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Clinical Review

Clinical review: introduction of antipsychotics into primary health care

Revisão clínica: introdução de antipsicóticos na atenção primária à saúde

Revisión clínica: introducción de antipsicóticos en la atención primaria de salud

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Abstract

Antipsychotics are the first line of treatment for psychotic symptoms and syndromes. Psychosis can present itself as: delusions, hallucinations, disorganized thinking, and altered behavior. It is estimated that 13 to 23% of the population will experience these symptoms at some point in their lifetime. This clinical review aims to assist in the decision-making about when and how to introduce antipsychotics into primary health care, considering their effectiveness, side effect profile, and the main care practices for relevant comorbidities. A literature review was carried out in the electronic databases PubMed, BMJ Best Practice, and UpToDate — electronic databases summarizing evidence — from October to November 2020. Articles that addressed the introduction of antipsychotics into primary health care, in patients over 18 years of age, published after 2010, in Portuguese, English, Spanish or French, were included. A total of 76 articles were considered eligible. Of these, 27 were selected for full reading. The antipsychotic should be recommended for anyone who experiences a first episode of psychosis. Preferably, the therapeutic choice should be part of a person-centered shared decision-making, considering the side effects. There is no superiority in effectiveness between one antipsychotic or another, not even between groups. The profile of efficacy, adverse effects, safety, and tolerability of the main drugs available were analyzed, facilitating decision-making regarding the introduction of antipsychotics. Due to the scarce national literature, it was not possible to analyze the specific profile for the Brazilian population.

Keywords: Psychotic disorders; Primary health care; Antipsychotic agents.

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Resumo

Os antipsicóticos são a primeira linha de tratamento para os sintomas psicóticos e suas síndromes. A psicose pode se apresentar como: delírios, alucinações, desorganização do pensamento e alteração do comportamento. Estima-se que 13 a 23% da população os apresente em algum momento ao longo da vida. Esta revisão clínica pretende auxiliar na tomada de decisão sobre quando e como introduzir antipsicóticos na atenção primária à saúde, levando em conta sua eficácia, o perfil de efeitos colaterais e os principais cuidados com as comorbidades relevantes. Realizou-se revisão da literatura nas bases de dados eletrônicos United States National Library of Medicine (PubMed), BMJ Best Practice e UpToDate — sumarizadores de evidência — no período de outubro a novembro de 2020. Foram incluídos artigos que abordassem a introdução de antipsicóticos na atenção primária, em maiores de 18 anos, com publicação após 2010, em português, inglês, espanhol ou francês. Foram obtidos 76 artigos considerados elegíveis. Destes, 27 foram selecionados para leitura integral. O antipsicótico deve ser recomendado para qualquer pessoa que apresente um primeiro episódio de psicose. Preferencialmente, a escolha terapêutica deve fazer parte do plano conjunto, centrado na pessoa, levando em conta os efeitos colaterais. Não há superioridade na eficácia entre um antipsicótico ou outro, nem mesmo entre grupos. Analisou-se o perfil de eficácia, efeitos adversos, segurança e tolerabilidade dos principais fármacos disponíveis, facilitando a tomada de decisão perante a introdução dos antipsicóticos. Pela escassa literatura nacional, não foi possível analisar o perfil específico para a população brasileira.

Palavras-chave: Psicoses; Atenção primária à saúde; Antipsicóticos.

Resumen

Los antipsicóticos son la primera línea de tratamiento de los síntomas psicóticos y sus síndromes. La psicosis puede presentarse como: delirios, alucinaciones, pensamiento desorganizado y comportamiento alterado. Se estima que del 13 al 23% de la población los presenta en algún momento de su vida. Esta revisión clínica tiene como objetivo ayudar en la toma de decisiones sobre cuándo y cómo introducir los antipsicóticos en la atención primaria de salud, teniendo en cuenta su efectividad, el perfil de efectos secundarios y la atención principal de las comorbilidades relevantes. Se llevó a cabo una revisión de la literatura en las bases de datos electrónicas PubMed, BMJ Best Practice y Uptodate – bases de datos electrónicas que resumen la evidencia – de octubre a noviembre de 2020. Criterios de inclusión: artículos que hayan abordado la introducción de antipsicóticos en atención primaria, mayores de 18 años, publicados después de 2010, en portugués, inglés, español o francés. Se consideraron elegibles 76 artículos. De estos, 27 fueron seleccionados para lectura completa. El antipsicótico debe recomendarse a cualquier persona que tenga un primer episodio de psicosis. Preferiblemente, la elección terapéutica debe formar parte del plan conjunto, centrado en la persona, teniendo en cuenta los efectos secundarios. No hay superioridad en la efectividad entre un antipsicótico u otro, ni siquiera entre grupos. Sintetizar el perfil de eficacia, efectos adversos, seguridad y tolerabilidad de los principales fármacos disponibles, facilitando la toma de decisión sobre la introducción de antipsicóticos. Debido a la escasa literatura nacional, no ha sido posible analizar el perfil específico de la población brasileña.

Palabras clave: Trastornos psicóticos; Atención primaria de salud; Antipsicóticos.

INTRODUCTION

Antipsychotics are considered the first line of treatment for psychotic symptoms and their syndromes and, therefore, they should be within the scope of family and community medicine as well as of primary health care (PHC) services. Psychosis can occur in several forms, in a gradient involving four main symptoms: delusions, hallucinations, disorganized thinking, and altered behavior. It is estimated that 13 to 23% of the population will experience these symptoms at some point during their lifetime, while 1 to 4% will meet criteria for psychotic disorders.[1,2]

Among the various psychotic disorders, schizophrenia stands out, not only because of its diagnostic and prognostic complexity, but also because it reduces life expectancy by approximately 20 years, with medical comorbidities being its main associated factor.[3] Thus, PHC professionals must be able to provide comprehensive care, including treatment, considering that findings related to the side effects of antipsychotics raise important public health issues.[4]

The implementation of guidelines on the subject provides very limited evidence,[5] but the international literature recommends that antipsychotic treatment be performed by a psychiatry professional (C).[6,7] In Brazil, PHC itself is often responsible for this attribution.[8] Evidence-based interventions are not easily

applied in practice, as accessing and using the database is not simple for most health providers in most countries worldwide.[9] Thus, this clinical review seeks to assist family and community physicians, as well as generalists, in making decisions about when and how to introduce antipsychotics into PHC, considering their efficacy, adverse effect profile, and the main care practices for the relevant comorbidities — regardless of the etiology of the psychosis condition.

METHODS

A literature review was conducted in the United States National Library of Medicine (PubMed) electronic database, including data and information from the BMJ Best Practice and UpToDate websites — electronic databases summarizing evidence — from October to November 2020.

The articles used by the search strategy were individually evaluated according to the following inclusion criteria: articles addressing the introduction of antipsychotics into primary health care among individuals over 18 years of age, published after 2010, in Portuguese, English, Spanish, or French languages.

The search in the databases was guided by the following descriptors obtained from the Health Science Descriptors (DeCS): “Psychotic Disorders and Drugs for Primary Health Care”; “Psychotic Disorders and Drug Therapy and Drugs for Primary Health Care”; in Portuguese, “Transtornos Psicóticos AND Atenção Primária à Saúde”; “Psychotic Disorders and Drug Therapy and Primary Health Care.”

A total of 76 articles were considered eligible. Of these, 27 were selected after reading the abstracts, based on the inclusion criteria. The final selection for fully reading the articles comprises systematic reviews, meta-analyses, and guidelines. At the end of the review, the analysis of the use of antipsychotics in pregnant and lactating women was dismissed due to the limited evidence available.

Throughout the text, the Strength of Recommendation Taxonomy (SORT) evidence classification can be observed, based on characteristics of the reviewed studies: A — based on consistent and good-quality patient-oriented evidence; B — based on inconsistent or limited-quality patient-oriented evidence; C — based on consensus, usual practice, opinion, disease-oriented evidence or case series.[10]

When and how to initiate pharmacological treatment

An antipsychotic should be recommended for anyone experiencing a first episode of psychosis (A).[11,12] Initially, the assessment should be comprehensive, including medical conditions and primary psychiatric disorders, and treatment should be indicated regardless of etiology, as remission rates for the first symptoms in the short-term are high.[7] The continuity of the etiological investigation of psychosis is paramount; and when it is caused by an organic medical condition, it must be treated for the underlying cause in addition to the antipsychotic.[13]

For stable patients with no signs of agitation or aggressiveness, the choice of the antipsychotic and its route of administration should be part of the person-centered shared decision-making, together with the patient. After surveying the medical history, risks, and benefits of each drug, the choice must be jointly made by the patient and the physician, also considering the view of the caregiver, if applicable (A).[11,14,15] Even in clinical conditions of acute agitation and aggressiveness, it is important to keep in mind the profile of adverse effects, monitor them, and avoid overdose.[14]

Despite some recommendations, there is no superiority in the efficacy of one antipsychotic or another, not even among its pharmacologic classes.[7] In the long-term, there is some evidence that suggests

the superiority of second-generation antipsychotics, in addition to the significant differences in the side effect profile, which must be considered in the decision shared with the person.[15,16] Clozapine is the only drug that proves to be significantly more effective, even in cases of treatment-resistant schizophrenia, and is considered the gold standard antipsychotic (A).[12,17] However, it should not be used as a first-line treatment because of its profile of side effects, even life-threatening ones, such as agranulocytosis, and it is administered only for people who have not responded to two different antipsychotic trials (B).[6,11,13,15] In Table 1 we summarize the scientific evidence for each drug, its doses, and side effect profile. Those belonging to the 2020 National List of Essential Drugs (*Relação Nacional de Medicamentos* – RENAME), which are available from the basic and specialized pharmaceutical care component of the Brazilian Unified Health System (SUS), were marked with an asterisk (*).[18]

The purpose of mental health care should be to promote effective treatment as soon as possible to reduce the duration of untreated psychosis regardless of etiology — taking into account the high morbidity and low long-term response in the case of schizophrenia (A).[7,13,15] It should start with low doses because the sensitivity to the response is greater in the first episodes, (A)[7,11,15,16] without disregarding psychosocial interventions.[6] In general, it is suggested to start one antipsychotic at a time and not combine them, with the exception of treatment-resistant cases, only after a therapeutic trial with clozapine, as there are no proven benefits that increase the chance of interaction and the potentiation of adverse effects (B).[6,13,15] The use of depot or long-acting injectable antipsychotics for the first episode is uncertain, but should be considered if adherence is poor, unknown, or if it is the user's preference (A).[6,7,15]

The beginning of treatment should be seen as a therapeutic trial aimed at reaching the ideal dosage, with good adherence for four weeks (A).[6,7] The medication should be continued for at least two weeks, unless significant drug intolerance occurs. The assessment of dose and response should be monitored in the initial phase and documented in a clinical record, justifying any changes in the medication or its discontinuation (C).[7] If there is no response to the medication after four weeks, change should be considered and, if there is a partial response, the case should be reevaluated within eight weeks (C).[11] This change must be made carefully, gradually reducing the dose of the drug in use and increasing that of the newly selected drug, in such a way that the combination is only allowed in the short-term within this context, in order to avoid rebound (C).[13,14]

For people who respond to treatment, the use of the antipsychotic should continue to ensure the relief of symptoms and reduce the risk of recurrence.[16] The duration of maintenance therapy should be at least 18 months (C)[7,11] and, in case there is a diagnosis of schizophrenia, two to five years or more (A).[11,15] Continuous treatment should always be preferred to intermittent treatment strategies, considering this possibility only for people who do not accept maintenance therapy or if there are other contraindications such as high sensitivity to side effects.[6,16] Among the causes of discontinuation of antipsychotics, weight gain and sedation stand out.[12] A meta-analysis compared ethnic differences for psychosis treatment and demonstrated that Latin Americans and African Americans tend to receive more first-generation antipsychotics than second-generation antipsychotics, which may suggest a lower quality treatment for these minorities.[19]

Monitoring and follow-up

The shared decision regarding screening, risks of adverse effects, and management of comorbidities must constitute the criteria for initiating and maintaining the interventions proposed by the healthcare

Table 1. Synthesis of results of the clinical review, including information on the doses, side effects, and specificities of the antipsychotics.

		Initial dose	Therapeutic dose	Maximum dose	Presentation	Adverse effects									Specific monitoring
						Movement	Blood glucose	Dyslipidemia	Weight gain	Prolonged QTc	Sudden death	Drowsiness	Sexuality	Others	
1st generation	*CHLORPROMAZINE	75–100 mg/day[15,25]	300–600 mg/day[25]	800 mg/day[15,25]	TAB: 25 mg, 200 mg; OS: 40 mg/mL and 5 mg/mL	High risk[12]	High risk[20]	High risk[20]	High risk [3,20]	Medium risk[4]	–	High risk[12]	–	Photosensitivity[6]	Use of sunscreen[6]
	*HALOPERIDOL	1–5 mg/day[13,15,25]	4–10 mg/day[13,25]	10–20 mg/day[15,25]	TAB: 1 mg, 5 mg; OS 2 mg/mL; IS (haloperidol decanoate): 5 mg/mL, 70.52 mg/mL	High risk[12]	Low risk[20]	Low risk[20]	Low risk[3,12,20]	If EV: High risk/ If PO: Medium risk[4]	PO: Medium risk[26] /If EV: High risk[4]	Low risk[12]	High risk[23]	Prolactinemia[12]	If EV: ECG monitoring and avoid it in case of high cardiovascular risk[4]
	THIORIDAZINE	88 mg/day[25]	200–500 mg/day[25]	800 mg/day[25]	TAB: 10 mg, 25 mg, 50 mg, 100 mg, 200 mg	–	High risk[20]	High risk[20]	Medium risk[20]	High risk[4]	Medium risk[26]	–	High risk[23]	–	ECG monitoring and avoid it in case of high cardiovascular risk[4]
2nd generation	AMISULPRIDE	50–100 mg/day[15]	300–800 mg/day[15,25]	1000-1200 mg/day[15,25]	TAB: 50 mg, 200 mg	Low risk[12]	Low risk[20]	Low risk[20]	Low risk[3,20]	–	–	Low risk[12]	–	–	–

Continue...

Table 1. Continuation.

		Initial dose	Therapeutic dose	Maximum dose	Presentation	Adverse effects									Specific monitoring
						Movement	Blood glucose	Dyslipidemia	Weight gain	Prolonged QTc	Sudden death	Drowsiness	Sexuality	Others	
2nd generation	ARIPIPRAZOLE	5–10 mg/day[15]	10–20 mg/day[15,25]	15–30 mg/day[15,25]	TAB: 10 mg, 15 mg, 20 mg, 30 mg; SO: 1 mg/mL	Low risk[12]	Low risk[20]	Low risk[20]	Low risk[1,6]	Low risk[4,12]	–	Low risk[12]	Low risk[23]	Lower risk of sexual dysfunctions[23]	–
	ASENAPINE	10 mg/day[15]	–	20 mg/day[15]	TAB: 5 mg, 10 mg	Low risk[12]	Low risk[20]	Low risk[20]	Low risk[3,20]	Low risk[4,12]	–	–	–	–	–
	*CLOZAPINE	12.5–25 mg[15,25]	25–500 mg/day[15,25]	800–900 mg[15,25]	TAB: 25 mg, 100 mg	Low risk[12]	High risk[20]	Medium risk[17,20]	High risk[3,13,17,20]	Low risk[4]	Medium risk[26]	High risk[12]	High risk[23]	Fatal agranulocytosis[12]	Blood count[13]
	LURASIDONE	40 mg/day[15]	–	160 mg/day[15]	TAB: 20 mg, 40 mg, 80 mg	High risk[12]	Low risk[20]	Low risk[20]	Low risk[3,12,20]	Low risk[4,12]	–	Low risk[12]	–	–	–
	*OLANZAPINE	2.5–5 mg/day[15,25]	10–20 mg/day[15,25]	30 mg/day[15]	TAB: 2.5 mg, 5 mg, 10 mg	Low risk[12]	High risk[20]	High risk[20]	High risk [3,12,13,20]	Low risk[4]	Medium risk[26]	Medium risk[17,20]	High risk23	–	–
	PALIPERIDONE	3 mg/day[15,25]	6–9 mg/day[25]	12 mg/day[15,25]	TAB: 3 mg, 6 mg, 9 mg	Low risk[12]	Low risk[20]	Low risk[20]	Medium risk[3]	Low risk[4,12]	–	Low risk[12]	–	Prolactinemia[12]	–

Continue...

Table 1. Continuation.

		Initial dose	Therapeutic dose	Maximum dose	Presentation	Adverse effects									Specific monitoring
						Movement	Blood glucose	Dyslipidemia	Weight gain	Prolonged QTc	Sudden death	Drowsiness	Sexuality	Others	
2nd generation	PIMOZIDE	2 mg/day[25]	4–6 mg/day[25]	10 mg/day[25]	TAB: 1 mg, 4 mg	–	–	–	–	High risk[4]	High risk[26]	–	–	–	ECG monitoring and avoid it in case of high cardiovascular risk[4]
	*QUETIAPINE	25–100 mg/day[15,25]	300–800 mg/day[15,25]	750–1000 mg/day[15,25]	TAB: 25 mg, 50 mg, 100 mg, 200 mg, 300 mg, 400 mg	Low risk[12]	Medium risk[20]	Medium risk[20]	Medium risk[3,20]	Medium risk[4]	Medium risk[26]	Medium risk[12]	Low risk[23]	–	–
	*RISPERIDONE	0.5–1 mg/day[15]	2–6 mg/day[15,25]	6–8.5 mg/day[15,25]	TAB: 0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg; IS: 25 mg, 37.5 mg, 50 mg	Low risk[12]	Medium risk[20]	Medium risk[20]	Medium risk[3,20]	Low risk[4]	Medium risk[26]	Low risk[12]	High risk[23]	Prolactinemia[12]	–
	ZIPRASIDONE	20–40 mg/day[15,25]	80–160 mg/day[15,25]	160–200 mg/day[15,25]	TAB: 40 mg, 80 mg	High risk[12]	Low risk[20]	Low risk[20]	Low risk[12]	Medium risk[4]	–	Medium risk[12]	Low risk[23]	–	–

TAB: tablet; OS: oral solution; IS: injectable solution; EV: endovenous administration; PO: oral administration; ECG: electrocardiogram.

team, involving the person and their caregivers.[3] Prevention and screening measures are known to be routinely neglected among individuals who use antipsychotics,[20] even women, who are less likely to undergo screening tests for breast cancer, for example.[21] In addition, especially regarding schizophrenia, a significant proportion of individuals tend to develop diabetes or have other cardiovascular risk factors (especially smoking, overweight, obesity, and harmful alcohol use).[3] Thus, in Table 2 we summarize the main recommendations for monitoring users of antipsychotics.

Table 2. Synthesis of recommendations for clinical monitoring of antipsychotics use.

	Monitoring
At every appointment	Actively assess adverse effects, response to treatment, adherence, and overall physical health (movement disorders, nutritional status, and level of physical activity).[6]
Before starting	BP, HR, laboratory tests (FBG, HbA1C, lipid profile, prolactin), waist circumference, BMI, cardiovascular risk calculators.[3,6]
12 weeks	BP, HR, laboratory tests (FBG, HbA1C, lipid profile), waist circumference, BMI, cardiovascular risk calculators.[3,6]
Annually	BP, HR, laboratory tests (FBG, HbA1C, lipid profile), waist circumference, BMI, cardiovascular risk calculators.[3,6]
Electrocardiogram	In case of risk factors: over 65 years of age, hypokalemia, hypomagnesemia, long QT syndrome, family history of sudden death, history of heart disease, concurrent use of other medications that prolong the QTc interval, liver diseases, endocrinopathies, neuropathies.[4]

BP: blood pressure; HR: heart rate; FBG: fasting blood glucose; HbA1C: glycated hemoglobin test; BMI: body mass index.

Cardiovascular risk assessment related to the use of antipsychotics may show evident signs within eight to 12 weeks of treatment,[6,7] suggesting the use of cardiovascular disease risk prediction models such as QRISK3 (A).[3] The use of electrocardiogram as a routine test to monitor heart changes still has inconsistent evidence, mainly related to the effective cost of reducing mortality (C). However, it is suggested that it be requested in the following scenarios: high cardiovascular risk; the antipsychotic in question has an established Torsades de Pointes risk or long QT segment; overdose; cardiovascular symptoms or a combination of other drugs that prolong QT (C).[4,14,20] In addition, when the drug used has a higher risk of hyperprolactinemia, it is essential to pay attention to changes in the breasts and bones, especially in women (B).[14]

Next, we describe the main adverse effects found in the literature, complementing the synthesis shown in Table 1. According to the Pan American Health Organization (PAHO), adverse effects are understood as “any undesirable medical occurrence that may present during treatment with a medication without necessarily having a causal relationship with this treatment”.[22]

Adverse effects

Movement

Movement disorders caused by antipsychotics can be grouped into neurological and anticholinergic disorders. The former include Parkinsonian effects (tremor at rest, akinesia, rigidity), acute dystonia (slow and prolonged muscle spasms), akathisia (subjective feeling of agitation), neuroleptic malignant syndrome

(fever, sweating, confusion, increased blood pressure and pulse rate, muscle stiffness, kidney failure), tardive dyskinesia (abnormal involuntary movements of the tongue, head, face, mouth), and seizures. Conversely, the latter may be peripheral (dry mouth, blurred vision, constipation, urinary retention) and central (intense agitation and delirium).[13]

Parkinsonian effects should be managed by reducing the dose of the antipsychotic and, if necessary, by introducing biperiden.[13] The prophylactic use of antiparkinsonian drugs aiming at reducing the incidence of extrapyramidal side effects should be evaluated on an individual basis, as their recommendation has no substantial evidence.[16]

Metabolic

Metabolic abnormalities related to antipsychotics significantly contribute to the increase in cardiovascular morbidity and mortality (A),[3,13] especially when added to failures in managing the monitoring of potential cardiovascular risks in people with all types of mental disorders, particularly psychosis.[3]

Adverse metabolic effects are more evident in conditions of: social vulnerability; first episode of psychosis with no previous history of antipsychotic use; children and adolescents.[20]

Weight gain associated with the use of antipsychotics mainly occurs in the first three months of treatment. From a physiological point of view, weight gain may be related to the increase in circulating leptin during the use of these drugs. Lipid changes, hyperglycemia, and insulin resistance can occur even without the resulting weight gain. In addition to lifestyle (B), other adverse metabolic effects of drugs (A), pharmacogenetic differences between individuals (B), and the direct effects of some antipsychotics on insulin secretion (B), their use consist in an important risk factor for diabetes and cardiovascular diseases. Therefore, replacing the drug for one with lower associated weight gain should be considered (B).[3,20]

OTHER SECTIONS

In addition to adverse metabolic and motor effects, the use of antipsychotics includes sedation, orthostatic hypotension, increased prolactin, leukopenia, agranulocytosis, sexual alterations, jaundice, elevated liver enzymes, photosensitivity, skin rashes, and retinal pigmentation. The increase in therapeutic doses increases the risk of adverse effects even without providing additional efficacy benefit, in addition to the risk of acute toxicity, characterized by hypotension, tachycardia, hyperthermia, arrhythmia, dizziness, dystonia, and seizures.[13]

The increase in prolactin, defined as the sustained increase in levels above the laboratory reference value, has multifactorial causes that, together with the use of certain antipsychotics, are significant and may present clinically with amenorrhea, galactorrhea, sexual dysfunction, and osteoporosis.[12] Hyperprolactinemia is a common effect in first-generation antipsychotics and in the use of risperidone,[21] as well as effects related to sexual dysfunction,[23,24] suggesting that psychosis is not solely responsible for sexual alterations.[23]

In addition to the association with hyperprolactinemia,[24] antipsychotics distinctively affect areas of the sexual response cycle, namely: interest (sexual drive), arousal (vaginal lubrication or erection), and orgasm.[23,24] Some reviews show inconsistent evidence that an antipsychotic has a higher profile of this side effect, but they highlight that it is common among those who use these drugs and that they significantly interfere with quality of life and the impact of treatment.[24]

FINAL CONSIDERATIONS

In this review, we highlight the importance of primary healthcare professionals delving deeper into the care involved in the treatment of people with psychosis, as these professionals consider the subject in their entirety.

It was possible to observe the efficacy profile, adverse effects, safety, and tolerability of the main drugs available, facilitating decision-making regarding the introduction of antipsychotics into primary health care.

There are major limitations in the available evidence regarding treatment provided in the context of primary health care and person-centered care, considering that most of the reviews and guidelines were produced by psychiatry. Furthermore, there are still many uncertainties regarding the phase of maintenance and adherence to treatment as well as the management of some specific adverse effects. Due to the scarce national literature, we could not analyze the specific efficacy and tolerability profile for the Brazilian population, nor the cost, as many drugs differ from international presentations.

CONFLICT OF INTERESTS

Nothing to declare.

AUTHORS' CONTRIBUTIONS

DMC: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. GAP: Conceptualization, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. RNB: Conceptualization, Data Curation, Formal Analysis, Writing – original draft.

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