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THERAPEUTIC MANAGEMENT OF DYSTHYMIA (PERSISTENT DEPRESSIVE DISORDER): LONG-TERM STRATEGIES AND REMISSION

MANEJO TERAPÊUTICO DA DISTIMIA (TRANSTORNO DEPRESSIVO PERSISTENTE): ESTRATÉGIAS DE LONGO PRAZO E REMISSÃO

MANEJO TERAPÉUTICO DE LA DISTIMIA (TRASTORNO DEPRESIVO PERSISTENTE): ESTRATEGIAS A LARGO PLAZO Y REMISIÓN

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ABSTRACT

Persistent Depressive Disorder (PDD), previously known as dysthymia, is characterized by a chronic, progressive, and often treatment-resistant course, associated with significant functional impairment and continuous reduction in quality of life. This study aimed to analyze contemporary therapeutic strategies for the management of dysthymia, with an emphasis on long-term approaches and factors associated with clinical and functional remission. It is a literature review conducted through searches in PubMed and the Virtual Health Library, covering studies published in the last five years, focusing on pharmacological, psychotherapeutic, neurobiological, and technological interventions related to PDD. The analyzed studies highlight that PDD involves neurobiological alterations in subcortical structures associated with motivation and the reward system, contributing to its chronicity and limited response to conventional antidepressants. In pharmacological management, favorable evidence has been observed for the use of bupropion, lamotrigine, and, in treatment-resistant cases, amantadine, indicating promising therapeutic alternatives. The combination of pharmacotherapy and psychotherapy, especially Cognitive-Behavioral Therapy, has demonstrated greater efficacy in reducing symptoms and preventing relapses. Furthermore, psychological interventions based on digital technology showed a positive impact on quality of life improvement and ongoing treatment support. It is concluded that the management of

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Persistent Depressive Disorder requires an integrated, longitudinal, and individualized approach that considers the neurobiological, psychosocial, and clinical aspects involved in the chronification of the disorder. The combination of targeted pharmacological interventions, structured psychotherapy, and digital technologies constitutes a relevant strategy to promote clinical stability, sustained remission, and reduction of the functional impact of PDD.

Keywords: Persistent Depressive Disorder. Dysthymia. Therapeutic Management. Remission. Pharmacotherapy. Psychotherapy. Amantadine. Chronic Apathy.

RESUMO

O Transtorno Depressivo Persistente (TDP), anteriormente denominado distimia, caracteriza-se por um curso crônico, progressivo e frequentemente refratário, associado a prejuízos funcionais significativos e comprometimento contínuo da qualidade de vida. Este estudo teve como objetivo analisar as estratégias terapêuticas contemporâneas voltadas ao manejo da distimia, com ênfase nas abordagens de longo prazo e nos fatores associados à remissão clínica e funcional. Trata-se de uma revisão bibliográfica, realizada a partir de buscas nas bases PubMed e Biblioteca Virtual em Saúde, contemplando estudos publicados nos últimos cinco anos, com foco em intervenções farmacológicas, psicoterapêuticas, neurobiológicas e tecnológicas relacionadas ao TDP. Os estudos analisados evidenciam que o TDP envolve alterações neurobiológicas em estruturas subcorticais associadas à motivação e ao sistema de recompensa, contribuindo para sua cronicidade e resposta limitada aos antidepressivos convencionais. No manejo farmacológico, destacam-se evidências favoráveis ao uso da bupropiona, lamotrigina e, em casos resistentes, da amantadina, indicando alternativas terapêuticas promissoras. A associação entre farmacoterapia e psicoterapia, especialmente a Terapia Cognitivo-Comportamental, demonstrou maior eficácia na redução dos sintomas e na prevenção de recaídas. Ademais, intervenções psicológicas baseadas em tecnologia digital apresentaram impacto positivo na melhora da qualidade de vida e no suporte contínuo ao tratamento. Conclui-se que o manejo do Transtorno Depressivo Persistente requer uma abordagem integrada, longitudinal e individualizada, que considere os aspectos neurobiológicos, psicossociais e clínicos envolvidos na cronificação do transtorno. A combinação entre intervenções farmacológicas direcionadas, psicoterapia estruturada e tecnologias digitais configura-se como estratégia relevante para promover estabilidade clínica, remissão sustentada e redução do impacto funcional do TDP.

Palavras-chave: Transtorno Depressivo Persistente. Distimia. Manejo Terapêutico. Remissão. Farmacoterapia. Psicoterapia. Amantadina. Apatia Crônica.

RESUMEN

El Trastorno Depresivo Persistente (TDP), anteriormente denominado distimia, se caracteriza por un curso crónico, progresivo y frecuentemente refractario, asociado a un deterioro funcional significativo y a un compromiso continuo de la calidad de vida. Este estudio tuvo como objetivo analizar las estrategias terapéuticas contemporáneas para el manejo de la distimia, con énfasis en los enfoques a largo plazo y en los factores asociados con la remisión clínica y funcional. Se trata de una revisión bibliográfica realizada a partir de búsquedas en PubMed y la Biblioteca Virtual en Salud, que incluyó estudios publicados en los últimos cinco años, con un enfoque en intervenciones farmacológicas, psicoterapéuticas, neurobiológicas y tecnológicas relacionadas con el

TDP. Los estudios analizados evidencian que el TDP involucra alteraciones neurobiológicas en estructuras subcorticales asociadas con la motivación y el sistema de recompensa, contribuyendo a su cronicidad y a la respuesta limitada a los antidepresivos convencionales. En el manejo farmacológico, se destacan evidencias favorables al uso de bupropión, lamotrigina y, en casos resistentes, amantadina, lo que indica alternativas terapéuticas prometedoras. La combinación de farmacoterapia y psicoterapia, especialmente la Terapia Cognitivo-Conductual, ha demostrado mayor eficacia en la reducción de síntomas y la prevención de recaídas. Además, las intervenciones psicológicas basadas en tecnología digital mostraron un impacto positivo en la mejora de la calidad de vida y en el soporte continuo al tratamiento. Se concluye que el manejo del Trastorno Depresivo Persistente requiere un enfoque integrado, longitudinal e individualizado, que considere los aspectos neurobiológicos, psicosociales y clínicos implicados en la cronificación del trastorno. La combinación de intervenciones farmacológicas dirigidas, psicoterapia estructurada y tecnologías digitales constituye una estrategia relevante para promover la estabilidad clínica, la remisión sostenida y la reducción del impacto funcional del TDP.

Palabras clave: Trastorno Depresivo Persistente. Distimia. Manejo Terapéutico. Remisión. Farmacoterapia. Psicoterapia. Amantadina. Apatía Crónica.

1 INTRODUCTION

Persistent Depressive Disorder (PDD), historically referred to as dysthymia, represents a chronic and debilitating form of unipolar depression that manifests for a minimum of two years. In the advent of the DSM-5, dysthymia was consolidated with chronic major depressive disorder under the nomenclature of PDD, reflecting the persistent and often refractory nature of this condition (Matsuzaka et al., 2021; MacDonald and Horton, 2021). Although symptoms may be less acute than in a typical major depressive episode, the chronicity of the disorder results in profound functional impairment and a drastic reduction in patients' quality of life (Schefft et al., 2024).

The management of Persistent Depressive Disorder (Dysthymia) is a unique clinical challenge, as we are not only dealing with an acute "episode", but with a melancholic mood state that has become part of the patient's identity.

Unlike classic major depression, dysthymia requires a "marathon" approach, where the focus is not only on suppressing symptoms, but on restructuring quality of life and social functioning.

PTD has a chronic course, wide clinical heterogeneity, and often limited response to conventional antidepressants, factors that contribute to poor prognosis and greater functional impairment to patients (Matsuzaka et al., 2022). Neurobiological evidence indicates the presence of structural changes in subcortical regions related to motivation and the reward system, such as the putamen and nucleus accumbens, suggesting an association between the chronicity of the depressive condition and specific brain impairments (Hung et al., 2023). Additionally, digital psychotherapeutic interventions based on cognitive-behavioral therapy have shown the potential to reduce depressive symptoms and promote improved quality of life, a particularly relevant outcome in the evaluation of therapeutic strategies for chronic depression (Schefft et al., 2024).

The pathophysiology of dysthymia involves complex structural and neurobiological changes, including evidence of atrophy in subcortical nuclei that differ from those seen in non-chronic depressions (Hung et al., 2023). The clinical challenge lies not only in achieving symptomatic remission, but in maintaining long-term stability and managing residual symptoms, such as chronic apathy (Morin et al., 2025). Contemporary therapeutic management requires an integrated approach, combining advanced pharmacotherapy, psychotherapeutic interventions, and, increasingly, the use of digital technologies for continuous support (Krzystanek et al., 2023; Schefft et al., 2024).

PTD does not begin only as a complete clinical picture, appearing first as mild depressive symptoms, irritability, apathy, somatic complaints, disruptive behavior, and through complaints with linguistic markers (Fursov et al., 2025). These mild symptoms are the greatest predictors of the future diagnosis of dysthymia, which is a silent and progressive onset disorder, which is constituted from subclinical symptoms that can be misinterpreted, depression in children and adolescents often presents a clinical picture that differs from the onset in adulthood, making initial diagnosis difficult, increasing the failure in early recognition, which leads to late diagnosis (Styss et al., 2025).

Thus, the probability of ruling out depression/dysthymia is greater than predicting who will develop the disorder, and the psychological reading of the initial signs is essential so that the subject does not consolidate, over the years, a chronic pattern of disinvestment from himself and the world. When the initial signs mentioned above are not read and recognized as depressive manifestations, what begins as a mild symptom ends years later as structural apathy, where suffering begins to organize itself silently and progressively, resulting in a picture of apathy so profound that it will require further investigations that may differentiate dysthymia from neurodegenerative processes (Morin et al., 2025). PTD, therefore, is not only characterized by the prolonged presence of depressive symptoms, it appears in language, in the way of thinking, in the organization of life, and in a gradual transformation of the individual's relationship with his or her own life experience (Fursov et al., 2025).

Despite advances in therapeutic strategies aimed at depressive disorders, the management of Persistent Depressive Disorder still lacks systematized approaches that prioritize sustained remission and the preservation of psychosocial functioning over time. Many interventions remain predominantly focused on symptomatic reduction, with less emphasis on the subjective, neurobiological, and functional processes implicated in the chronicity of the condition. In this context, it is relevant to integrate emerging pharmacological evidence, structured psychotherapeutic interventions, and continuous technological resources. Thus, the present study proposes to critically analyze contemporary therapeutic strategies for the longitudinal management of PTD, focusing on clinical stability and long-term remission.

2 METHODOLOGY

The present investigation is configured as a narrative review of the literature, structured with the aim of examining and compiling the most current scientific evidence about the therapeutic management of dysthymia (Persistent Depressive Disorder). Bibliographic research was carried out in the PubMed database, using the descriptors "Dysthymia", "Treatment" and "Diagnosis", articulated by the Boolean operators AND and OR, in accordance with the Medical Subject Headings (MeSH). Additionally, the search was expanded to the Virtual Health Library (VHL), using the DeCS/MeSH descriptors "Psychology", "Depression" and "Dysthymia", combined by the Boolean operators AND/OR, in order to contemplate productions that articulate psychological, clinical and diagnostic aspects of Persistent Depressive Disorder. The search strategy delimited the inclusion of articles published in the last five years, prioritizing studies with full access and written in English. Productions that did not have a direct link with the remission and long-term strategies of the TDP were disregarded, as well as duplicate publications or reviews without explicit methodological rigor. The selection process involved the analysis of titles and abstracts, followed by the critical reading of the full texts to confirm their relevance. The synthesis of information was organized in a qualitative and descriptive way, focusing on the integration of new therapies and neurobiological findings.

3 RESULTS AND DISCUSSION

3.1 NEUROBIOLOGICAL ALTERATIONS AND DIFFERENTIAL DIAGNOSIS

Recent neuroimaging studies indicate that patients with PDD have reduced gray matter volumes in specific subcortical nuclei, such as the putamen, pallidus, and thalamus, compared to individuals with non-chronic major depressive disorder (Hung et al., 2023). These differences suggest that the chronicity of depression may lead to distinct brain atrophy processes, which reinforces the need for early and sustained interventions to prevent the progression of structural damage.

In addition, the clinical distinction between dysthymia and states of chronic apathy after major depressive episodes is vital. Persistent apathy can mimic the low-energy symptoms of dysthymia, but often requires further diagnostic investigations, such as the use of biomarkers and PET scans to rule out underlying neurodegenerative processes (Morin et al., 2025).

In this aspect, the differential diagnosis is essential to distinguish neurological and psychiatric disorders, due to the symptomatic overlap, especially apathy, which can lead to the diagnosis of both neurodegenerative diseases and mood disorders. This scenario, together with the chronic and insidious course of PARD, represents a challenge for clinical analysis. Thus, it is relevant to differentiate PDD from other psychiatric disorders, such as Major Depressive Disorder (MDD), which shares affective symptoms of the depressive spectrum, as well as functional and psychomotor symptoms, such as persistent fatigue, reduced energy, and decreased participation in daily and social activities. However, a more intense symptomatic course is observed in MDD, characterized by seizures accompanied by total or partial remission, in addition to suffering being reported as an episode rather than as a persistent symptom. (American Psychiatric Association, 2022).

3.2 PHARMACOLOGICAL STRATEGIES AND ADJUNCTIVE THERAPIES

Evidence available in the literature indicates that the combination of psychotherapeutic strategies with pharmacological treatment exerts a complementary effect, resulting in greater efficacy in the management of dysthymia. Cognitive behavioral therapy (CBT) has robust evidence, especially when associated with antidepressants. Among the most used drugs are sertraline, fluoxetine, paroxetine and imipramine. However, in cases of drug failure, there are no well-established standardized and specific recommendations for this population (Schefft et al., 2024; Krzystanek et al., 2023).

Conventional pharmacotherapy often fails to achieve complete remission in TDP. Bupropion has stood out as an effective and well-tolerated option, and is often preferred due to its favorable profile regarding weight gain and sexual dysfunction, common side effects in other classes of antidepressants (MacDonald and Horton, 2021).

For resistant cases, new approaches are being explored:

- **Lamotrigine:** Adjunctive use of lamotrigine has shown promise in cases of PDD refractory to selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), aiding in mood stabilization and symptom remission (Matsuzaka et al., 2021).
- **Amantadine:** Case series studies indicate that amantadine, due to its dopaminergic properties and antagonism to the NMDA receptor, may act effectively in reducing dysthymic symptoms, offering a new avenue for off-label treatment of chronic patients (Krzystanek et al., 2023).

Regarding the treatment of resistant dysthymia, in an open and naturalistic case study, amantadine proved to be an effective candidate, presenting therapeutic effects even at low doses, good tolerability and maintenance of the clinical effect after its discontinuation. In addition, one of the main findings refers to the speed of action, considering that, in general, it takes about three months to observe signs of improvement with drugs such as sertraline, while amantadine demonstrated significant improvement in depressive symptoms in the first month of treatment, with progressive intensification of the clinical response throughout the therapeutic maintenance. (Krzystanek et al., 2023).

3.3 USE OF AMANTADINE IN DYSTHYMIA WITH A PREDOMINANCE OF ANHEDONIA

Amantadine has been investigated as a therapeutic alternative in the treatment of bipolar depression, especially in conditions marked by anhedonia, apathy and fatigue, symptoms often associated with dysthymia and resistant depressive states. The efficacy of the drug seems to be mainly related to its pro-dopaminergic action, since the dysfunction of the reward system and the reduction of dopaminergic activity are implicated in the pathophysiology of anhedonia and motivational loss.

Observational clinical studies and case series described by Krzystanek et al. demonstrate that patients with bipolar depression and dysthymia show significant improvement in depressive symptoms, particularly anhedonia, in the first weeks of amantadine use. This early effect differentiates the drug from conventional antidepressants, which generally require longer periods for clinical response.

The findings of Krzystanek et al. indicate that amantadine may act as a modulator of the brain's reward system, partially restoring responsiveness to reinforcing stimuli and reducing core symptoms such as apathy, anhedonia, and lack of motivation. However, despite the promising results, the authors emphasize the need for controlled studies, with a larger number of participants and prolonged follow-up, to confirm the efficacy and safety of amantadine in the treatment of bipolar depression.

3.4 PSYCHOLOGICAL AND TECHNOLOGICAL INTERVENTIONS

The neurobiological changes observed in PDD do not appear suddenly, they are the accumulated result of a prolonged process of unidentified subclinical psychological suffering, a late outcome of a silent and progressive psychological process. Recent

studies indicate that mild depressive symptoms, irritability, and somatic complaints precede the establishment of PDD by years, without being interpreted as depressive manifestations (Styss et al., 2025). This gradual process is also associated with persistent experiences of emotional deprivation, structural loneliness, and impoverishment of relational life, which progressively shape the way the subject perceives themselves and the world (Fursov et al., 2025). This suggests that dysthymia is progressively constituted from subtle psychological signals that escape the traditional biomedical reading, reinforcing the importance of continuous and technologically mediated psychological interventions for the longitudinal management of the disorder.

In this context, the relevance of long-term psychological interventions based on the identification and continuous monitoring of subjective and subtle symptoms is highlighted, such as those assessed by clinical scales aimed at initial changes in the psychic experience, such as the SPI-CY (*Schizophrenia Proneness Instrument, Child and Adolescent version*) and the SIPS (*Structured Interview for Psychosis-Risk Syndromes*)), both used in young people with High Clinical Risk (CHR) (Styss et al., 2025). These instruments show that mild manifestations, often disregarded in clinical practice, can precede the development of persistent depressive conditions by up to two years, indicating the need for therapeutic strategies that start early and are maintained over time.

Psychotherapy, specifically Cognitive Behavioral Therapy (CBT), remains critical in long-term management. Recently, internet-based interventions (IBIs) have emerged as a powerful tool to increase access to treatment. The CBT-based "Selfapy" platform has been shown in randomized controlled trials to be able to significantly reduce symptom severity and improve the quality of life of patients with dysthymia, both in therapist-guided and self-guided modalities (Schefft et al., 2024). The effectiveness of these digital tools suggests that ongoing patient support and education are key to maintaining remission outside of the traditional clinical setting.

Remission in Persistent Depressive Disorder should not be understood only as the fall in depressive symptoms, but also as the recovery of the individual's emotional, social, and occupational functioning. Evidence indicates that, even after clinical improvement, many patients remain with residual symptoms, such as persistent apathy, motivational impoverishment, and relational withdrawal, factors that contribute to the maintenance of suffering and increase the risk of relapse. Thus, therapeutic strategies that integrate continuous monitoring, prolonged psychotherapeutic interventions, and psychosocial

support are essential for the consolidation of therapeutic gains and for long-term functional remission (Morin et al., 2025; Schefft et al., 2024).

4 CONCLUSION

The study shows that the therapeutic management of Persistent Depressive Disorder requires a longitudinal, integrated, and multidimensional approach. The analyzed research demonstrates that the chronicity of the condition involves not only neurobiological alterations, but also a gradual process of deterioration of the subjective experience, which reinforces the importance of early recognition of subtle signs and preventive interventions throughout development. The most recent pharmacological strategies, associated with structured psychotherapies and the growing use of digital technologies, show promise to increase therapeutic efficacy and favor the maintenance of remission. Thus, it becomes evident that continuous care, adapted to individual needs and based on rigorous clinical follow-up, is essential to reduce the functional impact of the disorder and to promote a significant improvement in the quality of life of patients. In view of this, it is concluded that progress in the treatment of PDD depends on the integration of technological innovation, consistent psychotherapeutic practices, and well-targeted pharmacological interventions, consolidating a care model that prioritizes prevention, stability, and sustained remission.

The studies analyzed present a comprehensive view of different treatments and conditions related to apathy and persistent depression, ranging from pharmacological interventions to the identification of possible neurodegenerative conditions. The efficacy of treatments such as lamotrigine, amantadine and bupropion has been highlighted as promising for patients with persistent depressive disorders, especially in cases resistant to conventional treatments.

Lamotrigine, specifically, has been shown to be an effective alternative for resistant depression, relieving both depressive and anxiety symptoms, without the need for benzodiazepines. Amantadine has also been shown to be effective, especially in resistant dysthymia cases, with good results in terms of relieving depressive symptoms, although with more studies needed to validate its long-term effects.

Bupropion, in turn, was compared with other antidepressants, and its efficacy in terms of response and remission was considered equivalent, with the advantage of having fewer adverse effects related to sexual dysfunction.

In addition, cases of chronic apathy after episodes of major depression, described in a specific study, revealed a complex condition, where persistent apathy was observed without the presence of dysthymia or a diagnosis of neurodegeneration. This phenomenon was associated with anomalies in the mesial frontal cortex, but without a progression to typical dementia conditions, such as frontotemporal dementia or Parkinson's disease. The temporary response to zolpidem indicated a possible therapeutic path, suggesting that modulation of the cortical-subcortical network may be effective in treatments of persistent apathy.

In addition, the findings reinforce the need for future research with longitudinal designs and an interdisciplinary approach, capable of investigating in an integrated way the neurobiological, psychological, and functional markers of Persistent Depressive Disorder. The deepening of this field of investigation may contribute to the improvement of diagnostic strategies and to the development of more precise, personalized therapeutic interventions oriented to the maintenance of remission over time.

In summary, the findings suggest that while more clinical studies are still needed to solidify therapeutic approaches and accurately diagnose these conditions, treatments such as lamotrigine, amantadine, bupropion, and zolpidem offer promising results for the management of persistent depressive disorders and chronic apathy. The interactions between psychiatric and neurological factors, as well as the neuropsychological and neuroimaging characteristics of patients, point to an urgent need for interdisciplinary research and a deeper understanding of the pathophysiology of these conditions.

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