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In-depth analysis of antipsychotic-induced akathisia: An integrative literature review

Análise aprofundada da acatisia induzida por antipsicóticos: Uma revisão integrativa da literatura

Análisis en profundidad de la acatisia inducida por antipsicóticos: Una revisión integrativa de la literatura

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Abstract
Background: Antipsychotic-induced akathisia poses a significant challenge in clinical practice due to its frequent oversight in diagnosis and associated severe consequences such as suicidal behavior and compromised treatment adherence. Understanding the underlying mechanisms and implementing effective management strategies are imperative in addressing this clinical concern. Objective: provide an updated understanding of the correlation between antipsychotics and akathisia, discussing its pathophysiology, diagnosis, assessment, and current as well as prospective treatment options. Methods: An integrative literature review was conducted utilizing Pubmed and Virtual Health Library databases, supplemented by additional resources to broaden the study's scope. Results and Discussion: Among the 204 studies analyzed, 17 met the criteria for inclusion in the review, complemented by 7 articles focusing on assessment scales. The study explores the impact of neuroleptic medications on akathisia's pathophysiology, diagnostic approaches, symptomatology, assessment tools, and management strategies. Conclusion: Robust research endeavors are crucial to consolidate evidence, identify gaps, and offer a holistic perspective on akathisia. The profound comprehension of the condition reveals paths to enhance patients' quality of life.
Keywords: Akathisia; Antipsychotics; Movement disorders; Dopaminergic pathways; Dopamine.

Resumo

Contexto: A acatisia induzida por antipsicóticos representa um desafio significativo na prática clínica devido ao seu frequente subdiagnóstico e às graves consequências associadas, como comportamento suicida e comprometimento da adesão ao tratamento. Compreender os mecanismos subjacentes e implementar estratégias de manejo eficazes são imperativos para enfrentar essa preocupação clínica. Objetivo: Fornecer uma compreensão atualizada da correlação entre antipsicóticos e acatisia, discutindo sua fisiopatologia, diagnóstico, avaliação e as opções de tratamento atuais e prospectivas. Métodos: Foi realizada uma revisão integrativa da literatura utilizando as bases de dados Pubmed e Biblioteca Virtual em Saúde, complementada por recursos adicionais para ampliar o escopo do estudo. Resultados e Discussão: Entre os 204 estudos analisados, 17 atenderam aos critérios de inclusão na revisão, complementados por 7 artigos focados em escalas de avaliação. O estudo explora o impacto dos medicamentos neurolépticos na fisiopatologia da acatisia, abordagens diagnósticas, sintomatologia, ferramentas de avaliação e estratégias de manejo. Conclusão: Esforços robustos de pesquisa são cruciais para consolidar evidências, identificar lacunas e oferecer uma perspectiva holística sobre a acatisia. A profunda compreensão da condição revela caminhos para melhorar a qualidade de vida dos pacientes.

Palavras-chave: Acatisia; Antipsicóticos; Distúrbios do movimento; Vias dopaminérgicas; Dopamina.

Resumen

Contexto: La acatisia inducida por antipsicóticos representa un desafío significativo en la práctica clínica debido a su frecuente subdiagnóstico y a las graves consecuencias asociadas, como el comportamiento suicida y el compromiso de la adherencia al tratamiento. Comprender los mecanismos subyacentes e implementar estrategias de manejo eficaces son imperativos para enfrentar esta preocupación clínica. Objetivo: Proporcionar una comprensión actualizada de la correlación entre antipsicóticos y acatisia, discutiendo su fisiopatología, diagnóstico, evaluación y las opciones de tratamiento actuales y prospectivas. Métodos: Se realizó una revisión integrativa de la literatura utilizando las bases de datos Pubmed y Biblioteca Virtual en Salud, complementada por recursos adicionales para ampliar el alcance del estudio. Resultados y Discusión: Entre los 204 estudios analizados, 17 cumplieron con los criterios de inclusión en la revisión, complementados por 7 artículos enfocados en escalas de evaluación. El estudio explora el impacto de los medicamentos neurolépticos en la fisiopatología de la acatisia, enfoques diagnósticos, sintomatología, herramientas de evaluación y estrategias de manejo. Conclusión: Esfuerzos robustos de investigación son cruciales para consolidar evidencias, identificar brechas y ofrecer una perspectiva holística sobre la acatisia. La profunda comprensión de la condición revela caminos para mejorar la calidad de vida de los pacientes.

Palabras clave: Acatisia; Antipsicóticos; Trastornos del movimiento; Vías dopaminérgicas; Dopamina.

1. Introduction

Movement disorders caused by psychiatric drugs are directly linked to the side effects of dopamine receptor blockers. These medications block dopaminergic D2 receptors and have the ability to trigger various extrapyramidal movement disorders, including akathisia (Friedman, 2020).

The term akathisia originates from the Greek "καθῑζειν," meaning inability to sit. It was first reported in 1902 in neurotic and hysterical patients, and later in 1923 in cases of idiopathic Parkinson's disease and post-encephalitic parkinsonism. It was only in 1947 that akathisia was officially recognized as an extrapyramidal complication induced by neuroleptic drugs (Shahidi et al., 2018).

The risk factors for the onset of akathisia symptoms need further clarification, but several associations have been identified. Patient age seems to play a crucial role, with an inversely proportional relationship observed in antipsychotic-induced akathisia; adolescents and children show higher susceptibility to developing extrapyramidal syndromes and akathisia compared to adults. Additionally, ethnicity may also be considered a risk factor, as caucasians appear to be less vulnerable to akathisia compared to other ethnic groups (Poyurovsky & Weizman, 2020).

Akathisia may arise as a side effect of antipsychotic, antiemetic, and selective serotonin reuptake inhibitor medications. The risk of developing akathisia in patients using typical antipsychotics are generally higher than the risk associated with atypical antipsychotics (Ali et al., 2021; Thippaiah et al., 2021).

Antipsychotic-induced akathisia is a severe condition capable of inflicting considerable suffering on the patient, increasing the risk of suicidal and aggressive behaviors. Additionally, it may compromise adherence to psychiatric treatments.

These factors underscore the crucial importance of diagnosing and treating akathisia properly. Despite its high incidence, it is often underdiagnosed or erroneously treated, sometimes being mistaken for other conditions, such as neurosis or agitated depression (Demyttenaere et al., 2019; Musco et al., 2019).

In this study, the integrative review aims to explore medical and scientific literature to provide an updated understanding of the correlation between akathisia and the antipsychotics responsible for inducing the condition.

2. Methodology

2.1 Study Type, Search Strategy, and Descriptors

This study constitutes an integrative literature review, following the model proposed by Souza, Silva, Carvalho (2010). This model guides the bibliographic research of a specific topic in six steps: (1) delimitation of the topic of interest and formulation of the guiding question, (2) sample collection methodology, (3) data extraction, (4) critical analysis of the data, (5) discussion of the results, and (6) presentation of the findings. The integrative review aims to create a comprehensive discussion based on the analysis of the literature, generate reflections, and propose new research directions (Souza et al., 2010).

The search strategy began with the formulation of the guiding question, followed by the selection of descriptors in Decs/Mesh - Health Sciences Descriptors (https://decs.bvsalud.org/). When the desired descriptors were not available in the thesaurus, equivalent or broader terms were chosen. This approach was adopted to secure a search method that encompassed a broader spectrum of publications relevant to the study scope.

The following descriptors were selected: “Akathisia”, “Drug-Induced”, “Antipsychotic Agents”, “Movement Disorders”, “Dopamine Antagonists”, and “Dopamine Pathways”.

The search was conducted in the Pubmed and Virtual Health Library (VHL) databases. A temporal filter was applied to cover studies published between 2018 and 2023, reflecting the most recent research and considering relevant advances in the understanding and treatment of akathisia.

2.2 Study Selection for the Integrative Review and Inclusion and Exclusion Criteria

Strict criteria were adopted for the selection of studies to maintain their relevance to the research. Inclusion criteria comprised studies providing data related to akathisia, its diagnosis, pathophysiology, pharmacological mechanisms, and therapeutic approaches to alleviate its symptoms, published from 2018 to 2023, in any language. Articles not meeting the inclusion criteria, with unclear outcomes, unrepresentative samples, or not pertinent to the topic, were excluded. Experience reports, editorials, response letters, dissertations, theses, reflective texts, programs, policies, comments, and studies lacking substantial information on akathisia were also excluded.

2.3 Study Screening

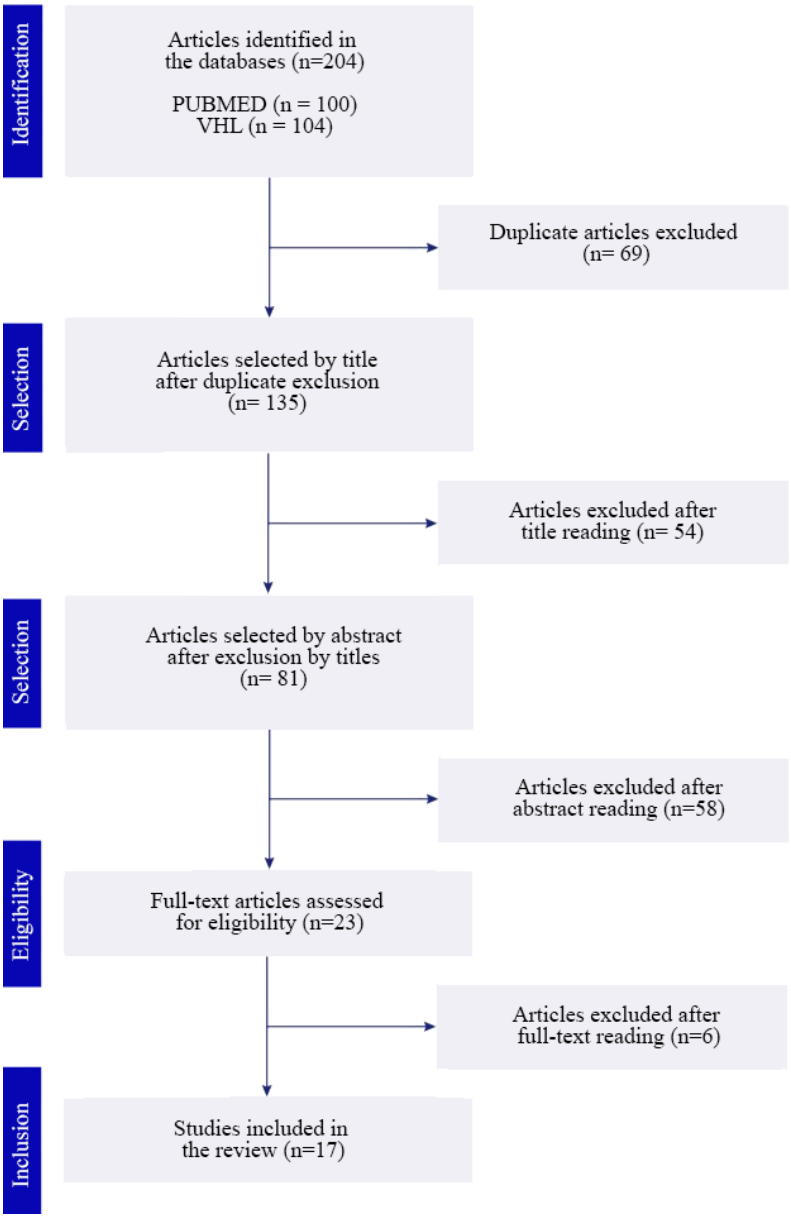
The screening of studies was conducted sequentially and coordinated to ensure the selection of the most relevant articles. Initially, 204 studies were identified in the databases. These studies were imported into the Rayyan software (https://www.rayyan.ai/), a review management platform that played a crucial role in the selection process. Rayyan facilitated the removal of duplicates and organization of articles, besides allowing objective voting among reviewers for inclusion or exclusion decisions. Voting at each screening stage was conducted blindly by 5 out of the 9 reviewers, meaning the reviewers were unaware of each other's opinions. To advance to the next selection phase, a majority was required, with at least 3 out of 5 reviewer votes in favor of inclusion.

After eliminating duplicates (69 articles excluded), the remaining 135 studies underwent screening based on the titles

of the citations identified in the databases. Any discrepancies among reviewers were discussed and resolved by consensus. Subsequently, 54 articles were excluded. The 81 studies that progressed to the next stage underwent abstract evaluation. At this stage, an additional 58 articles were excluded to ensure that only the most relevant studies adhering to the theme were retained. Finally, the remaining 23 studies were read in full text, with a thorough analysis of their content. At this phase, 6 more articles were excluded for not meeting the inclusion criteria.

The final sample resulted in 17 studies that met all parameters established for the research (Figure 1).

Figure 1 - Study Screening Flowchart.



Source: Own elaboration (2024).

2.4 Additional Resources

To enhance the review, after the selection of the sample, the search was expanded beyond articles in databases, incorporating complementary sources, in order to fill in study gaps. Akathisia assessment scales were extracted from their original article sources, along with usage instructions. This detailed approach enhances the understanding of the tools used,

providing a deeper analysis of the study's components.

The careful selection of these sources resulted from evaluation and discussion among collaborators, aiming to broaden the scope and qualitatively enrich the data. This diversified approach surpasses the information available in databases, and strengthens the theoretical foundation of the integrative review.

3. Results

Seventeen studies were selected for analysis regarding akathisia, including its diagnosis, pathophysiology, pharmacological mechanisms, and therapeutic approaches employed to mitigate its symptoms. Table 1 provides details on the authors, publication years, journals in which the studies were published, and their main objectives and conclusions.

Table 1 - characterization of the sample extracted from databases.

AUTHOR/YEAR	JOURNAL	THEME/OBJECTIVES	CONCLUSION
Ali et al., 2021	*PLoS ONE*	Evaluate the magnitude and prevalence of antipsychotic-induced extrapyramidal effects.	The prevalence is high, and management should emphasize prevention and early intervention.
Campos et al., 2021	*Revista Chilena de Psiquiatria Y Neurologia de La Infancia y Adolescencia*	Recommendations for preventing, recognizing, and treating antipsychotic-induced akathisia.	Early detection and treatment are essential to avoid complications.
Chow et al., 2020	*Pharmacotherapy*	Review the incidence of akathisia in patients using second-generation antipsychotics.	Akathisia should be monitored when prescribing these medications.
Demyttenaere et al., 2019	*CNS Drugs*	Evaluate the risk of akathisia in patients treated with novel second-generation antipsychotics (NAPs).	NAPs significantly increase the risk of akathisia, with variations among the drugs.
Friedman, 2020	*Parkinsonism & Related Disorders*	Evaluate the relationship between drug-induced movement disorders by psychiatric drugs not blocking dopamine receptors.	Tremors are the main motor adverse effect, mainly associated with SSRIs.
Martino et al., 2023	*Movement Disorders*	Evaluate the psychometric quality of instruments for antipsychotic-associated movement disorders.	No instrument achieved the highest rating, indicating the need for improvements.
Musco et al., 2019	*Journal of Clinical Psychopharmacology*	Evaluate characteristics of patients with extrapyramidal symptoms (EPS) related to dopamine receptor-blocking agents (DRBAs).	Younger and higher BMI patients are more prone to certain movement disorders.
Nagaoka et al., 2022	*Journal of Pharmacological Sciences*	Search for drugs that can reduce the risk of akathisia when used with dopamine D2 receptor antagonists.	Acetaminophen was effective medication in suppressing akathisia.
Poyurovsky; weizman, 2018	*Journal of Clinical Psychopharmacology*	Analyze the efficacy of low-dose Mirtazapine in treating acute akathisia induced by antipsychotics.	Mirtazapine showed efficacy and good tolerability, but large-scale studies are needed.
Poyurovsky; weizman, 2020	*Drugs*	Evaluate antipsychotic-induced akathisia and its treatment.	Low-dose Mirtazapine is effective and well-tolerated in treating akathisia.
Shahidi et al., 2018	*Tremor and Other Hyperkinetic Movements*	Report cases of late akathisia (LA) with asymmetric and upper body presentation.	LA can present asymmetrically and predominantly in the upper body, even with normal brain images.
Sienaert; van harten; rhebergen, 2019	*Handbook of Clinical Neurology*	Manage clozapine-induced akathisia with gabapentin enacarbil.	Gabapentin enacarbil was effective, allowing for increased clozapine dosage.
Takeshima et al., 2018	*Clinical Psychopharmacology and Neuroscience*	Manage clozapine-induced akathisia with gabapentin enacarbil.	Gabapentin enacarbil was effective, allowing for increased clozapine dosage.

Thippaiah; fargason; birur, 2021	*Psychopharmacology Bulletin*	Review available rescue agents for akathisia symptoms when dose adjustment is not feasible.	Various safe and effective agents are available for treating akathisia, with good prognosis if treated early.
Wu et al., 2023	*European Neuropsychopharmacology*	Analyze the relationship between antipsychotic doses and akathisia risk.	Akathisia induction varies depending on the antipsychotic and dose administered.
Yang et al., 2022	*BMC Psychiatry*	Report a case of withdrawal akathisia after reducing Amisulpride dose and discontinuing Benzatropine.	Abrupt dose reductions can trigger withdrawal akathisia; slow reduction and monitoring are recommended.
Zareifopoulos et al., 2021	*European Review for Medical and Pharmacological Sciences*	Define akathisia pathophysiology and assess its management.	Discontinuation of the inducing drug and symptomatic relief medications are essential in managing akathisia.

Source: Own elaboration (2024).

Table 2 presents the authors, publication years, journals in which these works were published, along with the main themes explored in their original sources. The insights from these supplementary materials were crucial in the identification of the most effective tools to evaluate akathisia's severity.

Table 2 - characterization of complementary assessment scales incorporated in the review.

AUTHOR/ YEAR	BOOK/JOURNAL	THEME
Barnes, 1989	*The British Journal of Psychiatry: The Journal of Mental Science*	BARS Assesment Scale
Inada, 1996	*Seiwa Shoten Publishers*	DIEPSS Assesment Scale
Inada, Yagi, Miura, 2002	*Schizophrenia Research*	DIEPSS Assesment Scale
Chouinard et al., 1980	*Canadian Journal of Neurological Sciences*	ESRS Assesment Scale
Chouinard, Margolese, 2005	*Schizophrenia Research*	ESRS Assesment Scale
Matson et al., 1998	*Research in Developmental Disabilities*	MEDS Assesment Scale
Cassady et al., 1997	*Psychiatry Research*	MPRC Assesment Scale

Source: Own elaboration (2024).

4. Discussion

4.1 Pathophysiology of Akathisia

Several classifications of akathisia are proposed, considering not only the symptom profile but also the onset time and persistence of symptoms. Acute akathisia typically manifests within two weeks of starting treatment with dopamine signaling antagonistic drugs, during dose escalation, or transitioning to a high-potency agent. If symptoms occur after this initial period, they are characterized as tardive akathisia. When symptoms persist for extended periods, exceeding several months, they are then categorized as chronic akathisia. In addition to these categories, withdrawal akathisia stands out, a phenomenon that occurs when there is abrupt discontinuation or dose reduction of antipsychotic medication (Chow et al., 2020).

In terms of pathophysiology, akathisia is a movement disorder often observed as a side effect of medications, related to dysfunction in the striatal circuit of the basal ganglia. Blockade of dopamine D2 receptors is the main mechanism behind antipsychotic-induced movement disorders, inhibiting nigrostriatal signaling. Antipsychotics with higher affinity for the D2 receptor compared to the 5-HT2A receptor have an increased potential to manifest akathisia. This phenomenon is also linked to

an imbalance in dopamine, serotonin and noradrenergic neurotransmitters in the basal ganglia. Activation of the β1 adrenergic receptor, located in the amygdala and nucleus accumbens shell, results in overactivation of noradrenergic neurons, culminating in states of dysphoria and involuntary movements (Campos et al., 2021; Wu et al., 2023; Zareifopoulos et al., 2021).

In addition to dopamine, other neurotransmitters associated with akathisia are gamma-aminobutyric acid (GABA) and serotonin (5-HT). GABA plays a crucial role in motor regulation, interacting with dopamine and serotonin through dependent signaling, inhibiting the nigrostriatal system. Hypothetically, increased serotonin is related to reduced dopamine signaling, resulting in akathisia (Campos et al., 2021; Wu et al., 2023).

Understanding treatment is significantly influenced by the drug's receptor affinity. The 5-HT2A receptor, although having the potential to trigger akathisia, demonstrates a robust anti-akathisia effect when exposed to an antagonist at low doses. This was observed in the case of mirtazapine, an atypical antidepressant with antagonism towards 5-HT2A. After blocking this receptor, there is an increase in dopamine transmission in the nigrostriatal pathway (Poyurovsky & Weizman, 2018).

4.2 Psychotropic Drugs Akathisia Inducing Potential

Psychotropic drugs with a higher propensity for movement-related side effects include antipsychotics and selective serotonin reuptake inhibitors (SSRIs).

ANTIPSYCHOTICS

Neuroleptics, as well as other drugs that act as D2 receptor antagonists, can trigger side effects, with akathisia being one of the most prevalent movement disorders. First-generation antipsychotics such as chlorpromazine, haloperidol, levomepromazine, trifluoperazine, and zuclopenthixol carry a higher risk of inducing akathisia compared to second-generation ones such as aripiprazole, risperidone, olanzapine, and quetiapine. Both classes of medications perform postsynaptic blockade of D2 receptors. However, first-generation antipsychotics exhibit a more pronounced affinity for these receptors compared to second-generation ones, thus contributing to a greater likelihood of extrapyramidal symptoms (Thippaiah et al., 2021; Zareifopoulos et al., 2021).

The propensity to trigger akathisia varies considerably among different neuroleptics. Most of these drugs follow a dose-response curve, usually monotonic or hyperbolic. This suggests that higher doses increase the likelihood of this side effect compared to lower doses. With the exception of quetiapine and sertindole, which have shown negligible risks (Wu et al., 2023). Furthermore, rapid dose escalation and antipsychotic polypharmacy are predisposing factors for the condition (Poyurovsky & Weizman 2020). On the other hand, there are reports of akathisia cases associated with the discontinuation or gradual reduction of typical antipsychotic medications, although it is a rare phenomenon (Yang et al., 2022).

The following table (Table 3), adapted from Poyurovsky & Weizman (2020), demonstrates the relationship between antipsychotics and their potential to induce Akathisia.

Table 3 - Akathisia-inducing capacity of neuroleptics.

ANTIPSYCHOTIC	USUAL THERAPEUTIC DOSE (mg)	AKATHISIA-INDUCING POTENTIAL
Haloperidol	5–10	High
Aripiprazole	10–15	Moderately High
Cariprazine	1,5–6	Moderately High
Risperidone	1–4	Moderately High

Paliperidone	3–6	Moderate
Ziprasidone	120–160	Moderate
Lurasidone	40–80	Moderate
Asenapine	10–20	Moderate
Brexpiprazole	2–4	Moderate
Chlorpromazine	300–900	Moderate
Olanzapine	10–15	Low
Iloperidone	12–24	Low
Quetiapine	150–750	Very Low
Clozapine	300–800	Very Low

Source: adapted from Poyurovsky & Weizman (2020).

SSRIs

The exact mechanism triggered by selective serotonin reuptake inhibitors (SSRIs) is not yet fully understood, as experimental data primarily come from studies in rats. However, there are suggestions that the dorsal raphe nucleus sends serotonergic stimuli, inhibiting neurons in the ventral tegmental area, thus reducing dopamine release in the mesocortical and mesolimbic pathways. This effect is achieved by inducing high doses of 5-HT2A and 5-HT2C antagonists (Thippaiah et al., 2021; Zareifopoulos et al., 2021).

4.3 Signs and Symptoms

Akathisia is a syndrome whose signs and symptoms may resemble other psychiatric disorders such as psychosis, anxiety, mania, attention deficit/hyperactivity disorder, agitated depression, and Parkinson's disease (Friedman, 2020). Clinically, it is characterized by subjective discomfort and restlessness. The objective experience includes a perceived need for movement in the trunk and limbs, evidenced by signs of continuous and repetitive rocking throughout the day. In severe cases, patients feel an irresistible need to move even when sitting, with legs often constantly moving, alternately crossing. This manifestation differs from restless legs syndrome (RLS), in which patients report discomfort in the legs and the compulsion to move them, with worsening at night associated with the disruptive impact on sleep. Early distinction is crucial for therapeutic approach as there are variations in the treatment line (Campos et al., 2021; Zareifopoulos et al., 2021). Akathisia can be classified regarding the onset of signs and symptoms. Generally, an acute manifestation occurs in the first days of treatment or with the increase in the dose of antipsychotics. It may also arise during withdrawal or discontinuation of treatment, approximately two weeks after, being self-limited and usually disappearing within six weeks. Less common is chronic akathisia, which persists for more than three months (Campos et al., 2021). Extrapyramidal symptoms have a negative impact on patient adherence and quality of life, increasing the risk of suicidal, aggressive, and violent behaviors (Nagaoka et al., 2023).

4.4 Assessment Scales and Tools

There are several scales and screening tools available, designed to assist physicians in clinical practice. The use of these tools can significantly increase the sensitivity and specificity of diagnosis and monitoring, providing a more accurate and

effective approach to treatment (Sienaert et al., 2019).

BARS Scale

The Barnes Akathisia Rating Scale (BARS), conceived by Barnes (1989), represents a simple and easy-to-use approach for the assessment of acute extrapyramidal effects. This scale is employed to determine the initial severity of symptoms, monitor progress over time, and assess response to treatment. It consists of the evaluation of four distinct items. The first item involves an objective assessment aimed at quantifying the persistence of movements during the evaluation period, covering both occasional and constant movements. The second item comprises subjective criteria addressing the perception and awareness of restlessness associated with agitation. The third item evaluates the patient's discomfort level regarding restlessness. The fourth item aims to describe the severity of symptoms (Thippaiah et al., 2021). With a total of nine questions, the scale is administered while the patient is seated and standing, observing their movements and also considering everyday situations in the ward. Each component is scored from 0 to 3, resulting in a total score ranging from 0 to 9. The Clinical Global Assessment of Akathisia uses a 5-point scale (0 to 4) to complement the assessment (Barnes, 1989). The highlighted assessment instrument stands out for its notable ease and speed of administration. Furthermore, its public availability facilitates widespread access. A distinctive feature is the absence of the need for formal training, making it accessible to a variety of users. Despite its advantages, it is important to mention a significant limitation due to the lack of sufficient data on some psychometric properties (Martino et al., 2023).

DIEPSS Scale

The Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS), developed in 1994 and published by Inada (1996), is a comprehensive tool consisting of eight individual symptoms and a global assessment. Its purpose is to identify extrapyramidal symptoms that may arise during treatment with antipsychotics. Specific symptoms include gait, bradykinesia, sialorrhea, muscle rigidity, tremor, akathisia, dystonia, and dyskinesia (Inada, 1996). The global assessment provides a measure of the overall severity of symptoms. The DIEPSS classifies extrapyramidal symptoms into four categories: parkinsonism (items 1 to 5), akathisia (item 6), dystonia (item 7), and dyskinesia (item 8). Each symptom is assessed on a scale of 0 (normal) to 4 (severe). Evaluations are performed at treatment initiation and continue in weeks 1, 2, 3, 4, 6, and 8 after treatment initiation, until its discontinuation. For inclusion in all analyses, patients must have an initial assessment and at least one assessment after treatment initiation (Inada, 2002). This scale presents notable advantages, being publicly available and allowing a comprehensive assessment of various movement disorders, with precise application of specific terminology for each type of disorder. Its versatility stands out when used by different groups, increasing its applicability. However, challenges such as the relatively prolonged time required for administration and the requirement of training for assessors should be considered, factors that may influence its efficiency in clinical settings (Martino et al., 2023).

ESRS Scale

The Extrapyramidal Symptom Rating Scale (ESRS), developed by Chouinard (1980), is a tool designed to assess four main types of antipsychotic-induced movement disorders: parkinsonism, akathisia, dystonia, and dyskinesia (Chouinard et al., 1980). The scale consists of two parts. The first is a questionnaire with seven points to be evaluated, considering the patient's verbal report on the duration, frequency, and intensity of symptoms over a week. This section addresses symptoms such as slowness, balance difficulty, tremors, restlessness, among others. The second part consists of a clinical assessment, where the examiner observes and scores physical symptoms such as tremors, bradykinesia, posture, and balance. Additionally, the ESRS includes specific assessments for dystonia and dyskinesia, analyzing involuntary movements in various body regions. The ESRS

uses a scale of 0 to 3 to score the subjective examination, where symptoms are assessed on a severity scale (0 = Absent; 1 = Mild; 2 = Moderate; 3 = Severe) (Chouinard & Margolese, 2005). The scale presents several advantages, such as ease of scoring due to clear definitions of each disorder, being a comprehensive tool for the assessment of all major movement disorders. Additionally, it is available for public use. However, for its administration, training is required to ensure accurate assessments. The scale may not be appropriate for use in cases of acute akathisia, and it is important to note that it is protected by copyrights (Martino et al., 2023).

MEDS Scale

The Matson Evaluation of Drug Side Effects scale (MEDS), developed by Matson et al. (1998), is a comprehensive tool that allows detailed assessment of adverse effects of psychotropic medications. The MEDS methodology includes both objective and subjective questions, requiring information obtained through interviews with team members familiar with the patient, as well as requesting medical history and patient records. The MEDS consists of 90 items, meticulously distributed into nine distinct categories, providing a specialized approach to monitoring the presence and severity of various side effects resulting from the use of these medications. The nine categories are divided into specific systems. These include the cardiovascular and hematologic system, the gastrointestinal system, the endocrinogenitourinary system, and the system related to eyes, ears, nose, and throat. Additionally, there is also a category for skin, allergies, and temperature. The central nervous system (CNS) is subdivided into four categories: General CNS, Dystonia, Parkinsonism/Dyskinesia, and Akathisia. Each of these sections covers five to 14 symptoms, allowing for a detailed and specialized analysis of each domain. The MEDS assigns scores to each item based on the severity and duration of symptoms occurring in the last two weeks. The scale uses a rating ranging from 0 to 2 for severity (0 = no problem, 1 = mild to moderate problem, 2 = severe or profound problem) and for duration (0 = less than one month, 1 = between 1 and 12 months, 2 = more than 12 months) (Matson et al., 1998). The tool has the advantage of being comprehensive and having accessible terminology, allowing for a complete and detailed assessment of the patient and facilitating communication among different healthcare professionals. However, the lack of a standardized training procedure may lead to variations in scale application and interpretation. Additionally, uncertainty about copyrights may restrict its use in certain contexts, as copyright protection implies limitations on the use, reproduction, distribution, or modification of the scale without proper permission from the intellectual property holder (Martino et al., 2023).

MPRC Scale

The Maryland Psychiatric Research Center Scale (MPRC) is a valuable tool that assesses involuntary movements associated with neuropsychiatric disorders. This scale, developed by Cassady et al. (1997), plays a crucial role in characterizing and understanding motor symptoms in psychiatric patients. The MPRC is comprehensive, covering a wide range of involuntary movements, including tremors, muscle rigidity, and other signs often associated with movement disorder conditions. The scale consists of 28 items assessing different body regions such as tongue, face, hands, and legs. Each item is scored to reflect the perceived severity of the involuntary movement, providing a detailed and comprehensive assessment. The scale uses a scoring system from 0 to 7 to assess the severity of three conditions: Dyskinesia, Parkinsonism, and Akathisia. Each score reflects the intensity of the symptom, ranging from absence (0) to maximum intensity (7). Although the MPRC is not a diagnostic tool, it provides a sensitive and effective approach to assessing movement disorders, being especially useful in research contexts (Cassady et al., 1997). This scale has advantages such as being publicly available, allowing broad access, and offering a detailed assessment of different forms of hyperkinesia. Moreover, the anchor points are well-defined, simplifying its application. However, a disadvantage is the ambiguity in the nomenclature of hyperkinetic phenomena, which may lead to confusion in result interpretation, requiring professionals' familiarity with the terminology for accurate assessment (Martino et al., 2023).

Table 4 - Summarized details on the use of the akathisia assesment scales.

SCALE NAME	AVERAGE APPLICATION TIME (IN MINUTES)	NUMBER OF ITEMS ASSESSED	RECOMMENDED TYPE OF AKATHISIA
BARS	2-5	9	Acute + Tardive
DIEPSS	20	8 + symptoms	Tardive
ESRS	10	7 + symptoms	Tardive
MEDS	10	90	Acute + Tardive
MPRC	10-20	28	Tardive

Source: adapted from Martino et al. (2023).

The selection of the appropriate instrument to assess side effects in psychiatric patients requires careful analysis of the specific characteristics of each scale discussed. Each tool, from the simplicity of the BARS Scale to the comprehensiveness of the MPRC Scale, presents unique advantages and challenges. It is crucial to recognize that, regardless of the choice, the use of these instruments serves as a valuable resource for diagnosis and monitoring the patient's progress. Continuous research and ongoing improvement of these tools are essential to overcome identified limitations, highlighting the ongoing importance of research aimed at enhancing the reliability and effectiveness of the instruments already available (Martino et al., 2023).

4.5 Management and Treatment

Regarding the treatment of antipsychotic-induced akathisia, individualized measures for each patient should be considered, taking into account aspects related to different factors such as neurodevelopment, the magnitude of akathisia, pharmacological regimen, and its respective clinical response. There are two main strategies in the appropriate management of akathisia caused by antipsychotic medications. First, there is the need to alter the antipsychotic drug regimen. Second, the introduction of adjunct medications with potential anti-akathisia effects (Campos et al., 2021).

The appropriate adjustment of antipsychotics to prevent the onset of akathisia is one of the primary clinical goals. Avoiding rapid dose escalation and polypharmacy, along with administering a minimal effective dose, are fundamental measures to reduce the risk of akathisia. Gradual dose reduction or switching to a different antipsychotic with lower potential for causing akathisia is advised. However, such measures may increase the risk of worsening psychotic symptoms due to the loosening of the drug's effect. The high incidence of akathisia, associated with the risks of switching antipsychotics and the limitations of preventive approaches, prompted a search for safe and effective drugs to alleviate akathisia symptoms (Poyurovsky & Weizman, 2018).

Non-selective beta-blockers, notably propranolol, are considered the gold standard and first-line treatment for akathisia. Beta-blockers were the first class of drugs recognized for akathisia treatment and continue to be studied in clinical trials. They are the class of medication with the highest level of evidence in the akathisia treatment process. Before prescribing, contraindications must be ruled out. It should be initially administered at a low dose (10mg) and gradually titrated until a dosage ranging from 40 mg to 80 mg is reached, depending on the patient's clinical response, with attention to the patient's heart rate and blood pressure control (Campos et al., 2021; Zareifopoulos et al., 2021).

When the use of propranolol is contraindicated, or when such a drug is ineffective or poorly tolerated, the use of 5-HT2A receptor antagonists is indicated, more specifically mirtazapine at a dose of 7.5 mg to 15 mg per day. Although the mechanism of the anti-akathisia effect provided by mirtazapine is not fully elucidated, it is believed to be related to its 5-HT2A

antagonistic effect. The use of mirtazapine may be able to 'restore' a prevalence of 5-HT2A blockade over D2 receptor antagonism, elevating dopaminergic transmission in the nigrostriatal pathway, and consequently causing a reduction in the risk of akathisia. The anti-akathisia effect through the use of mirtazapine (7.5 mg) is similarly rapid, with the response rate comparable to the higher dose of 15 mg. Administering mirtazapine at a low dosage (7.5 mg) for a mean period of 10.3 days is able to maintain the positive anti-akathisia effect and exhibit good tolerability in patients with akathisia caused by aripiprazole and risperidone (Poyurovsky & Weizman, 2018; Poyurovsky & Weizman, 2020).

A third treatment option is benzodiazepines. Initially, these drugs should be administered in low doses, gradually adjusted according to the therapeutic result, for as short a time as possible to avoid side effects and the risk of dependence. Clonazepam is a benzodiazepine responsible for reducing the overall excitability state of the central nervous system via agonist action on GABA-A receptors and indirectly increasing dopamine levels. The use of clonazepam (0.5-2.5mg over a period of 7 to 14 days in the treatment of akathisia caused by antipsychotics yielded significantly expressive results. Given the high risk of tolerance, cognitive effects, and dependence, clonazepam is used for short-term treatment of akathisia induced by antipsychotics. It is initiated at a low dosage, gradually increased, aiming to reach the lowest effective therapeutic dose. In addition to this medication, diazepam (5mg-15mg) and lorazepam (1mg-2mg) are also used for treatment, although they have low evidence. Once symptoms stabilize, gradual reduction of benzodiazepines is recommended (Thippaiah et al., 2021).

Regarding anticholinergic agents, although they have shown efficacy in treating acute dystonia and antipsychotic-induced parkinsonism, they are not indicated for treatment due to the high risk of side effects and low evidence. A recent review demonstrated that the evidence from studies supporting the administration of anticholinergic drugs such as biperiden and benztropine for the treatment of akathisia is highly limited, and the use of these drugs is highly associated with a range of side effects such as blurred vision, urinary retention, constipation, and cognitive impairment. The combined administration of antipsychotics with strong anticholinergic properties and anticholinergic drugs further favors side effects. The available data denote a questionable anti-akathisia effect provided by anticholinergics and limited therapeutic value in antipsychotic-induced akathisia (Campos et al., 2021).

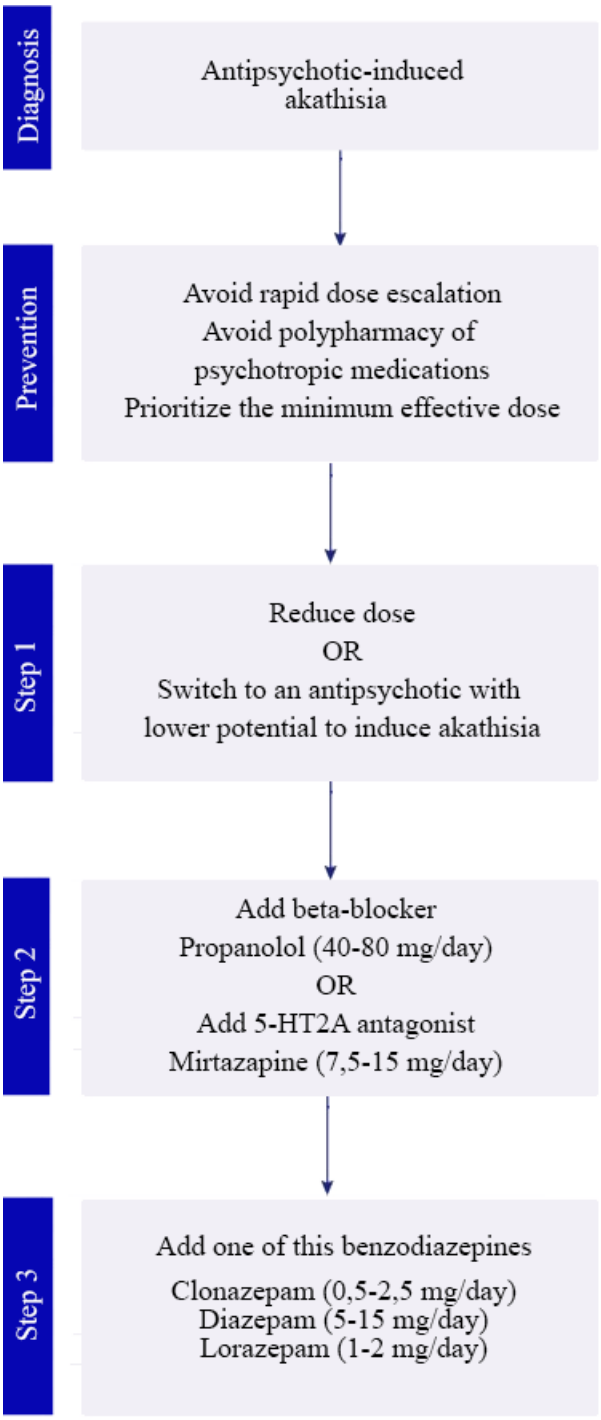
Gabapentin and its prodrug, gabapentin enacarbil (GE), have been considered potential options in the treatment of akathisia, as reported in case studies. Although there are successful reports, the lack of robust evidence still prevents these drugs from being widely accepted as established options. The exact mechanism by which gabapentin and GE improve akathisia is not fully understood, but there are suggestions that increasing GABA activity in the brain and regulating areas with dopamine dysfunction may play a crucial role. More comprehensive studies are needed to validate these mechanisms, determining if these drugs represent an effective and valuable intervention for akathisia treatment (Takeshima et al., 2018).

It is also essential to highlight the importance of Cochrane systematic reviews conducted by Lima et al. (2002), Rathbone & Soares-Weiser (2006), and Lima et al. (2004). These studies show the existing gaps in clinical research on akathisia and underscore the need for more recent research for a deeper and contemporary understanding of this clinical phenomenon.

In summary, treatment requires a multifaceted approach, carefully considering patient peculiarities. Strategies for modifying antipsychotic regimens and introducing adjunct medications such as beta-blockers, 5-HT2A inhibitors, and benzodiazepines stand out as valuable options. However, it is essential to weigh the benefits and risks associated with each intervention, gradually adjusting doses and closely monitoring the clinical response. Balancing the advances made with current studies and the constant need for updates and research in the field is crucial to better guide akathisia treatment.

In Figure 2, a revised treatment scheme is proposed based on the literature analyzed. This scheme incorporates the latest advancements in akathisia treatment, ensuring it reflects the most modern and effective approaches.

Figure 2 - Flowchart of acute antipsychotic-induced akathisia management



Source: Own Elaboration, 2024.

5. Conclusion

The meticulous investigation of akathisia culminates in significant reflections on the understanding and management of this extrapyramidal movement syndrome. Defined as a condition characterized by motor restlessness, akathisia presents itself as a diagnostic challenge, often overlapping with other psychiatric pathologies. The importance of dopaminergic pathways, particularly in the context of D2 receptors, stands out as a crucial point in the etiology of akathisia, driving the need for further investigations into these neurochemical mechanisms.

The main pharmacological classes associated with the induction of akathisia, from antipsychotics to SSRIs, delineate a

complex scenario that requires constant vigilance and individualized adaptations in treatment. The incorporation of assessment scales not only serves as an objective tool for diagnosis and monitoring but also represents a milestone in clinical accuracy by allowing informed and strategic interventions.

However, questions emerge that inspire future research. A detailed understanding of neurochemical mechanisms demands deeper studies on dopamine interactions in its different pathways. The search for more effective treatments with fewer side effects is a frontier to be crossed. Additionally, the role of genetics in susceptibility to akathisia and prevention strategies are areas deserving further exploration.

In this regard, longitudinal studies addressing the course of akathisia over time, investigating risk factors, and delineating specific interventions may offer valuable pathways. Understanding the variable response to different classes of drugs in different patients is also a worthy area of exploration, suggesting the need for robust clinical trials and comparative studies.

Furthermore, research on GABA and the potential efficacy of gabapentin as modulators of these specific neurochemical systems offer a window to explore alternative pharmacological interventions. Studies dedicated to understanding anticholinergic agents may also influence the expression of new horizons. Robust, meticulously designed clinical trials represent fertile ground to validate and compare the relative efficacies of different interventions, solidifying the foundation of clinical knowledge.

In a broader context, the need for systematic reviews and meta-analyses becomes evident. Conducting these studies helps consolidate existing evidence, identify knowledge gaps, and provide a broader view of current approaches.

In contemplating the future of akathisia research, the need for an interdisciplinary and collaborative approach is undeniable. Collaborations among neurologists, psychiatrists, pharmacology researchers, and mental health professionals can contribute to substantial advancements. Integrating different perspectives and specialties is essential to unraveling the mysteries of akathisia and optimizing therapeutic strategies.

Akathisia, despite its complexity, is an evolving field, offering opportunities to enhance patients' quality of life and refine clinical practices in the psychiatric field. The continuity of this scientific journey promises to uncover new nuances about this disease, in an era of transformative discoveries and advances in the understanding and treatment of this multifaceted syndrome.

Conflict of Interest

The authors declare no conflicts of interest related to this research. Additionally, no relevant affiliations or financial involvement with any organization or entity that has a financial interest in or conflict with the subject matter or materials discussed in the study.

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