regulation of the hypothalamic H_1 receptor, NPY and AgRP pathways, as well as by reducing activity [67]. A study suggests that the effect of antipsychotic drugs is strongly correlated with their affinity for H1 and alpha1 receptors [66]. In fact, H_1 receptors knockout mice had hyperphagia, decreased expression of uncoupling protein-1 mRNA and gradually developed mature-onset obesity [68] and intracerebroventricular application of an H_1 receptor agonist decreased the food intake, while hypothalamic H1 receptor antagonism increased the food intake [69, 70]. On the other hand, the role of α_1 receptors on food intake is not clear, because pretreatment of rodents with phentolamine, a non seletive α-adrenergic antagonist, induces a decrease in the food intake induced by electrical stimulation of the lateral hypothalamic area [71]. Studies suggest that D_2 and 5-HT_2A receptors can also contribute to these changes in the energy homeostasis [72-75]. Striatal D_2 receptor availability is reduced in very obese individuals in proportion to their body mass index [75]. Striatal D_2 receptors are downregulated in obese rats, in addition, lentivirus-mediated knockdown of striatal D2 receptors rapidly accelerates the development of addiction-like reward deficits and the onset of compulsive-like food seeking in rats with extended access to palatable high-fat food [74]. In rats, it was demonstrated

that 5HT_2A, but surprisingly not 5HT_2C, receptor is critical for weight-loss, anorexia and fat mass reduction induced by central GLP-1R activation [73]. Central 5HT_2A receptors are also required for peripherally injected liraglutide to reduce feeding and weight [73].

Until the present study, there has been no systematic review or meta-analysis that addresses the ASD in individuals assessed on the five domains of the ABC scale. The ABC scale is one of the few scales developed to measure psychiatric symptoms and behavioural disorders exhibited by individuals in five domains: irritability, agitations, lethargy/social withdrawal, hyperactivity and inadequate speech [76].

The studies presented high values of heterogeneity for some variables; however, the direction of the associations was consistent for all variables of the ABC scale. Furthermore, the risk of publication bias (Egger's test) was not significant (p>0.05), favouring the reliability of the data. In some variables, it was not possible to evaluate the publication bias due to the insufficient number of studies that evaluated the effect of risperidone in each autism domain. In addition, the included studies do not describe factors that may cause heterogeneity and cause bias. Thus, differences were attributed to the clinical and epidemiological specificities of ASD and to the different contexts in which the studies were performed [77, 78]. The heterogeneity may have been caused by the psychometric data of the included studies. According to Doebler *et al*. [79], in diagnostic meta-analyses, the sensitivities and specificities observed may vary between studies and there may be heterogeneities. Even in randomised trials for therapeutic intervention, there may be heterogeneity because the randomisation was not focused on the hypothesis in question, but on the intervention. Moreover, heterogeneity can be caused by the way the tests were evaluated [80].

In our meta-analysis, the general ABC indicated that prolonged use of risperidone is essential for decreasing the clinical signs of ASD [31, 81]. This data is of great importance for the medical field, since risperidone is prescribed, for the most part, for patients with aggression, self-mutilation and/or excessive irritation and not for treatment of stereotypy, inadequate speech or lethargy [10]. To date, there is no specific drug for ASD; however, risperidone could be this drug according to our observations. Although the improvement in all domains of ABC, including lethargy and speech development, gave rise to the improvement of the total score, irritability was the most apparent one.

The improvement in the total score of the ABC scale is related to an improvement of the individual in all domains evaluated, including lethargy and speech development. However, apparently, the domain that most contributed to the improvement of symptoms was irritability. The behaviour most associated with ASD, and generates more worries for relatives, is aggressiveness. In their daily lives, this behaviour can lead to a reduction of the quality of life, a greater level of stress and less availability of educational and social support. According to our meta-analysis, it is suggested that risperidone has greater efficacy in the treatment of irritability and hyperactivity, both in the short and long term. However, we emphasize that the risk-benefit in its use should be evaluated.

ASD has been known to present with several layers, with each individual presenting with a particular characteristic or group of characteristics. Among these variations, there is hyperactivity associated with autism. The restless and agitated child will have much less capacity for social interaction and eye contact, for example. Through our meta-analysis, it can be concluded that the use of risperidone for a short period of time generates a greater benefit for hyperactive behaviour. The literature has no consensus on the effectiveness of long-term treatment [26, 82], but our meta-analysis was able to demonstrate that risperidone is effective in treating hyperactivity for short and long time periods, as well as demonstrating a large effect as compared to placebo. Lamperti *et al.*, [31] highlighted that aripiprazole is a more effective drug than risperidone in improving inattention in ASD patients, but concludes that risperidone acts more significantly on the hyperkinetic symptoms of Asperger's Syndrome. Concomitantly, Ghanizadeh *et al.*, [24] have shown that both aripiprazole and risperidone lower all ABC subscale scores, including irritability, agitation, lethargy, social withdrawal, stereotypical behaviour, hyperactivity, nonconformity and inadequate speech.

Of great clinical importance, two new outcomes are presented in this study. Firstly, risperidone was apparently efficacious for the treatment of inappropriate speech and lethargy in individuals with ASD. Secondly, it was possible to infer that risperidone benefits speech structure and development, as well as social interaction/lethargy for short and long-term treatment as compared to baseline, and for short-time treatment, as compared to placebo. Speech is a method of underpinning social interaction. ASD causes a deviation in the child's speech development, leading him/her to regress in the organisation and social intention of speech, or when he/she speaks, the child does not make it socially significant, not in accordance with the context, and can also present echolalia, inversions of jargon and pronouns. To date, there has been no consensus in the literature on the efficacy of risperidone for improving speech [26, 34, 40, 46, 53, 83]; however, this meta-analysis has shown that the use of risperidone leads to symptom improvement.

The data found here corroborate with those found by the study by Nikvarz *et al.* [30] where an improvement in the speech of children with ASD was observed following short-term treatment with risperidone. An improvement in communication over a short term of 4 weeks was also mentioned. Rezaei *et al.*, [28] observed that risperidone reduces behavioural problems, but also suggested that there be behavioural interventions to further increase drug efficacy and the child's readiness in the development of speech and language skills.

One of the most significant and worrying behavioural axes in ASD is stereotypy. Stereotyping is a behaviour characterised by repetitive actions and of great interest of the individual, without there being an objective or end purpose. Although some studies report ineffectiveness [40, 46, 84], risperidone is able to reduce short- and long-term ASD stereotypies. Although not a preponderant factor in clinical evaluations, lethargy always showed a decrease when risperidone was used [37, 53]. Our meta-analysis was in disagreement with the literature, as it demonstrated efficacy in lethargy symptoms of the ABC scale, independent of treatment time. Furthermore, there was no consensus on the efficacy of risperidone over placebo [83]. However, it has been possible to evaluate only the short time effect of risperidone compared to placebo, with the meta-analysis showing an effect in favour of risperidone. Pandina *et al.*, [46] demonstrated significant improvements in the ABC "lethargy/social withdrawal" subscale after 8 weeks of risperidone treatment. In contrast, Ghaeli *et al.*, [34] reported a significant improvement in social interactions, based on changes in the ABC "lethargy / social retraction" subscale, after 4 weeks, indicating the efficacy of risperidone in the treatment of autism [34]. These results are consistent with the results obtained by McCracken *et al.* [58], who demonstrated a significant reduction in the placebo-controlled risperidone assay in the stereotype, hyperactivity and irritability subscales of the ABC scale with 8 weeks of study.

Our meta-analysis revealed that risperidone has the ability to induce weight gain in individuals with ASD. This finding is consistent with previously published studies of risperidone use. In a 12-week prospective study evaluating weight gain in adolescents, the average weight gain was 3.9 kg from baseline to the endpoint [85]. Our data showed a greater weight gain than reported by Fung *et al.* [20] (3.78 kg *vs* 1.6 kg, respectively). Regarding the problem of differentiating the weight gain related to the growth of the medication effect, the average annual weight gain of the age group and the time of use must be taken into consideration.

Our study suggested that risperidone treatment increases waist circumference. Fat accumulation in the abdominal region has been described as the type of obesity that poses the greatest health risk to individuals. The incidence of diabetes, atherosclerosis, gout, urinary stones and sudden cardiac death is high in obese people, but one aspect of adiposity that draws attention is the regional distribution of body fat, which is often associated with the abdominal region [86].

The metabolic effects of risperidone should be considered when planning the treatment strategy for these patients. Baseline measurement of weight, height and waist circumference and any monitored changes should be conducted. It has been recommended that plasma glucose, lipid and prolactin be monitored and individualised follow-up conducted [87]. Strategies for managing drug-induced weight gain include therapeutic approaches such as lifestyle changes and pharmaceutical intervention. However, prescribing medications to overcome adverse effects should be avoided whenever possible.

Continuation of treatment with risperidone is essential for the improvement of the symptoms and quality of life of autistic patients. Troost *et al.*, [53] observed that discontinuation of the drug causes a 60% increase in irritability scores on the ABC scale. Another study demonstrated that discontinuation caused an increase in the hyperactivity factor and irritability [84]. Furthermore, Zuddas *et al.*, [61] observed that risperidone contributed to the improvement of sleep disorder in individuals and that the discontinuation of risperidone caused its return.

Risperidone has a large inter-individual variation in pharmacokinetic parameters, such as plasma drug concentration, oral clearances or drug half-life, which can be attributed

to several factors, such as age, body weight, medication and genetic variations [88]. Pharmacogenetic studies have focused on the polymorphism of CYP enzymes, with CYP2D6 being the most studied. The CYP2D6 gene is extremely polymorphic with more than 90 known allele variants. The polymorphism of the CYP2D6 gene is responsible for the inter-individual and interracial differences in drug metabolism [89]. The genetic variability in the pharmacodynamics of individuals with identical concentrations of risperidone in plasma and tissue can still vary extensively in their responses. Genetic variants in molecular targets directly involved in the action of the drug may be associated with the response to the drug. Variants of these genes are more likely to have a small effect with several loci involved, each contributing to the phenotype to a small and variable degree. So far, most dopaminergic and serotonergic receptors have been studied as predictors of response to psychotropic drug therapy [90, 91]. We know that genetic factors can influence the efficacy and safety of risperidone, however, due to the protocol established for the search and selection of articles, it was not possible to perform a meta-analysis, considering the pharmacogenetics between inter-individuals and interracial individuals with autism.

Some methodological limitations exist with our analyses. These include the limited number of relevant studies in some domains of ABC scale and waist circumference. This highlights the need for larger and longer trials, using a control group to establish the efficacy of risperidone in improvement in all ASD domains, as well as the association of weight gain and waist circumference.

A limitation of this meta-analysis comes from the methodological limitations of the included studies; 46% of the included studies were assessed to have a high risk of bias in the quality analysis with the Risk of Bias Cochrane Tool, particularly in the domains of randomisation and blinding. We recommend that future studies include a flowchart with information about the method of recruitment and allocation of patients and blinding of patients and researchers, in addition to other details related to the process, to improve replicability and better inform readers about the potential bias.

CONCLUSION

The reviewed studies indicated that long-term use is not necessary to obtain an improvement in the symptoms of ASD, since it is possible to observe this with 8 weeks of treatment. Apparently, the continuous use of the medicine promotes a better evolution of the clinical condition. Although risperidone has the strongest evidence of reduced irritability and hyperactivity in individuals with ASD, it also was effective in reducing all behavioural axes of ASD. In this study, it was possible to suggest the efficacy of risperidone for the treatment of lethargy and inadequate speech, since there was previously insufficient evidence. However, we emphasize that the risk-benefit in its use should be evaluated.

This paper demonstrated that there is a significant association between weight gain and risperidone administration. Weight gain may be associated with fat accumulation, especially in the abdominal region. The few data available did not allow us to draw definitive conclusions because there are few studies that have evaluated weight gain associated with fat accumulation. Finally, we emphasise that risperidone can be used for a long period.

In summary, this systematic review of interventional studies with meta-analysis suggests that risperidone treatment improves the clinical condition and the quality of life of the autistic individual.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

SUPPLEMENTARY MATERIAL

Supplementary material is available on the publisher's website along with the published article.

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