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ORIGINAL ARTICLE

Antipsychotic-induced movement disorders: integrative review

Distúrbios do movimento induzidos pelo uso de antipsicóticos: revisão integrativa

Maria Eduarda Antunes de Meira[1], Giuliano Mannrich[2], Nathalia Nahas Donatello[1], Daiana Cristina Salm[1,*]

[1]*Universidade do Sul de Santa Catarina (UNISUL). Palhoça, Santa Catarina, Brasil.*
[2]*Sociedade Nacional de Fisioterapia Esportiva e Atividade Física. Florianópolis, Santa Catarina, Brasil.*

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KEYWORDS

Antipsychotics
Movement disorders
Abnormal Involuntary Movement Scale

ABSTRACT

Objective: To identify movement disorders induced by antipsychotics.
Methods: We selected clinical trials from MEDLINE and LILACS databases without publication date restriction. Studies of antipsychotics as a pharmacological intervention, compared or not to other interventions were included (combined treatments were not included). The primary outcome was movement disorders. Two independent reviewers analyzed the studies and summarized them in an electronic spreadsheet. We assessed the quality of the selected studies using the PEDro scale.
Results: Five studies were included in this review. In these studies, it was possible to identify the main psychiatric symptoms and their severity, as well as dyskinetic movements. When a reduction in dyskinetic movements was observed in treatments with both atypical and typical antipsychotics, there were adverse effects. Those included excessive sedation, loss of body mass, vomiting, and leukocytopenia.
Conclusion: This study verified the findings in literature on the effects of antipsychotics, including the type of medication, dosage, and form of administration, as well as instruments used to assess the outcome related to movement disorders. It was not possible to determine the best therapeutic dose for managing the disorders due to the significant distinction in dosages and medications. All five studies had some effect related to the drug use or its withdrawal.

*Corresponding author:
Universidade do Sul de Santa Catarina (UNISUL), Campus Grande Florianópolis.
Addr..: Av. Pedra Branca, 25. Palhoça, SC, Brasil | CEP: 88.137-270
Phone: +55 (48) 98490-7241
E-mail: daianasalm@hotmail.com (Salm DC)

This study was carried out at the *Universidade do Sul de Santa Catarina (UNISUL).*

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PALAVRAS-CHAVE

Antipsicóticos
Transtornos do movimento
Escala de Movimento Involuntário Anormal

RESUMO

Objetivo: Identificar os distúrbios do movimento induzidos pelo uso de antipsicóticos.
Métodos: Foram selecionados ensaios clínicos nas bases de dados MEDLINE e LILACS, sem restrição de data de publicação. Foram incluídos estudos de tratamento com antipsicóticos como intervenção farmacológica comparado ou não a outras intervenções (tratamentos combinados não foram incluídos). O desfecho principal foram os distúrbios do movimento. Os artigos foram analisados por dois revisores independentes e sumarizados em uma planilha eletrônica. A qualidade dos artigos foi avaliada pela escala PEDro.
Resultados: Foram incluídos cinco artigos nesta revisão. Nesses estudos foi possível identificar os principais sintomas psiquiátricos e sua severidade, assim como os movimentos discinéticos. Ainda assim, quando apresentaram redução dos movimentos discinéticos tanto nos tratamentos com antipsicóticos atípicos quanto típicos, houve efeitos adversos, como sedação excessiva, perda da massa corporal, vômitos, leucocitopenia de forma isolada.
Conclusão: O presente estudo verificou os achados encontrados na literatura sobre os efeitos dos antipsicóticos, incluindo o tipo de medicação, posologia e forma de administração, bem como os instrumentos utilizados para a avaliação do desfecho relacionado aos distúrbios do movimento. Não foi possível verificar a melhor dose terapêutica para o manejo dos distúrbios, devido a grande distinção nas dosagens e medicações. Todos os cinco artigos incluídos apresentaram algum efeito relacionado à medicação utilizada ou à retirada da mesma.

INTRODUCTION

The World Health Organization (WHO) understands mental health as a state of well-being in which an individual is aware of his/her abilities, can cope with everyday stress, can work productively and can contribute to his/her community[1].Therefore, mental health is more than just the absence of mental or behavioral disorders[2].

In 2001, the WHO estimated that approximately 450 million people had mental or behavioral disorders, and only a small portion was undergoing treatment[2]. In 2018, mental, neurological, and substance use disorders accounted for 10% of the global disease burden and 30% of the non-fatal disease burden[3].

In 2019, Brazil had 17.47% prevalence of mental or behavioral disorders[4]. The Brazilian Unified Health System (SUS) offers drug treatment for these cases, which include atypical antipsychotics[5]. Antipsychotic agents, also known as neuroleptics, are a class of drugs used to treat the symptoms of psychosis, as they decrease the intensity of hallucinations and illusions[6,7]. These can be classified into typical and atypical according to their chemical structure and pharmacological properties[6,8].

These drugs are associated with the risk of developing alterations, such as metabolic, which influence the increase in body mass, cholesterol, and glucose concentrations[9], as well as changes in consciousness level, like sedation and drowsiness[10].There are also movement disorders such as akathisia and tardive dyskinesia[10-12]. Movement disorders occur to the drug's action in the nigrostriatal region of the basal ganglia and its endocrine action by inhibiting the tuberoinfundibular pathway. However, the appearance of these disorders can be classified as acute or chronic since it depends on the length of use and medication dosage[8].

The main movement disorders related to the acute effect of antipsychotics are dystonia and akathisia. Dystonia is characterized by involuntary muscle contractions that lead to twisting movements, repetitive movements, or abnormal postures; akathisia, on the other hand, refers to feelings of anxious discomfort and the uncontrollable need to move[8,13].

With prolonged use of antipsychotics, chronic effects such as dyskinesia, dystonia, akathisia, myoclonus, delayed tremor, and tics appear. Tardive dyskinesia comprises choreoathetoid movements with at least three months of antipsychotic treatment, without other identifiable causes for the movement disorder[13]. Tardive akathisia occurs slowly and does not disappear with drug discontinuation and is diagnosed when these clinical signs have been present for at least one month[13].A study showed that the most common movement disorders after 12 weeks of antipsychotic medication are akathisia, tremor, and parkinsonism. The authors found that the effects directly relate to the drug's dose[14].

A broad understanding of antipsychotics and their effects on movement disorders associated with dose and treatment length is relevant. Since these adverse effects directly impact the quality of life of individuals undergoing these medications, such as problems with mobility, self-care, daily activities, anxiety, and depression[15]. Knowing that there are still disagreements in the literature about the dosage and duration of treatment associated with the use of antipsychotics and their adverse effects on movement, the objective of the present study was to identify movement disorders induced by the use of antipsychotics.

METHODS

This research is characterized as an integrative review[16,17].

Search strategy

We performed the electronic search in April 2021 in the Medical Literature Analysis and Retrieval System Online (MEDLINE/PubMed) and Latin American and Caribbean Health Literature (LILACS) databases without

restricting the publication date. We restricted our study design to clinical trials. The search terms used were ((“*akathisia*/acatisia/*acatisia*” OR “*dystonia*/distonia/*distonia*” OR “*tics*/tiques/*tiques*” OR “*myoclonus*/mioclonus/*mioclonía*” OR “*dyskinesia*/discinesia/*discinesia*” OR “*movement disorders*/distúrbios do movimento/*transtornos del movimiento*”) AND (“*neuroleptics*/neurolépticos/*neurolépticos*”)).

Eligibility Criteria

We included clinical trials on treatment with antipsychotics as a pharmacological intervention compared or not to other interventions, whose primary outcome was movement disorders. We excluded studies that combined treatments. Groups could or not have other drugs associated since most patients treated with antipsychotics have other comorbidities. However, the movement disorder outcome was defined as the main one to demonstrate one of the main side effects of the medications in use. Duplicates or studies not in Portuguese, English, or Spanish were excluded.

Data extraction and analysis

Two independent reviewers selected and analyzed the studies. Initially, titles and abstracts were read to verify whether they met the eligibility criteria. Then, they read in full the selected studies and summarized them in spreadsheets in the Microsoft Office Excel® program. The extracted data were organized in tables: name of authors, publication date, groups (characteristics and existence of a control group), sample size, the form of intervention (dose, route of administration, and antipsychotics' active ingredient), movement disorders, and main findings.

Study quality assessment

Two independent reviewers assessed the included studies' quality using the PEDro scale. The scale has 11 items, which are assigned a score of 1 (except for the first item) up to a final score of 10 points. Studies were classified according to the following scores: < 4 are considered low quality, 4 to 5 are acceptable quality, 6 to 8 are good quality, and 9 to 10 are excellent methodological quality for both pharmacological and non-pharmacological studies[18].

RESULTS

We found 169 studies according to the descriptors previously selected in the databases. Of these, 164 studies were excluded for not meeting the established eligibility criteria, and five were included in the review (Figure 1).

Table 1 shows the characteristics of the five studies included in this review. The clinical diagnoses were schizophrenia, autism spectrum disorder, and Alzheimer's disease associated with dementia. Additionally, typical antipsychotics were flupentixol, fluphenazine, molindone hydrochloride, haloperidol, and chlorpromazine hydrochloride. The atypical antipsychotics were clozapine, risperidone, and quetiapine hemifumarate.

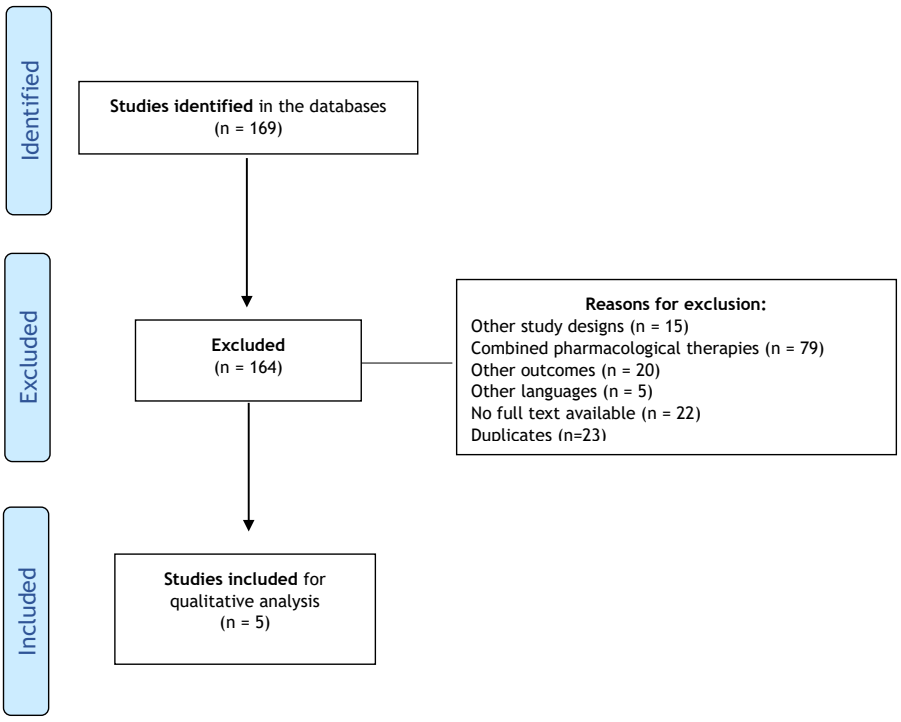

Figure 1 - Flowchart of the reviewed studies.

The sum of the samples of the selected studies[19-23] was 184 individuals. Only four studies[19-22] showed a distinction in the participant's sex, with a predominance of females (n = 66; 55%). Regarding the age group, three studies[19,20,23] had an average of 38 to 50 years; one study[21] was conducted with children aged approximately 7 years, while another[22] was conducted with elderly people with a mean age of 80 years.

Table 2 shows the main observed effects of antipsychotics from the included studies. The main findings observed were psychiatric symptoms, dyskinetic movements, symptom severity, and dyskinetic movements in both atypical and typical antipsychotic treatments. Also, the observed adverse effects of some antipsychotic administrations were excessive sedation, loss of body mass, vomiting, and leukocytopenia.

Table 3 presents the results of the methodological quality analysis using the PEDro scale. It was possible to verify that two studies had a score of 4, being considered low quality, one had a score of 6, and the other two had a score of 8, considered good quality. We also identified that the least methodological contemplation was in blinding.

DISCUSSION

This study summarizes findings from the literature on the effects of antipsychotics, including the type of medication, dosage, and form of administration, as well as the instruments used to assess movement disorders. All five studies included had some effect related to the medication use or withdrawal, corroborating with the findings of Ceraso et al.6, who observed that antipsychotics were associated with increased movement disorders in the research participants.

Participants in the studies included in this review were predominantly females. Guidelines for prescribing antipsychotics do not differ between sexes. However, studies have already shown pharmacokinetic and pharmacodynamic differences between men and women[24-26]. There is a concordance among preclinical, clinical, and epidemiological studies that report the protective role of estrogens in neuronal development, synaptic plasticity, and neuronal excitability, which influence the onset of schizophrenia and fluctuations in disease severity[27-30].

Nevertheless, a study has shown that other hormones such as estradiol establish resistance at the onset of schizophrenia due to their potential to neutralize stress in lesions[28], given that estradiol also acts in the modulation of dopaminergic, GABAergic, serotonergic, glutamatergic, noradrenergic, and cholinergic neurotransmission[27,30]. Those neurotransmitters are responsible for the onset of schizophrenia symptoms. Thus, these effects indicate that elevated levels of cerebral estradiol tend to decrease the severity of psychosis[29].

The difference in estrogen levels between the sexes seems to be an important factor since men with schizophrenia have an earlier onset compared to women. Furthermore, only women have a second peak of incidence, around the time of menopause, when estrogen levels decrease[29,30]. The incidence of schizophrenia is higher in men between 15 and 25 years. However, from 25 to 35 years there is a homogeneous distribution between sexes, while from 35, the diagnoses occur predominantly in women[31,32]. These data corroborate the results found in this study, in which patients diagnosed with schizophrenia were predominantly women aged between 35 and 50.

Although sex is an important and challenging factor for understanding the underlying pathology, the use of antipsychotics presents undesirable effects, such as those related to movement disorders, which are associated with the established dose and mechanism of action[33]. Our review found that the main drugs prescribed were typical antipsychotics, such as fluphenazine, flupentixol, molindone, haloperidol, and chlorpromazine, which act by inhibiting dopaminergic, noradrenergic, cholinergic, and histaminergic neurotransmission. Alternatively, atypical ones, such as clozapine, risperidone, and quetiapine, act by blocking dopamine D2 receptors and the serotonin receptor 5-HT2A[33]. Among the drugs mentioned in this study, only fluphenazine, flupentixol, and molindone are not available by the SUS, according to the National List of Essential Drugs[34].

Another study conducted a follow-up after seven years of pharmacological treatment and observed that more than 73% of patients were on depot antipsychotics (flupentixol and fluphenazine), and 70% had received this drug for more than seven years[23]. Still, there was a low prevalence of adverse effects such as rigidity and tremor and 10 cases of mild akathisia (n = 64). Evidence is diverse regarding flupentixol and fluphenazine and their side effects. Corroborating the study mentioned, a systematic review suggested that extrapyramidal adverse effects were significantly lower for people who received fluphenazine decanoate compared with oral antipsychotics[35].

Two studies have compared the action of different typical antipsychotics on dyskinetic movements[19,20]. One study[19], after comparing the effects of molindone hydrochloride and haloperidol in participants who had tardive dyskinesia after a 3-month follow-up, found that molindone has less therapeutic potential. However, this finding does not allow us to conclude that molindone is less likely to contribute to tardive dyskinesia, following the systematic review that shows that this drug is not superior to typical drugs in causing movement disorders[19,36]. Another study showed a higher incidence of dyskinesia with chlorpromazine (typical antipsychotic) compared to clozapine (atypical) at 11 weeks[20], which corroborates research that compared the effects of clozapine and showed a lower incidence of movement disorders compared to other antipsychotics[37].

A study that evaluated the continuous use of risperidone for 6 months in children observed an improvement in the global condition of the participants only during the use of the medication. In the short and long terms, two children had dyskinesias due to withdrawal[21]. A systematic review showed that about 25% of people using risperidone in the adult population need other drugs to alleviate extrapyramidal effects;

Table 1 — *Characteristics of selected studies.*

Studies	Characteristics of the studies	Intervention form	Active principle
Curson et al. (1985)[23]	*N* (64) *Age* (50,3 years) *Gender* (not specified) *Clinical diagnosis* (Schizophrenia with depression)	Group - **Depot fluphenazine** (n = 41): average dose: 25 mg/day. Group – **Depot flupentixol** (n = 6): unspecified dose. Group - **Oral antipsychotic** (n = 6): unspecified dose/no regular use. Group - **No medication** (n = 8): did not receive any medication. Group - **Lithium** (n = 3): unspecified dose/no regular use.	Depot fluphenazine Depot flupentixol
Glazer et al. (1990)[19]	*N* (18) *Age* (47 years) *Gender* (8 male and 10 female) *Clinical diagnosis* (Schizophrenia with tardive dyskinesia)	Group - **Molindone** (n = 9): 100% mean dose of 75 mg and 200% mean dose of 145 mg. Group - **Haloperidol** (n=9): 100% mean dose of 19.3 mg and 200% mean dose of 34.3 mg. Note: Dosage was determined by the occurrence of psychiatric symptoms or side effects. If there were no effects, the dose was increased 100% during the first to the second week, when about 200% dose equivalence of the antipsychotic medication.	Molindona Hydrochloride Haloperidol
Hong et al. (1997)[20]	*N* (40) *Age* (38,4 years) *Gender* (14 male and 26 female) *Clinical diagnosis* (Refractory schizophrenia)	Group - **Clozapine** (n = 20): 6 weeks with haloperidol 60 mg/day and after adaptation they were treated only with Clozapine 25 mg for 7 days and over the 11 weeks it reached an average dose of 543 mg/day. Group - **Chlorpromazine** (n = 20): 6 weeks with haloperidol 60 mg/day and after adaptation they were treated only with Clozapine 50 mg for 7 days and over the 11 weeks it reached an average of 1.183 mg/day.	Clozapine Chlorpromazine Hydrochloride
Malone et al. (2002)[21]	*N* (22) *Age* (7,1 years) *Gender* (18 male and 4 female) *Clinical diagnosis* (Autism Spectrum Disorder)	Group – **Risperidone** (n = 22): dose of 0.5 mg/day, which from the third day onwards could be increased up to 1mg/week. The dosage limit was up to 6 mg/day. The mean dose was 1.8 mg/day. Note: Dose escalation was flexible and individualized.	Risperidone
Paleacu et al. (2008)[22]	*N* (40) *Age* (82,2 years) *Gender* (14 male and 26 female) *Clinical diagnosis* (Alzheimer with dementia)	Group - **Quetiapine hemifumarate** (n = 40): average dose 200 mg/day. The dosage increase was gradual, being 25 mg/day in the first week and then 150 mg/day in the second week. Note: if the target dose was not reached, it was allowed an increase to a maximum of 300 mg/day.	Quetiapine hemifumarate

Table 2 — Effects of antipsychotics on movement disorders.

Movement disorders	Authors (year)	Assessment instruments	Outcomes	Results
Akathisia	Curson et al. (1985)[23]	- Present State Examination (PSE) - Extrapyramidal Symptom Rating Scale (ESRS) - Social Behavior Assessment Schedule (SBAS)	- Mental state - Side effects - Social behaviour	- There was no difference in reported mental status or social behavior. - There was a low prevalence of parkinsonian side effects (stiffness and tremor). - There were 10 cases of mild akathisia (n = 64).
Dyskinesia	Glazer et al (1990)[19]	- Brief Psychiatric Rating Scale for Schizophrenia (BPRS) - Abnormal Involuntary Movement Scale (AIMS) - Webster's scale (WPRS)	- Psychiatric Symptoms - Dyskinetic movements and parkinsonism	- Did not present the results of the psychiatric symptoms evaluation. - There was a statistical difference for the treatments with the added dosage (100 and 200%), when compared to haloperidol with a reduction in the score that evaluated dyskinetic movements.
Dyskinesia	Hong et al. (1997)[20]	- Clinical Global Impression of Change (CGI-C) - Scale of Positive and Negative Syndromes (PANSS) - Brief Psychiatric Rating Scale for Schizophrenia (BPRS) - Simpson Angus Akathisia Scale - Abnormal Involuntary Movement Scale (AIMS)	- Psychiatric symptoms - Dyskinetic movements	- Side effects in the clozapine group (n = 2): leukocytopenia and vomiting, nausea, and excessive sedation. - Side effects in the chlorpromazine group (n =2): jaundice, excessive sedation, and increased loss of body mass. - In the evaluation of psychiatric symptoms (n = 6), the group treated with clozapine showed a better therapeutic response when compared to chlorpromazine. - Dyskinetic movements were greater in the chlorpromazine group. - Tardive dyskinesia obtained interesting results in both groups (n =2).
Dyskinesia	Malone et al (2002)[21]	- Child Psychiatric Assessment Scale (CPRS) - Clinical Global Impression of Change (CGI-C) - Does not indicate the scale used to assess dyskinesia	- Severity of symptoms (Schizophrenia) - Psychiatric symptoms	- Improvement in psychiatric symptoms (after 1 month of treatment). - Risperidone showed short-term and long-term improvement in overall symptoms. - In the discontinuation period presented (n = 13). - In the short and long term only showed withdrawal dyskinesias after discontinuation (n = 2). - No extrapyramidal effects other than withdrawal dyskinesia were observed.
Movement disorders	Paleacu et al (2008)[22]	- Clinical Global Impression of Change (CGI-C) - Mini-State of Mental Examination (MMSE) - Simpson Angus Akathisia Scale - Abnormal Involuntary Movement Scale (AIMS) - Neuropsychiatric Inventory (NPI)	- Severity of symptoms (Schizophrenia) - Cognitive assessment - Assessment of movement disorders - Psychiatric symptoms	- High doses of quetiapine improved the assessment of psychiatric symptoms and symptom severity. - There was no difference between groups in the assessment of cognitive and movement disorders after treatment. In 15% of dropouts (n = 2) the reason was adverse effects related to extrapyramidal effects.

Table 3 — PEDro score of included studies.

Authors (year)	Curson et al. (1985)[23]	Glazer et al. (1990)[19]	Hong et al. (1997)[20]	Malone et al. (2002)[21]	Paleacu et al. (2008)[22]
Random distribution	N	N	Y	N	Y
Blind distribution	N	N	Y	Y	N
Similar prognostic indicators	N	Y	Y	Y	Y
Blinded participants	N	N	Y	N	Y
Blinded therapists	N	N	N	N	Y
Blinded evaluators	N	N	Y	N	N
Dropouts <15%	Y	N	N	N	Y
Treatment intention	Y	Y	Y	Y	Y
Statistical comparison between groups	Y	Y	Y	Y	Y
Predictive measures and variability	Y	Y	Y	Y	Y
Total (0 — 10)	4	4	8	6	8

Y - Yes; N - No

however, no data on tardive dyskinesia were found[38].Another study suggested that high-dose quetiapine improves psychiatric symptoms and symptom severity after 6 weeks and that there were no differences between groups in the assessment of movement disorders after treatment; however, parkinsonism and akathisia were observed in 15% participants who withdrew from the study[22]. These findings reinforce the results of a systematic review demonstrating that quetiapine can have adverse effects such as parkinsonism, tremor, and dystonia, which are lesser compared to typical antipsychotics[39].

The diagnosis of movement disorders involves a careful evaluation, and among the instruments to assess these disorders, there is already some clinical evidence for follow-up. In our review, the most described scales were the Abnormal Involuntary Movement Scale - AIMS[40], the Simpson Angus Akathisia Scale - ASA[41], the Extrapyramidal Symptoms Assessment Scale[42], and the Webster Scale[43]. These findings demonstrate that the use of validated instruments serves to monitor the effects related to antipsychotics, such as movement disorders[44].

Finally, the studies included in this review demonstrate limitations in the methodological quality evaluated using the PEDro scale. Mainly in the blinding aspects for the participants, therapists, and evaluators. Blinding is a necessary feature, among others, characterized by avoiding data measurement errors and research bias[45]. Furthermore, it was difficult to find studies that did not use concomitant drugs in clinical trials since movement disorders could be masked due to the use of other agents. Finally, it was possible to verify that three studies were classified as acceptable to good quality[20-22]. However, there was heterogeneity between the findings regarding the age of the participants, scales used to assess the outcomes, therapeutic dose, and form of administration.

CONCLUSION

This study verified the findings found in the literature on the effects of antipsychotics, including the type of medication, dosage, and form of administration, as well as the instruments used to assess outcomes such as movement disorders. All five studies included had some effect related to the medication used or its withdrawal. However, these studies demonstrate limitations in the methodological quality evaluated using the PEDro scale, mainly in the blinding aspects for the participants, therapists, and evaluators. There were limitations related to heterogeneity among the findings regarding the age of the participants, scales used to assess outcomes, therapeutic dose, and form of administration.

In this review, it was possible to observe the difficulty in finding studies that did not use concomitant drugs in clinical trials since movement disorders could be masked due to the use of other agents. Summarizing the main effects found in different age groups, the results of this review suggest that antipsychotics cause movement disorders. However, more clinical trials with adequate controls and blinding should be performed for better technical and scientific support.

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