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Breaking the Stigma: A Systematic Review of Antipsychotic Efficacy in Children and Adolescents with Behavioral Disorders

Nuno Manuel Sanfins

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica - Psiquiatria

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Breaking the Stigma: A Systematic Review of Antipsychotic Efficacy in Children and Adolescents with Behavioral Disorders

ORIENTADOR

Dr. Jacinto Azevedo

COORIENTADOR (se aplicável)

ASSINALE APENAS UMA DAS OPÇÕES:

É AUTORIZADA A REPRODUÇÃO INTEGRAL DESTE TRABALHO APENAS PARA EFEITOS DE INVESTIGAÇÃO, MEDIANTE DECLARAÇÃO ESCRITA DO INTERESSADO, QUE A TAL SE COMPROMETE.	☐
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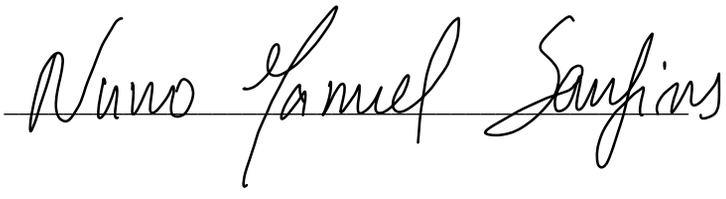
Assinatura conforme cartão de identificação: 

UC Dissertação - Declaração de Transparência relativamente à utilização de ferramentas de chatbot generativo baseadas em large language models

Eu, Nuno Samuel P. M. C. Sanfins, abaixo assinado, nº mecanográfico 201907276, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro que:

☒ Não procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* para nenhuma das tarefas no contexto do meu trabalho de Dissertação ou Monografia

☐ Procedi à utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia, encontrando-se todas as interacções (*prompts* e respostas) transcritas em anexo bem como a indicação das aplicações utilizadas.

Neste sentido, confirmo que a eventual utilização de ferramentas de *chatbox* generativo baseadas em *large language models* no contexto do meu trabalho de Dissertação ou Monografia foi exclusivamente descrita na sequência de *prompts* e respostas transcritos em anexo e nas aplicações indicadas.

Faculdade de Medicina da Universidade do Porto, 09/03/2025

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Systematic Review

Breaking the Stigma: A Systematic Review of Antipsychotic Efficacy in Children and Adolescents with Behavioral Disorders

Nuno Sanfins [1,*], Pedro Andrade [1] and Jacinto Azevedo [2]

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Abstract: Background/Objectives: Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are important behavior disorders in children and adolescents, often linked with long-term psychosocial problems. Antipsychotics are frequently prescribed to manage severe symptoms and improve behavior, but their efficacy in this population is still unclear and a lot of physicians are remittent in prescribing them. This systematic review aims to assess the effectiveness of antipsychotic treatment in reducing symptoms associated with ODD, and CD in children and adolescents. **Methods:** Studies that investigated how effective antipsychotic treatments are for children and teens diagnosed with Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) were reviewed. Only studies that met a few main criteria were included: participants were between 5 and 18 years old with an ODD or CD diagnosis; the treatment could be any type of antipsychotic – whether typical or atypical; the accepted study designs were randomized controlled trials (RCTs), cohort studies, systematic reviews with meta-analysis or observational studies. The outcomes of interest were reductions in aggressive or defiant behaviors, improvements in social functioning, and the occurrence of any adverse effects from the medications. There was no restriction on the language of publication, and studies published from 2000 to 2024 were considered. Studies that focused only on non-antipsychotic drugs or behavioral therapies, as well as case reports, expert opinions, and non-peer-reviewed articles did not meet the inclusion criteria. **Results:** The review consisted of 13 studies. The results suggest that some antipsychotic drugs—especially atypical antipsychotics—can substantially reduce aggressive and defiant behavior in children and adolescents who have oppositional defiant disorder (ODD) or conduct disorder (CD). Common side effects of these medications include weight gain, sedation, and metabolic problems. **Conclusions:** Although adverse effects are a concern, the potential of these medications to manage disruptive behaviors should not be overlooked. When used in combination with behavioral therapy and other forms of treatment, antipsychotics can markedly improve the outcomes of these very difficult-to-treat patients. Clinicians who treat these patients need to consider antipsychotics as a serious option. If they don't, they are denying their patients medication that could greatly benefit them.

Keywords: Oppositional Defiant Disorder, Conduct Disorder, antipsychotic treatment, atypical antipsychotics, behavioral disorders, disruptive behavior, systematic review

Academic Editor: Firstname Lastname

Received: date
Revised: date
Accepted: date
Published: date

Citation: To be added by editorial staff during production.

1. Introduction

Conduct Disorder (CD) and Oppositional Defiant Disorder (ODD) are disruptive behavior disorders that occur in children and adolescents. They are among the most common mental disorders affecting young people(1). These two disorders appear to be closely related, and children and adolescents diagnosed with them frequently exhibit aggressive, defiant, and antisocial behaviors(2). These behaviors can lead to many significant challenges in a young person's life, including academic problems, trouble with family and friends, and an increased risk of serious antisocial behavior and criminal activity in the

future(3). The treatment of these disorders is multifaceted, with behavioral therapies, family interventions, and medications being cornerstone approaches(4). Among pharmacological treatments, antipsychotic medications have been widely used, particularly for individuals with more severe presentations of aggression and defiance(5).

The debate is ongoing over how well disruptive behaviors of children with oppositional defiant disorder (ODD) and conduct disorder (CD) respond to treatment with antipsychotic medications(6). Atypical antipsychotic drugs (e.g., risperidone, aripiprazole), which have been more recently developed, do show some promise in reducing aggression and improving overall behavior, at least in the short term(7). But what does long-term use of these drugs in children portend for both mental and physical health? Concerns have been raised about potential side effects including (but not limited to) weight gain, sedation, and disturbances of metabolism(8).

Given the rather tenuous evidence and the potential dangers linked to antipsychotic treatment, it is important to work out whether these medications are effective for something like oppositional defiant disorder (ODD) or conduct disorder (CD). The purpose of this systematic review is to work out if antipsychotic drugs do (or do not) reduce disruptive behaviors. A secondary goal is to assess their corresponding side effects.

2. Materials and Methods

This systematic review was conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency, rigor, and methodological quality. The review protocol was registered with PROSPERO (ID: CRD420251009839).

The review encompassed studies that assessed the effectiveness of antipsychotic medications when given to children and adolescents with ODD and CD. Eligible studies had to meet a set of criteria:

1. Population: The studies had to involve participants who were children or adolescents (aged 5 to 18) with a diagnosis of ODD or CD.
2. Intervention: The studies had to evaluate the administration of any type of antipsychotic medication, whether typical or atypical.
3. Study Design: Only RCTs, cohort studies, systematic reviews with meta-analysis and observational studies were included.
4. Outcome Measures: The studies had to report some measures that indicated how well the medication was working.
5. Publication Language: The studies could be published in any language.
6. Date: The studies could have any date of publication from 2000 to 2024.

Studies were excluded based on the following criteria:

7. Population: Studies where ODD and/or CD were not the primary diagnosis. Studies where individuals had low IQ (<70) or comorbid autism spectrum disorder (ASD).
8. Intervention: Studies that focused solely on non-antipsychotic pharmacological interventions or solely on behavioral therapies.

A thorough literature search was performed to find studies that assess the effectiveness of antipsychotic drugs in treating youths diagnosed with ODD and CD. Electronic Database Search The subsequent electronic databases were investigated:

- PubMed/MEDLINE
- PsycINFO
- Cochrane Library
- EMBASE
- Web of Science

The terms of the search combined keywords and medical subject headings (MeSH) that pertained to the population, interventions, and outcomes of interest. The precise search string that was used was:

("Oppositional Defiant Disorder" OR "Conduct Disorder")
AND

("antipsychotic treatment" OR "atypical antipsychotics" OR "Risperidone" OR "Aripiprazole")

AND

("children" OR "adolescents")

AND

("aggression reduction" OR "behavioral improvement")

To find more studies that possibly fell outside the database searches, a tool called Connected Papers was used. Connected Papers is a visual tool that maps the relationships between scientific papers based on co-citation and bibliographic coupling. This tool helped uncover related studies by visualizing networks of research papers connected to the key articles already identified. The following steps were taken using Connected Papers:

- Seminal papers identified from the initial search were input into the tool.
- The network of connected papers was explored to find additional relevant studies.
- The titles and abstracts of these connected papers were screened for inclusion.

The reference lists of all included studies and pertinent systematic reviews were manually searched to find additional studies that met our inclusion criteria.

All identified studies underwent a two-step screening process. To start, the titles and abstracts of all articles were reviewed to determine relevance to the inclusion and exclusion criteria. Articles that passed this first test were then reviewed in full—two reviewers working independently decided on each article's eligibility. Where the reviewers' judgments didn't agree, the two first discussed the case. If they couldn't come to a consensus, a third reviewer was brought in to break the tie.

A standardized form was used to extract the data. The data extracted included:

- The study characteristics (author, year, country, study design).
- The characteristics of the participants (age, gender, diagnostic criteria, sample size).
- The intervention details (type of antipsychotic, dosage, treatment duration).
- The outcome measures (changes in behavior, social functioning, adverse effects).
- The results (statistical findings, effect sizes, significance levels).

Two reviewers did the data extraction independently. Discrepancies were resolved by consensus.

In this review, the risk of bias was assessed at the study level.

For experimental studies, particularly randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB) tool was employed, as it is highly recommended for assessing methodological rigor in such studies.

For systematic reviews of observational studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was applied. Alternatively, the quality assessment criteria provided by the National Institutes of Health (NIH) were considered, depending on the study design and characteristics.

Only studies classified as having a low risk of bias were included in this review. Studies with a high or unclear risk of bias were excluded to ensure the reliability of the findings.

3. Results

Of the 57 studies retrieved for detailed evaluation, 13 were fit for inclusion in the present study.

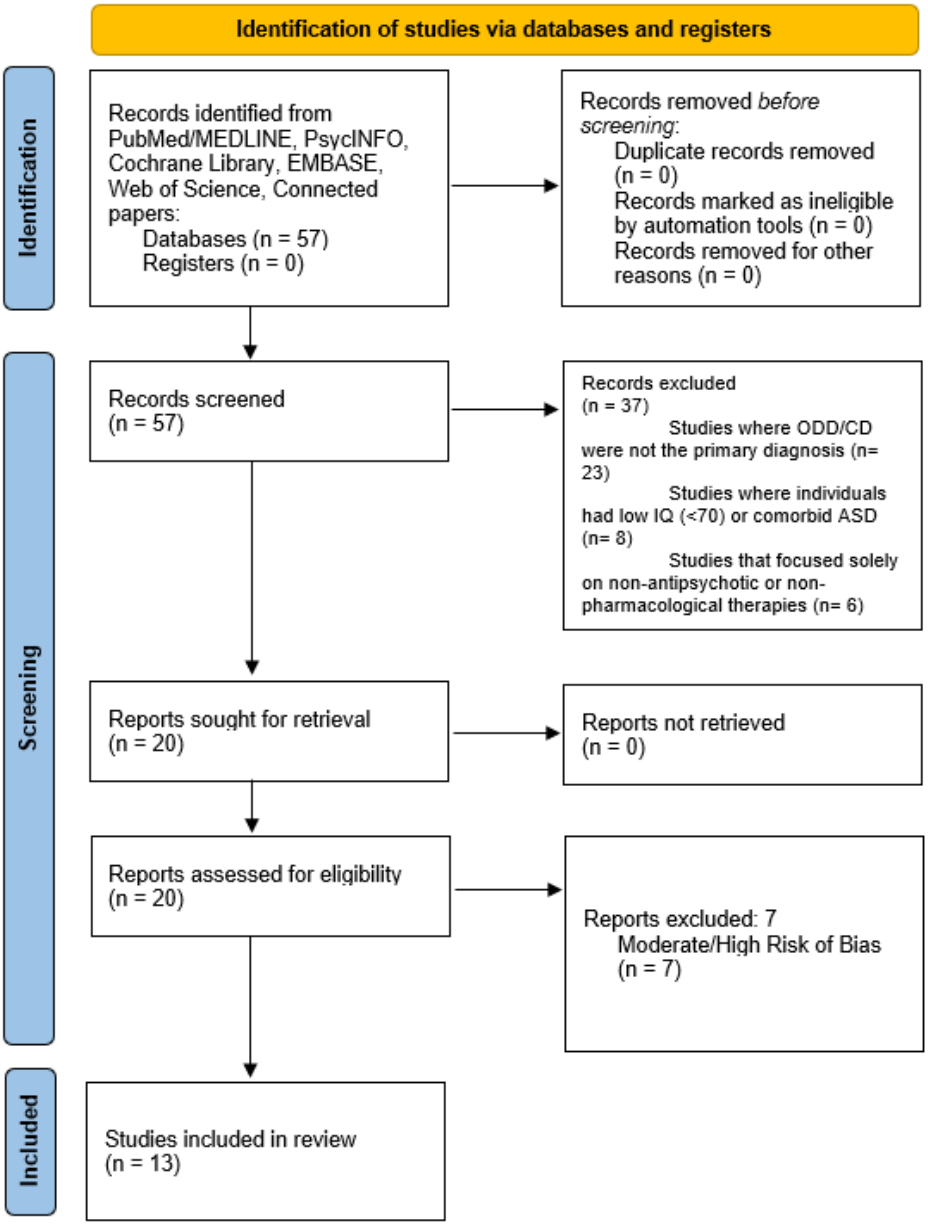

Figure 1. Paper Selection Flowchart.

3.1. General characteristics of the included studies

A total of 13 studies, 4 were RCTs, 2 were longitudinal, 3 open label, 1 retrospective, 3 systematic reviews with meta-analyses.

The psychopharmacologic therapies investigated predominantly involved atypical antipsychotic medications, particularly risperidone, aripiprazole, and olanzapine. Some trials looked at typical antipsychotics such as haloperidol and chlorpromazine; however, most examined the new atypical agents.

Table 1. Characteristics of the included studies.

Author and Year	Type of Study	Population	Intervention	Outcome Measurement Tool	Result
Juárez-Treviño et al., 2019(9)	16 week-long Randomized, double-blind, controlled trial	Twenty-four children with conduct disorder aged 6 to 16 years	Patients were randomized to receive either 0.3 mg/kg of clozapine or 0.025 mg/kg of risperidone on the first visit. Twelve subjects received clozapine and twelve received risperidone. Doses were increased to 0.6 mg/kg for clozapine and 0.05 mg/kg of risperidone during visit 2 (week 1) and were maintained until completion of the trial. The route of administration was by mouth.	The Modified Overt Aggression Scale score was used as the primary outcome of the study. Secondary outcomes were Child Behavior Checklist (CBCL) externalization (CBCL-E) and internalization factors; Aggression, Hyperactivity and Delinquency subscales of CBCL-E, Child Global Assessment Scale (CGAS), Barnes Akathisia Rating Scale, and Simpson-Angus Scale	Both antipsychotics were similarly effective in the primary outcome and in most of the secondary ones. Clozapine was more effective in CBCL-E, the delinquency subscale and the CGAS scores than risperidone (p =0.039, 0.010, and 0.021).
Loy et al., 2017(10)	Systematic Review with meta-analyses	10 Randomized controlled trials (2000-2014) of atypical antipsychotics versus placebo in children and youths aged up to and including 18 years, with a diagnosis of disruptive behavior disorders, including comorbid ADHD, involving a total of 896 children and youths	Atypical antipsychotics versus placebo	Aberrant Behavior Checklist (ABC) – Irritability subscale; the Overt Aggression Scale – Modified (OAS-M) Scale and the Antisocial Behavior Scale (ABS);	Using the Aberrant Behavior Checklist (ABC) – Irritability subscale: youths treated with risperidone show reduced aggression compared to youths treated with placebo (MD −6.49, 95% confidence interval (CI) −8.79 to −4.19; low-quality evidence). When combining the ABS Reactive subscale and the OAS-M, the SMD was −1.30 in favor of risperidone (95% CI −2.21 to −0.40, moderate-quality evidence) in comparison to placebo. Youths treated with risperidone only (138 participants) gained 2.37 kilograms (kg) more

					(95% CI 0.26 to 4.49; moderate-quality evidence) than those on placebo
Gadow et al., 2016(11)	52 week-long Longitudinal study	Children with co-occurring attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorder, and serious physical aggression who participated in a prospective, longitudinal study that began with a controlled, 9-week clinical trial comparing the relative efficacy of parent training + stimulant medication + placebo (Basic; *n*=84) versus parent training + stimulant + risperidone (Augmented; *n*=84).	Parent training + stimulant medication + placebo versus parent training + stimulant + risperidone	Parent-reported behavioral outcome and Clinical Global Impressions (CGI) severity score	Both randomized groups improved baseline to follow-up, but the three primary parent-reported behavioral outcomes showed no significant between-group differences. Exploratory analyses indicated Augmented (65%) was more likely (p=.02) to have a Clinical Global Impressions (CGI) severity score of 1-3 (normal to mildly ill) at follow-up than Basic (42%). Augmented had elevated prolactin levels, and Basic decreased in weight over time.
Findling et al., 2000(12)	10 week-long Randomized, double-blind, controlled trial	20 subjects who were outpatients who met DSM-IV criteria for conduct disorder as a primary diagnosis. Other inclusion criteria included being between ag~ 5 and 15 yean (inclusive), having at least a moderate degree of overall symptom severity as based on the Clinical Global Impression (CGI) Scale	Ten youths were randomly assigned to receive placebo, and 10 youths were randomly assigned to receive risperidone. Medications could be increased at weekly intervals during the first 6 weeks of the study from an initial dose of 0.25 mg or 0.50 mg each morning, depending on patient Wt. Patients weighing less than 50 kg had a maximum total daily dose of risperidone of 1.5 mg. Patients weighing 50 kg or greater had a maximum total daily dose of risperidone of 3.0 mg	Rating of Aggression Against People and Property Scale (RAAPP), Clinical Global Impressions (CGI) severity score	RAAP score difference from baseline: week 10 -0.16 (0.54) -1.65 (0.40) p=.03; CGI-S difference from baseline: week 10 -0.08 (0.66) -2.58 (0.49) p=.003
Reyes et al., 2006(13)	6 month-long Randomized, double-blind, controlled trial	Patients with disruptive behavior disorder (5-17 years of age and a range of intellect) who had responded to risperidone treatment over 12 weeks were randomly assigned to 6 months of double-blind treatment with either risperidone or placebo; Treatment was initiated in 527 patients, with 335 randomly	Maintenance versus withdrawal of risperidone treatment	The primary efficacy measure was time to symptom recurrence, defined as sustained deterioration on either the Clinical Global Impression severity rating (/2 points) or the conduct problem subscale of the	Time to symptom recurrence was significantly longer in patients who continued risperidone treatment than in those switched to placebo. Symptom recurrence in 25% of patients occurred after 119 days with risperidone and 37 days with placebo. Weight increased over the initial 12 weeks of treatment (mean weight z score change=0.2, SD=2.7, N=511), after which it plateaued.

		assigned to a double-blind maintenance condition		Nisonger Child Behavior Rating Form (/7 points).	
Masi et al., 2006(14)	Retrospective study	Clinical records of the first 23 adolescents diagnosed as having a CD, diagnosed with a clinical interview (K-SADS), either pure or with comorbid diagnoses, and treated with olanzapine	All patients were started on a dose of 2.5 mg olanzapine at bedtime, with weekly increase of 2.5–5 mg/day. Drug titration end point (maximum 20 mg/day) was determined by clinical response, age, weight and side effects. During olanzapine treatment adjunctive medications doses were held constant.	Modified Overt Aggression Scale (MOAS), Clinical Global Impression-Improvement (CGI-I) and Children Global Assessment Scale (CGAS)	Based on both an improvement of at least 50% at MOAS and a score 1 or 2 at CGI-I, 14 out of 23 patients (60.9%) were classified as responders at the end of the follow-up. Significant improvement at the last observation was found in MOAS ($P < 0.001$) and CGAS ($P < 0.001$) scores. Mean weight gain at the end of the follow-up was 4.6 +/- 3 kg.
Findling et al., 2006(15)	8 week-long, open-label outpatient trial	Seventeen children of ages 6 to 12 years, with a primary diagnosis of CD	Patients weighing less than 35 kg began treatment with a single morning dose of 25 mg quetiapine. Patients weighing more than 35 kg began treatment with 25 mg quetiapine in the morning and 25 mg quetiapine 1 hour before bedtime. Each patient's study medication dose was increased until a total daily dose of approximately 3mg/kg/day was reached by the end of week 1. This dose was then maintained until the end of week 2. Patients treated with more than 25 mg quetiapine per day were dozed twice daily. If doses were not equally divisible by two, then the higher dose was administered in the morning unless side effects precluded this strategy. After completion of the end of week 2 of PK sampling, patients could then have their medication increased to either a total daily dose of 6 mg/kg/day or 750 mg/day (whichever was lower). Dose increases from 25 mg/week to 50 mg/week were permitted up to the end of week 7.	Rating of Aggression Against People and/or Property Scale (RAAPPS), Nisonger Child Behavior Rating Form (NCBRF), and the Conners Parent Rating Scale (CPRS-48).	At the end of week 8, the **CPRS T scores** showed the following changes compared to baseline: The Conduct score decreased from 92.1 (7.5) at baseline to 70.2 (21.1), with a highly significant improvement ($p \leq .001$). The Learning score dropped from 87.1 (9.3) to 74.5 (16.7), with a highly significant improvement ($p \leq .001$). Psychosomatic scores decreased from 56.0 (13.7) to 51.4 (13.0), although this change was not significant. Impulse scores improved from 75.1 (5.6) to 66.1 (14.3), with a significant improvement ($p \leq .01$). Anxiety scores showed a slight decrease from 50.0 (10.5) to 48.2 (10.4), with no significant difference. Hyperactivity scores dropped from 87.8 (6.7) to 73.8 (17.2), showing a highly significant improvement ($p \leq .001$). For the **NCBRF subscales** at the end of week 8: The Compliant score increased from 4.7 (2.5) to 5.7 (3.7). Adaptive scores rose from 3.1 (1.6) to 4.6 (2.2). Conduct scores improved significantly, dropping from 37.3 (5.1) to 25.4 (14.4) ($p \leq .001$). Insecure scores decreased from 20.1 (6.3) to 12.8 (8.2), with a highly significant improvement (p

					≤ .001). Hyperactive scores reduced from 20.9 (3.4) to 15.8 (6.4), showing improvement. Self-injury scores decreased from 3.2 (2.6) to 2.5 (3.0). Self-isolated scores improved from 7.5 (4.2) to 5.1 (4.4), with a significant improvement (p ≤ .01). Sensitive scores decreased from 8.4 (3.4) to 5.7 (3.6), showing a highly significant improvement (p ≤ .001). Fifteen (88.2%) of the 17 dosed patients experienced an adverse event during the study. The most frequently reported side effects included the following: fatigue (n = 11), nasal congestion (n = 8), headache (n = 7), nausea (n = 4), sedation (n = 4), increased appetite (n = 4), vomiting (n = 3), stomach pain (n = 3), irritability (n = 2), and fever (n = 2). The overall median increase in weight in these 12 patients was 2.3 kg (p <.001).
Kronenberger et al., 2007(16)	12 week-long prospective, open-label study	24 adolescents (aged 12–16 years) with a diagnosis of ADHD-combined type and disruptive behavior disorder (n 4 with oppositional-defiant disorder; n 20 with conduct disorder)	Subjects received 3 weeks of OROS methylphenidate monotherapy titrated to 54 mg/day and then received 9 weeks of adjunctive quetiapine (given b.i.d., with a maximum dose of 600 mg/day) for those subjects who remained symptomatic	Rating of Aggression Against People and Property (RAAPP), Modified Overt Aggression Scale (MOAS). The MOAS, Clinical Global Impressions–Severity (CGI-S)	For the RAAPP (Rating of Aggression Against People and Property), the baseline score was 4.3 (0.4), which decreased to 3.2 (0.6) after MPH monotherapy and further to 2.0 (0.8) after the addition of quetiapine. Paired t-tests indicated statistically significant reductions, with a t-value of 10.5 (p < .001) from baseline to MPH and 5.8 (p < .001) from MPH to MPH + quetiapine. In the MOAS (Modified Overt Aggression Scale Total Score), baseline scores were 229.0 (194.3). After MPH treatment, scores dropped to 73.7 (57.9), and after quetiapine was added, scores decreased further to 26.3 (33.0). Paired t-tests showed significant reductions, with a t-value of 4.4 (p < .001) from baseline to MPH and 3.6 (p < .01) from MPH to MPH + quetiapine. The CGI-S (Clinical Global Impressions—Severity) score began at 5.3 (0.6) at baseline,

					decreased to 4.1 (0.8) with MPH, and further to 3.2 (0.9) after quetiapine was added. Paired t-tests indicated significant improvements, with a t-value of 6.8 ($p < .001$) from baseline to MPH and 6.5 ($p < .001$) from MPH to MPH + quetiapine.
Findling et al., 2009(17)	2 week-long, open label, three-center study	12 children (6–12 years) and 11 adolescents (13–17 years) with CD and a score of 2–3 on the Rating of Aggression Against People and/or Property (RAAPP)	Initially, the protocol used the following dosing of aripiprazole: subjects <25 kg, 2 mg=day; subjects 25–50 kg, 5 mg=day; subjects >50–70 kg, 10 mg=day; and subjects >70 kg, 15 mg=day. Due to vomiting and sedation, this schedule was revised to: <25 kg, 1 mg=day; 25–50 kg, 2 mg=day; >50–70 kg, 5 mg=day; and >70 kg, 10 mg=day.	Rating of Aggression Against People and=or Property (RAAPP), Clinical Global Impressions–Severity (CGI-S) s	On day 1, the mean RAAPP scores were 3.00 ± 0.63 for children and 2.64 ± 0.50 for adolescents. By day 14, both groups had a median RAAPP score of 2, which remained stable through month 36 (children: $p<0.05p < 0.05$p<0.05; adolescents: $p<0.05p < 0.05$p<0.05). The average decrease in RAAPP scores from baseline to month 36 was 1.00 ± 1.00 for children and 0.75 ± 0.96 for adolescents. Children's mean CGI-S score at baseline was 4.27 ± 1.01 (moderately ill), decreasing to 3 (mildly ill) by day 14 ($p<0.05p < 0.05$p<0.05) and to 2 (borderline ill) by month 36 ($p<0.01p < 0.01$p<0.01). Adolescents showed a similar improvement, with the median CGI-S score decreasing from 4 at baseline to 2 by day 14 ($p<0.01p < 0.01$p<0.01) and remaining at this level through month 36. Additionally, by day 14, 63.6% of children and 45.5% of adolescents were rated as "much" or "very much improved" on the CGI-I score, with this percentage increasing to 66.7% of children and 100% of adolescents by month 36 ($p<0.01p < 0.01$p<0.01 for both age groups).
Gadow et al., 2014(18)	9 week-long longitudinal study	168 children between 6 and 12 years of age with evidence of serious physical aggression as defined by parent-report to a blinded clinician of Level 3 or greater Overt Aggression Scale–M (OAS-M) rating	Open trial of parent training and stimulant medication for 3 weeks. Participants failing to show optimal clinical response were randomly assigned to Basic or Augmented therapy for an additional 6 weeks.	Overt Aggression Scale–M (OAS-M), Clinical Global Impression [CGI]	Compared with Basic therapy, children receiving Augmented therapy experienced greater reduction in parent-rated ODD severity (p=.02, Cohen's d=0.27) and peer aggression (p=. 02, Cohen's d=0.32), but not ADHD or CD symptoms. Fewer children receiving Augmented

		of assault against objects (broke several things in anger), others (assault resulting in serious physical injury to another), or self (cut, bruised, burned self but only superficially;) and severe disruptive behavior (≥ 90th percentile NCBRF D-Total); DSM-IV criteria for any subtype of ADHD plus ODD (n=124) or ODD and CD (n=44); and a rating of at least moderately ill by a blinded clinician (severity score ≥4 Clinical Global Impression [CGI])	At the completion of the baseline assessment, the primary caregiver started parent training, which continued throughout the 9-week intervention, and all children began an open trial of stimulant monotherapy, usually Osmotic Release Oral System (OROS) methylphenidate. If unable to tolerate medication or unable to swallow pills, an alternative stimulant was offered. During the first 3 weeks, the primary clinician adjusted stimulant to achieve an optimal therapeutic response defined as a CGI-Improvement score of 1 by a blinded clinician and a parent-rated NCBRF D-Total score <15 (within 0.5 SD of the normative mean). If participants did not show a sufficient clinical response at Week 3, or if they showed deterioration at Week 4 through Week 6 (i.e., dropped below a blinded CGI of 1 or had a NCBRF D-Total >15), the second agent (risperidone or placebo) was added to the treatment package. The mean Week 9 dose of methylphenidate was 45±15 mg/day (Basic) and 46±17 mg/day (Augmented) (p=.88). For the second medication, mean doses were 1.9±0.7 mg/day (placebo) and 1.7+0.6 mg/day (risperidone) (p=.07).		(16%) than Basic (40%) therapy were rated by their parents as impaired by ODD symptoms at Week 9/endpoint (p=.008). Teacher ratings indicated greater reduction in ADHD severity (p=.02, Cohen's d =0.61) with Augmented therapy, but not for ODD or CD symptoms or peer aggression.
Pringsheim et al., 2015(6)	Systematic review with meta-analysis	11 RCTs of antipsychotics (8 studied risperidone, 1 studied quetiapine, 1 studied haloperidol, and 1 studied thioridazine); Most studies included youth with ODD or CD, with and without ADHD.	Antipsychotics vs placebo	Nisonger Child Behavior Rating Form, the Aberrant Behavior Checklist, the CGI scale, the Child Aggression Scale, the Rating of Aggression Against People or Property Scale, the Conners Parent–Teacher	The SMD between risperidone and placebo for disruptive behavior and aggression was 0.60 (95% CI 0.31 to 0.89; I2 = 0%, P < 0.001); CGI-S scores decreased from 5.9 at randomization to 3.4 at end point with quetiapine, compared with a decrease from 5.5 to 5.0 with placebo (P = 0.007); Haloperidol was significantly different from placebo on measures of hostility and aggression (magnitude of effect not reported).

				Questionnaire, and the OAS	small difference between thioridazine and placebo on the Conduct Problems subscale of the Conners Teacher Questionnaire (magnitude of effect not reported).
Shafiq et al., 2018(19)	Systematic review with meta-analysis	3 RCTs which compare risperidone to placebo for oppositional behavior or conduct problems in children and youth with average IQ	Risperidone was administered at a dose of 0.5 – 4.0 mg per day	NCBRF typical IQ Disruptive behavior total, Rating of Aggression Against People and Property (RAAPP) and Conners' Parent Rating Scale Revised – Long Version (CPRS-L)	The cumulative results of the three trials demonstrated a SMD of −0.64 (95% CI −0.89 to −0.40, I 2 = 0%, P < 0.00001) (see Figure 4) for the risperidone group compared to the control group after 8 –10 weeks of treatment. Jahangard et al.(20) observed a weight gain of 4.2 kg for the risperidone group compared to 0.74 kg for the placebo group. Aman et al. (21)reported a 1.8 kg weight gain in the risperidone group compared to −1.2 kg in the placebo group
Connor et al., 2008(22)	7-week, randomized, double-blind, placebo-controlled pilot study	Subjects had to be between the ages of 12 and 17 years inclusive and to meet criteria for a primary psychiatric diagnosis of conduct disorder. In addition, patients had to have a moderate-to-severe degree of aggressive behavior as documented by an overt aggression scale score>=25 and at least moderate severity of symptoms as documented by a Clinical Global Impressions–Severity (CGI-S) score>=4 at screen. Nine youths were randomly assigned to receive quetiapine, and 10 youths were randomly assigned to receive placebo.	Quetiapine and placebo were administered on a twice-daily schedule, morning and evening. Dosing began at 25 mg twice daily (b.i.d.) and could be increased by a maximum of 25 mg bid every 3 days through day 14 of the protocol. Titration was flexible and could be slowed or reduced if adverse events became problematic in the first two study weeks. By day 14, all subjects achieved a daily dose of at least 200 mg quetiapine (100 mg b.i.d.). On day 14, dosing continued to be flexible based on clinician assessed benefits and patient tolerability. After day 14, dosing could be increased by 50 mg b.i.d. to a daily total of 800 mg (400 mg b.i.d.) at the discretion of the study physician. Dose was titrated until parent report of meaningful clinical benefit or problematic side effects occurred. Total dose was reached at the end of week 5. The dose became fixed for the final 2 weeks of the study.	CGI-S scale and CGI-I scales; OAS rated weekly by parents	At study end point, 8 of the 9 subjects randomized to quetiapine were judged improved (CGII<=2), compared to only 1 of 10 subjects randomized to placebo (p=0.0006).

3.2. Narrative Analysis

This systematic review encompassed 13 studies that assessed the efficacy and safety of atypical antipsychotics and various other interventions for managing conduct disorder (CD) and oppositional defiant disorder (ODD) in children and adolescents. A summary of key findings follows.

3.2.1. Atypical Antipsychotics: Efficacy

- Juárez-Treviño et al. (2019)(9): Clozapine and risperidone were both found to be effective in significantly reducing aggression in children with conduct disorder. Clozapine showed some superior effects on externalizing symptoms and delinquency (p-values: 0.039, 0.010, 0.021).
- Pringsheim et al. (2015)(6): This meta-analysis of 11 RCTs (8 on risperidone, 1 each on quetiapine, haloperidol, and thioridazine) found that atypical antipsychotics significantly reduced disruptive behavior in children with ODD or CD, with an SMD of 0.60 (95% CI 0.31 to 0.89).
- Loy et al. (2017)(10): A systematic review that found atypical antipsychotics to be effective—particularly, risperidone—in reducing irritability and aggression, using tools such as the Aberrant Behavior Checklist to measure outcomes.
- Findling et al. (2006)(15): Quetiapine produced some significant improvements in aggression and behavioral symptoms among children diagnosed with conduct disorder. Of note was the significant weight gain across subjects that occurred during the trial (4.6 ± 3.9 kg).
- A randomized, double-blind, placebo-controlled study by Connor et al. (2008)(22) found that compared to placebo, quetiapine significantly improved aggressive behaviors, with 8 of 9 subjects on quetiapine showing clinical improvement ($p = 0.0006$).
- Shafiq et al. (2018)(19): A systematic review comparing risperidone to placebo in children with conduct problems showed significant reductions in disruptive behavior and aggression, with an SMD of -0.64 (95% CI -0.89 to -0.40). Weight gain was noted in the risperidone group.

3.2.2. Comparative Effectiveness

- Gadow et al. (2016)(11): A longitudinal study comparing parent training combined with stimulant plus placebo versus stimulant plus risperidone showed both interventions were effective, but the addition of risperidone did not provide significant extra benefit.
- Reyes et al. (2006)(23): Significantly, the maintenance treatment with risperidone delayed the time to recurrence of symptoms compared to placebo. This underscores the continued treatment imperative for maintained control of aggression and, presumably, for improved psychosocial functioning.
- Findling et al. (2009)(17): Compared to placebo, aripiprazole reduced aggression scores, but side effects, including sedation, necessitated dose adjustments during the study.
- Masi et al. (2006)(14): Efficacy was demonstrated with olanzapine in reducing aggression, with 60.9% of patients showing positive response to treatment; however, weight gain was noted.

3.2.3. Augmentation and Combination Therapy

- Gadow et al. (2014)(18): A 9-week longitudinal study comparing basic stimulant treatment to augmented therapy (stimulant plus risperidone) showed that augmentation provided greater reductions in aggression with peers but had no significant effect on ADHD or ODD symptoms.
- Kronenberger et al. (2007)(16): After treating the initial stage with methylphenidate, quetiapine was prescribed for the remaining aggressive symptoms in adolescents.

This combination resulted in a significant ($p < 0.01$) decrease in aggression scores compared to previous ranks in which only methylphenidate was administered.

3.2.4. Dose-Dependent Efficacy and Long-Term Management

- Findling et al. (2000)(12) carried out a randomized, double-blind, placebo-controlled trial with youths having conduct disorder. They found that risperidone was better than placebo in reducing aggression as measured by the Rating of Aggression Against People and Property (RAAPP).
- Gadow et al. (2014)(18): A study involving 168 children with severe disruptive behavior reported significant improvements in aggression using parent training combined with stimulant medication. The study underscored the importance of individualized dosing to optimize treatment effects.

3.2.5. Safety and Adverse Effects

- Reyes et al. (2006)(13): Found that maintenance treatment with risperidone delayed the return of symptoms but was linked to weight gain and other adverse effects. The return of symptoms was significantly delayed in patients who continued risperidone.
- Connor et al. (2008)(22): Children treated with quetiapine experienced significant weight gain compared to those receiving a placebo. Although it was very effective for managing aggression, quetiapine had some very concerning side effects—profound sedation and an increased appetite.
- Shafiq et al. (2018)(19): Common adverse effects among children treated with risperidone included weight gain and sedation. However, the authors found risperidone to have significant efficacy in reducing conduct problems in children.

3.2.6. Summary of Effectiveness

In general, atypical antipsychotics, like risperidone, olanzapine, and quetiapine, worked well to reduce aggression and improve behavior in children and adolescents with disruptive behavior disorders. These drugs were effective when used alone (monotherapy) and when combined with other medications (augmentation), especially stimulant medications when children were diagnosed with a disorder like ADHD. Combining these drugs with antipsychotics often led to better outcomes for children and adolescents with serious behavior problems.

3.2.7. Safety Considerations

Adverse events were consistently reported, most notably weight gain, sedation, and metabolic changes. Reported weight changes were of special concern, with self-reported weight changes from baseline averaging a gain of about 4 kg across RCTs. Weight gain carries with it a host of negative health consequences and therefore should be taken into account when prescribing these drugs, despite the clear evidence of their efficacy.

4. Discussion

2.1. Comorbidity and its impact on treatment outcomes

Due to the complex nature of both CD and ODD, individuals with a primary diagnosis of one of these conditions very commonly have comorbid conditions, namely ADHD, anxiety and mood disorders(24).

While we tried to minimize the effects of these conditions by only selecting studies where the primary diagnosis was either CD or ODD and excluding those where patients had low IQ or ASD, comorbidities like ADHD complicate the already difficult problem of diagnosing and treating conduct problems, for two reasons.

First, they can make the symptoms of opposition and defiance or conduct problems less apparent, and thus more difficult to identify.

Secondly, some studies do not provide enough detail about the management of comorbidities, which limits our understanding of how these conditions might affect the

outcomes of the primary treatments being studied(25). This is an important issue for future research to resolve(26).

2.2. Limited time follow-up

Most studies follow participants for only a few months, which means we have scant data on the effect of these medications on children and adolescents over longer stretches of time. This dearth of data pertains not just to long-term secondary effects, but also to the rate of progression to antisocial personality disorder(27).

2.3. Implications for current practice

This literature review of existing research on the use of antipsychotic medications in children and adolescents with ODD and CD provides useful insights into the disorders' treatment, their safety, and efficacy. The review is comprehensive; it includes a wide range of study designs—from RCTs to cohort and observational studies—that together form a comprehensive and useful picture of the existing evidence.

Moreover, it includes as a primary criterion for inclusion in the analysis that the studies must have ODD or CD as their primary focus. That makes the conclusions drawn in the review more reliable, since it's one of the few reviews out there that singles out these disorders for treatment with antipsychotics.

It arms clinicians with evidence that antipsychotic treatment is an invaluable tool for managing CD and ODD, especially when paired with other treatment modalities, while calling attention to the need of closely monitoring potential side effects.

Additionally, there is a need for further research into tailored interventions for children and adolescents without comorbidities, as they are often overlooked in existing studies, which tend to focus on more complex cases involving multiple conditions(28).

2.4. Stigma in clinical practice

One of the surprising things brought to life by this review is the clear stigma that still exists not only to these patients (pediatric population), but also to the use of antipsychotic treatment in this age segment.(29)

This is clear by the fact that very few studies are conducted in these patients, reflecting a reluctance to study these children and adolescents.(10) The studies that exist are all done by a few psychiatrists, while the study of adult populations, especially those with more common and less socially frowned-upon pathologies (like depression) have a much more extensive number of researchers and papers.

As medical professionals, we should strive to minimize our biases and prejudices when conducting scientific research. And even though eliminating them is not possible, we think papers like this one help in shedding light on this reality and in moving the needle.(30)

Moreover, this review also shows the hesitation in giving antipsychotic treatment to pediatric populations. This is evident by the fact that there already exists plenty of evidence that these medications, when allied with other modalities of treatment, provide the most efficacious treatment of these conditions. So, why are we so unwilling to implement a tool that we've had for so long?

5. Conclusions

This systematic review illustrates that pharmacotherapy, especially with clozapine or risperidone, is effective for reducing aggressive and disruptive behaviour in children and adolescents diagnosed with ODD and CD. Although clozapine has been studied less frequently, its effectiveness seems to surpass that of risperidone, especially regarding improving delinquency traits and overall functioning. However, this agent also warrants mention in the context of pharmacovigilance because of the potential for serious side effects.

Older "typical" antipsychotics like haloperidol and thioridazine do not seem as effective for these behavioural disorders and have a profile of serious side effects.

Other antipsychotics like quetiapine and ziprasidone, which seem to work well in other populations, remain unstudied and therefore their efficacy cannot be determined. Additionally, there is an absence of research on children under the age of five, underscoring a critical gap in the literature.

Overall, antipsychotics are a helpful tool for managing aggression and irritability in children and adolescents with ODD and CD, providing a valuable mechanism of control when other treatment options have failed.

Further large-scale, long-term studies are required to grasp fully the long-term efficacy and safety of these medications.

Author Contributions: Conceptualization, NS and PA; methodology, NS and JA; software, NS; validation, NS, PA, and JA; formal analysis, NS and PA; investigation, NS and PA; resources, NS and PA; data curation, NS and PA; writing—original draft preparation, NS; writing—review and editing, PA; visualization, NS and JA; supervision, JA; project administration, JA. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to the use of publicly available data and the absence of direct participant involvement.

Informed Consent Statement: Patient consent was waived due to the use of anonymized data from publicly available sources and the absence of direct patient interaction.

Data Availability Statement: The data used in the analysis were derived from previously published studies, which can be accessed via the respective sources referenced throughout the manuscript.

Conflicts of Interest: The authors declare no conflict of interest.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page and paragraph/ table #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both. **- MANDATÓRIO**	Page 1: "**Breaking the Stigma: A Systematic Review of Antipsychotic Efficacy in Children and Adolescents with Behavioral Disorders "**
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	Page 1: **Background / Objectives:** Oppositional Defiant Disorder (ODD) and Conduct Disorder (CD) are important behavior disorders in children and adolescents, often linked with long-term psychosocial problems. Antipsychotics are frequently prescribed to manage severe symptoms and improve behavior, but their efficacy in this population is still unclear and a lot of physicians are remittent in prescribing them. This systematic review aims to assess the effectiveness of antipsychotic treatment in reducing symptoms associated with ODD, and CD in children and adolescents. **Methods:** Studies that investigated how effective antipsychotic treatments are for children and teens diagnosed with Oppositional Defiant

			Disorder (ODD) and Conduct Disorder (CD) were reviewed. Only studies that met a few main criteria were included: participants were between 5 and 18 years old with an ODD or CD diagnosis; the treatment could be any type of antipsychotic – whether typical or atypical; the accepted study designs were randomized controlled trials (RCTs), cohort studies, systematic reviews with meta-analysis or observational studies. The outcomes of interest were reductions in aggressive or defiant behaviors, improvements in social functioning, and the occurrence of any adverse effects from the medications. There was no restriction on the language of publication, and studies published from 2000 to 2024 were considered. Studies that focused only on non-antipsychotic drugs or behavioral therapies, as well as case reports, expert opinions, and non-peer-reviewed articles did not meet the inclusion criteria. **Results:** The review consisted of 13 studies. The results suggest that some antipsychotic

			drugs—especially atypical antipsychotics—can substantially reduce aggressive and defiant behavior in children and adolescents who have oppositional defiant disorder (ODD) or conduct disorder (CD). Common side effects of these medications include weight gain, sedation, and metabolic problems. **Conclusions:** Although adverse effects are a concern, the potential of these medications to manage disruptive behaviors should not be overlooked. When used in combination with behavioral therapy and other forms of treatment, antipsychotics can markedly improve the outcomes of these very difficult-to-treat patients. Clinicians who treat these patients need to consider antipsychotics as a serious option. If they don't, they are denying their patients medication that could greatly benefit them.
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known. **– MANDATÓRIO** ***O rationale corresponde à justificação da importância da revisão sistemática***	Page 2: The debate is ongoing over how well disruptive behaviors of children with oppositional defiant disorder (ODD) and conduct disorder

			(CD) respond to treatment with antipsychotic medications(6). Atypical antipsychotic drugs (e.g., risperidone, aripiprazole), which have been more recently developed, do show some promise in reducing aggression and improving overall behavior, at least in the short term(7). But what does long-term use of these drugs in children portend for both mental and physical health? Concerns have been raised about potential side effects including (but not limited to) weight gain, sedation, and disturbances of metabolism(8). Given the rather tenuous evidence and the potential dangers linked to antipsychotic treatment, it is important to work out whether these medications are effective for something like oppositional defiant disorder (ODD) or conduct disorder (CD). The purpose of this systematic review is to work out if antipsychotic drugs do (or do not) reduce disruptive behaviors. A secondary goal is to assess their corresponding side effects.

PRISMA 2009 Checklist

Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). **- MANDATÓRIO**	Page 2: 1. Population: The studies had to involve participants who were children or adolescents (aged 5 to 18) with a diagnosis of ODD or CD. 2. Intervention: The studies had to evaluate the administration of any type of antipsychotic medication, whether typical or atypical. 3. Study Design: Only RCTs, cohort studies, systematic reviews with meta-analysis and observational studies were included.
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number. **– FACULTATIVO**	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. **– MANDATÓRIO** ***É altamente recomendado, de acordo com as boas práticas da Cochrane, que não sejam aplicados critérios de exclusão baseados na língua e/ou data de publicação dos estudos.***	Page 2: 1. Population: The studies had to involve participants who were children or adolescents (aged 5 to 18) with a diagnosis of ODD or CD. 2. Intervention: The studies had to evaluate the administration of any type of antipsychotic medication, whether typical or atypical. 3. Study Design: Only RCTs, cohort studies, systematic reviews with meta-analysis and observational studies were included. 4. Outcome Measures: The studies had to report

			some measures that indicated how well the medication was working. 5. Publication Language: The studies could be published in any language. 6. Date: The studies could have any date of publication from 2000 to 2024. Studies were excluded based on the following criteria: 7. Population: Studies where ODD and/or CD were not the primary diagnosis. Studies where individuals had low IQ (<70) or comorbid autism spectrum disorder (ASD). 8. Intervention: Studies that focused solely on non-antipsychotic pharmacological interventions or solely on behavioral therapies.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. **– MANDATÓRIO** ***Em consonância com as boas práticas da Cochrane, é mandatório que se verifique pesquisa em pelo menos duas bases de pesquisa bibliográfica (idealmente, deverão ser pesquisadas duas bases generalistas e uma específica da área). No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, é altamente recomendado que uma das bases pesquisadas corresponda à CENTRAL ou a bases de ensaios clínicos como a ClinicalTrials.gov.*** ***Estudos de revisão da literatura em que a pesquisa decorra numa única base de dados não serão classificados como revisões sistemáticas.***	Page 3: A thorough literature search was performed to find studies that assess the effectiveness of antipsychotic drugs in treating youths diagnosed with ODD and CD. Electronic Database Search The subsequent electronic databases were

			investigated: • PubMed/MEDLINE • PsycINFO • Cochrane Library • EMBASE • Web of Science To find more studies that possibly fell outside the database searches, a tool called Connected Papers was used. Connected Papers is a visual tool that maps the relationships between scientific papers based on co-citation and bibliographic coupling. This tool helped uncover related studies by visualizing networks of research papers connected to the key articles already identified.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. **– MANDATÓRIO** ***A query de pesquisa deve ser obrigatoriamente disponibilizada. A utilização de filtros de pesquisa da InterTASC é altamente recomendada (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home)***	Page 3: ("Oppositional Defiant Disorder" OR "Conduct Disorder") AND ("antipsychotic treatment" OR "atypical antipsychotics" OR "Risperidone" OR "Aripiprazole") AND ("children" OR "adolescents") AND ("aggression reduction"

			OR "behavioral improvement")
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). **– MANDATÓRIO** ***As fases de selecção dos estudos primários devem ser descritas. Em consonância com as boas práticas da Cochrane, é mandatório que o processo de selecção envolva duas fases (fase de rastreio, em que os registos são seleccionados por título e abstract, e fase de inclusão, na qual se procede à leitura integral dos full texts). Em cada uma destas fases, o processo de selecção deve mandatoriamente envolver dois investigadores actuando de forma independente.***	Page 3: A thorough literature search was performed to find studies that assess the effectiveness of antipsychotic drugs in treating youths diagnosed with ODD and CD. Electronic Database Search The subsequent electronic databases were investigated: • PubMed/MEDLINE • PsycINFO • Cochrane Library • EMBASE • Web of Science The terms of the search combined keywords and medical subject headings (MeSH) that pertained to the population, interventions, and outcomes of interest. The precise search string that was used was: ("Oppositional Defiant Disorder" OR "Conduct Disorder") AND ("antipsychotic treatment" OR "atypical

			antipsychotics" OR "Risperidone" OR "Aripiprazole") AND ("children" OR "adolescents") AND ("aggression reduction" OR "behavioral improvement") To find more studies that possibly fell outside the database searches, a tool called Connected Papers was used. Connected Papers is a visual tool that maps the relationships between scientific papers based on co-citation and bibliographic coupling. This tool helped uncover related studies by visualizing networks of research papers connected to the key articles already identified. The following steps were taken using Connected Papers: • Seminal papers identified from the initial search were input into the tool. • The network of connected papers was explored to find additional relevant studies. • The titles and abstracts of these

			connected papers were screened for inclusion
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. **– MANDATÓRIO** ***Trata-se de descrever de que forma se procedeu à extracção de dados dos estudos primários. Em consonância com as boas práticas da Cochrane, tal processo deverá envolver dois investigadores de forma independente.***	Page 3: A thorough literature search was performed to find studies that assess the effectiveness of antipsychotic drugs in treating youths diagnosed with ODD and CD. Electronic Database Search The subsequent electronic databases were investigated: • PubMed/MEDLINE • PsycINFO • Cochrane Library • EMBASE • Web of Science The terms of the search combined keywords and medical subject headings (MeSH) that pertained to the population, interventions, and outcomes of interest. The precise search string that was used was: ("Oppositional Defiant Disorder" OR "Conduct Disorder") AND ("antipsychotic treatment" OR "atypical

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			connected papers were screened for inclusion
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. **– MANDATÓRIO** ***Trata-se de descrever as variáveis para as quais foi obtida informação.***	Page 2: 1. Population: The studies had to involve participants who were children or adolescents (aged 5 to 18) with a diagnosis of ODD or CD. 2. Intervention: The studies had to evaluate the administration of any type of antipsychotic medication, whether typical or atypical. 3. Study Design: Only RCTs, cohort studies, systematic reviews with meta-analysis and observational studies were included. 4. Outcome Measures: The studies had to report some measures that indicated how well the medication was working. 5. Publication Language: The studies could be published in any language. 6. Date: The studies could have any date of publication from 2000 to 2024. Studies were excluded based on the following criteria: 7. Population: Studies

			where ODD and/or CD were not the primary diagnosis. Studies where individuals had low IQ (<70) or comorbid autism spectrum disorder (ASD). 8. Intervention: Studies that focused solely on non-antipsychotic pharmacological interventions or solely on behavioral therapies.
Risk of bias in individual studies / Risk of bias across studies	12/ 15	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. **– MANDATÓRIO** ***Em todas as revisões sistemáticas, deverá existir um processo de avaliação da qualidade dos estudos primários. No caso de revisões sistemáticas de estudos experimentais/ensaios clínicos aleatorizados, a aplicação dos critérios de risco de viés (Risk of Bias) da Cochrane é altamente recomendada. No caso de revisões sistemáticas de estudos observacionais, poderão ser seguidos os critérios ROBINS ou os critérios dos National Institutes of Health (https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools).***	Page 4: In this review, the risk of bias was assessed at the study level. For experimental studies, particularly randomized controlled trials (RCTs), the Cochrane Risk of Bias (RoB) tool was employed, as it is highly recommended for assessing methodological rigor in such studies. For systematic reviews of observational studies, the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool was applied. Alternatively, the quality assess-ment criteria provided by the National Institutes of Health (NIH) were considered, de-pending on the study design and characteristics. Only studies classified as having a low risk of bias were included in this review. Studies with a high or unclear risk of bias were excluded to ensure

			the reliability of the findings.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis. **– FACULTATIVO. APENAS NECESSÁRIO SE FOR FEITA META-ANÁLISE**	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. **– MANDATÓRIO**	Page 4: Figure 1 – Paper Selection Flowchart
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. **– MANDATÓRIO**	Page 5: Table 1 – Characteristics of the included studies
Risk of bias within and across studies	19/ 22	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12). **– MANDATÓRIO**	Page 5: Table 1 – Characteristics of the included studies
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot. **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency. **– FACULTATIVO. MANDATÓRIO APENAS SE FOR FEITA META-ANÁLISE**	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]). **– FACULTATIVO. APLICÁVEL APENAS SE FOR FEITA META-ANÁLISE**	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers). **– MANDATÓRIO**	Page 19: This literature review of existing research on the use of antipsychotic medications in children and adolescents with ODD and CD provides useful insights into the disorders' treatment, their safety, and efficacy. The review is comprehensive; it includes a wide range of

			study designs—from RCTs to cohort and observational studies—that together form a comprehensive and useful picture of the existing evidence. Moreover, it includes as a primary criterion for inclusion in the analysis that the studies must have ODD or CD as their primary focus. That makes the conclusions drawn in the review more reliable, since it's one of the few reviews out there that singles out these disorders for treatment with antipsychotics. It arms clinicians with evidence that antipsychotic treatment is an invaluable tool for managing CD and ODD, especially when paired with other treatment modalities, while calling attention to the need of closely monitoring potential side effects. Additionally, there is a need for further research into tailored interventions for chil-dren and adolescents without comorbidities, as they are often overlooked in existing stud-ies, which tend to focus on more complex cases involving multiple conditions(28).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias). **– MANDATÓRIO**	Page 19: Comorbidity and its impact on treatment

			outcomes Due to the complex nature of both CD and ODD, individuals with a primary diagno-sis of one of these conditions very commonly have comorbid conditions, namely ADHD, anxiety and mood disorders(24). While we tried to minimize the effects of these conditions by only selecting studies where the primary diagnosis was either CD or ODD and excluding those where patients had low IQ or ASD, comorbidities like ADHD complicate the already difficult problem of diagnosing and treating conduct problems, for two reasons. First, they can make the symptoms of opposition and defiance or conduct problems less apparent, and thus more difficult to identify. Secondly, some studies do not provide enough detail about the management of comorbidities, which limits our understanding of how these conditions might affect the outcomes of the primary treatments being studied(25). This is an important issue for fu-ture research to resolve(26). Limited time follow-up Most studies follow participants for only a few months, which means we

			have scant data on the effect of these medications on children and adolescents over longer stretches of time. This dearth of data pertains not just to long-term secondary effects, but also to the rate of progression to antisocial personality disorder(27).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research. **– MANDATÓRIO**	Page 20: This systematic review illustrates that pharmacotherapy, especially with clozapine or risperidone, is effective for reducing aggressive and disruptive behaviour in children and adolescents diagnosed with ODD and CD. Although clozapine has been studied less frequently, its effectiveness seems to surpass that of risperidone, especially regarding im-proving delinquency traits and overall functioning. However, this agent also warrants mention in the context of pharmacovigilance because of the potential for serious side ef-fects. Older "typical" antipsychotics like haloperidol and thioridazine do not seem as effec-tive for these behavioural disorders and have a profile of serious side effects. Other

			antipsychotics like quetiapine and ziprasidone, which seem to work well in other populations, remain unstudied and therefore their efficacy cannot be determined. Additionally, there is an absence of research on children under the age of five, underscor-ing a critical gap in the literature. Overall, antipsychotics are a helpful tool for managing aggression and irritability in children and adolescents with ODD and CD, providing a valuable mechanism of control when other treatment options have failed. Further large-scale, long-term studies are required to grasp fully the long-term efficacy and safety of these medications.
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. **– SEGUIR RECOMENDAÇÕES DA REVISTA**	

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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Article

Title

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† Current address: Affiliation.
‡ These authors contributed equally to this work.

Abstract: A single paragraph of about 200 words maximum. For research articles, abstracts should give a pertinent overview of the work. We strongly encourage authors to use the following style of structured abstracts, but without headings: (1) Background: place the question addressed in a broad context and highlight the purpose of the study; (2) Methods: describe briefly the main methods or treatments applied; (3) Results: summarize the article's main findings; (4) Conclusions: indicate the main conclusions or interpretations. The abstract should be an objective representation of the article, it must not contain results which are not presented and substantiated in the main text and should not exaggerate the main conclusions.

Keywords: keyword 1; keyword 2; keyword 3 (List three to ten pertinent keywords specific to the article; yet reasonably common within the subject discipline.)

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The template details the sections that can be used in a manuscript. Note that the order and names of article sections may differ from the requirements of the journal (e.g., the positioning of the Materials and Methods section). Please check the instructions on the authors' page of the journal to verify the correct order and names. For any questions, please contact the editorial office of the journal or support@mdpi.com. For LaTeX-related questions please contact latex@mdpi.com.

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The introduction should briefly place the study in a broad context and highlight why it is important. It should define the purpose of the work and its significance. The current state of the research field should be reviewed carefully and key publications cited. Please highlight controversial and diverging hypotheses when necessary. Finally, briefly mention the main aim of the work and highlight the principal conclusions. As far as possible, please keep the introduction comprehensible to scientists outside your particular field of research. Citing a journal paper [1]. Now citing a book reference [2,3] or other reference types [4,5]. Please use the command [6,7] for the following MDPI journals, which use author–date citation: Administrative Sciences, Arts, Behavioral Sciences, Businesses, Econometrics, Economies, Education Sciences, European Journal of Investigation in Health, Psychology and Education, Games, Genealogy, Histories, Humanities, Humans, IJFS, Journal of Intelligence, Journalism and Media, JRFM, Languages, Laws, Literature, Psychology International, Publications, Religions, Risks, Social Sciences, Tourism and Hospitality, Youth.

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Research manuscripts reporting large datasets that are deposited in a publicly available database should specify where the data have been deposited and provide the relevant accession numbers. If the accession numbers have not yet been obtained at the time of submission, please state that they will be provided during review. They must be provided prior to publication.

Interventionary studies involving animals or humans, and other studies require ethical approval must list the authority that provided approval and the corresponding ethical approval code.

This is an example of a quote.

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This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation as well as the experimental conclusions that can be drawn.

3.1. Subsection

3.1.1. Subsubsection

Bulleted lists look like this:

- First bullet;
- Second bullet;
- Third bullet.

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1. First item;
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3. Third item.

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All figures and tables should be cited in the main text as Figure 1, Table 1, etc.

Figure 1. This is a figure. Schemes follow the same formatting.

Table 1. This is a table caption. Tables should be placed in the main text near to the first time they are cited.

Title 1	Title 2	Title 3
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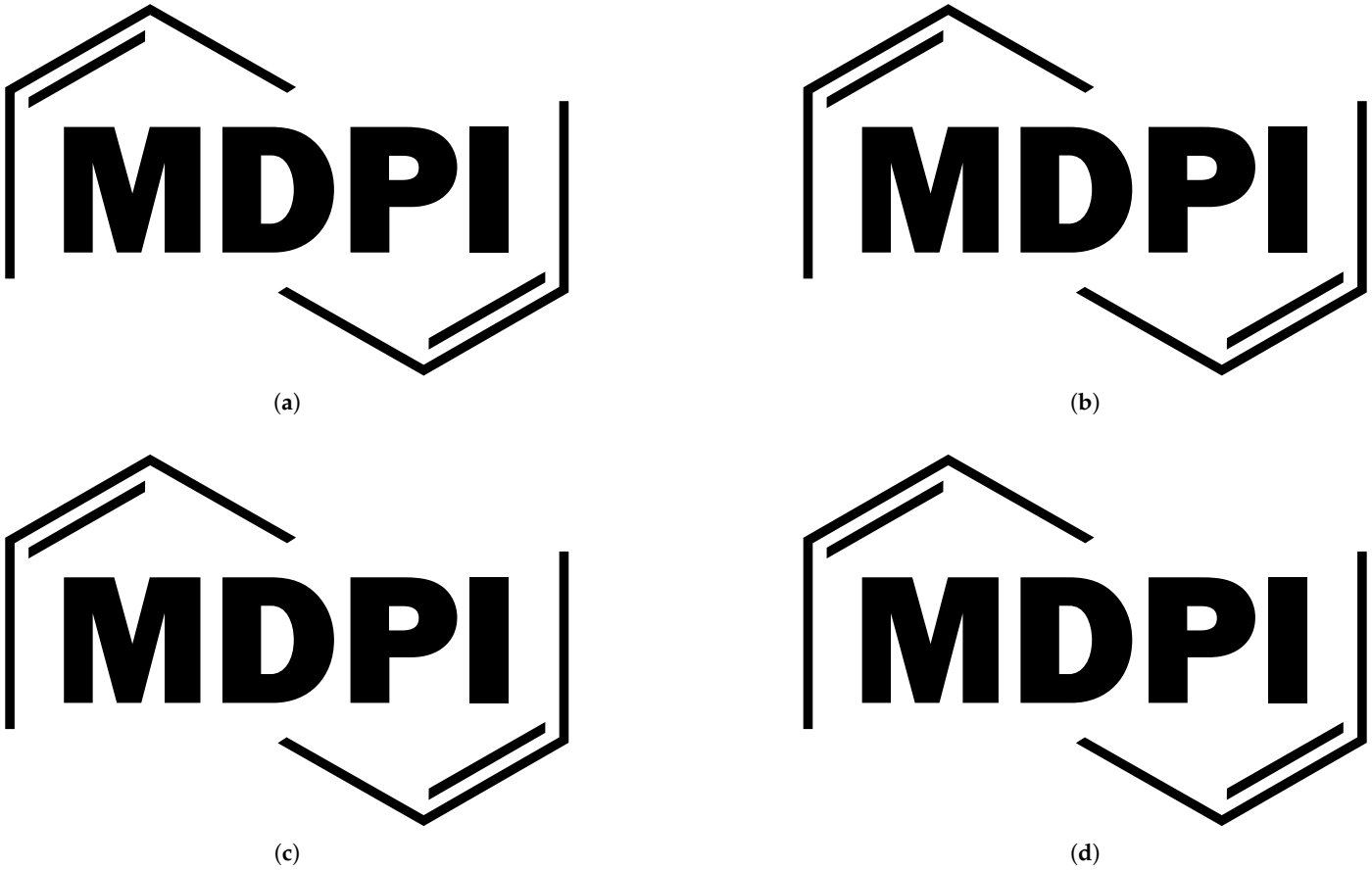
Entry 2	Data	Data [1]

[1] Tables may have a footer.

The text continues here (Figure 2 and Table 2).



(**a**) (**b**)

(**c**) (**d**)

Figure 2. This is a wide figure. Schemes follow the same formatting. If there are multiple panels, they should be listed as: (**a**) Description of what is contained in the first panel. (**b**) Description of what is contained in the second panel. (**c**) Description of what is contained in the third panel. (**d**) Description of what is contained in the fourth panel. Figures should be placed in the main text near to the first time they are cited. A caption on a single line should be centered.

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Title 1	Title 2	Title 3	Title 4
Entry 1 *	Data Data Data	Data Data Data	Data Data Data
Entry 2	Data Data Data	Data Data Data	Data Data Data

* Tables may have a footer.

Text.
Text.

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This is the example 1 of equation:

$$a = 1, \tag{1}$$

the text following an equation need not be a new paragraph. Please punctuate equations as regular text.

This is the example 2 of equation:

$$a = b + c + d + e + f + g + h + i + j + k + l + m + n + o + p + q + r + s + t + u + v + w + x + y + z \tag{2}$$

Please punctuate equations as regular text. Theorem-type environments (including propositions, lemmas, corollaries etc.) can be formatted as follows:

Theorem 1. *Example text of a theorem.*

The text continues here. Proofs must be formatted as follows:

Proof of Theorem 1. Text of the proof. Note that the phrase "of Theorem 1" is optional if it is clear which theorem is being referred to. □

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4. Discussion

Authors should discuss the results and how they can be interpreted from the perspective of previous studies and of the working hypotheses. The findings and their implications should be discussed in the broadest context possible. Future research directions may also be highlighted.

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Author Contributions: For research articles with several authors, a short paragraph specifying their individual contributions must be provided. The following statements should be used "Conceptualization, X.X. and Y.Y.; methodology, X.X.; software, X.X.; validation, X.X., Y.Y. and Z.Z.; formal analysis, X.X.; investigation, X.X.; resources, X.X.; data curation, X.X.; writing—original draft preparation, X.X.; writing—review and editing, X.X.; visualization, X.X.; supervision, X.X.; project administration, X.X.; funding acquisition, Y.Y. All authors have read and agreed to the published version of the manuscript.", please turn to the CRediT taxonomy for the term explanation. Authorship must be limited to those who have contributed substantially to the work reported.

Funding: Please add: "This research received no external funding" or "This research was funded by NAME OF FUNDER grant number XXX." and and "The APC was funded by XXX". Check carefully that the details given are accurate and use the standard spelling of funding agency names at https://search.crossref.org/funding, any errors may affect your future funding.

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Written informed consent for publication must be obtained from participating patients who can be identified (including by the patients themselves). Please state "Written informed consent has been obtained from the patient(s) to publish this paper" if applicable.

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Abbreviations

The following abbreviations are used in this manuscript:

MDPI	Multidisciplinary Digital Publishing Institute
DOAJ	Directory of open access journals
TLA	Three letter acronym
LD	Linear dichroism

Appendix A

Appendix A.1

The appendix is an optional section that can contain details and data supplemental to the main text—for example, explanations of experimental details that would disrupt the flow of the main text but nonetheless remain crucial to understanding and reproducing the research shown; figures of replicates for experiments of which representative data are

shown in the main text can be added here if brief, or as Supplementary Data. Mathematical proofs of results not central to the paper can be added as an appendix.

Table A1. This is a table caption.

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Entry 2	Data	Data

Appendix B

All appendix sections must be cited in the main text. In the appendices, Figures, Tables, etc. should be labeled, starting with "A"—e.g., Figure A1, Figure A2, etc.

References

1. Author 1, T. The title of the cited article. *Journal Abbreviation* **2008**, *10*, 142–149.
2. Author 2, L. The title of the cited contribution. In *The Book Title*; Editor 1, F., Editor 2, A., Eds.; Publishing House: City, Country, 2007; pp. 32–58.
3. Author 1, A.; Author 2, B. *Book Title*, 3rd ed.; Publisher: Publisher Location, Country, 2008; pp. 154–196.
4. Author 1, A.B.; Author 2, C. Title of Unpublished Work. *Abbreviated Journal Name* year, *phrase indicating stage of publication (submitted; accepted; in press)*.
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