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PSYCHOTIC DEPRESSION: ADVANCES IN PHARMACOLOGICAL AND PSYCHOTHERAPEUTIC TREATMENT

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Abstract: Psychotic depression (PD) is a severe subtype of major depressive disorder characterized by delusions and/or hallucinations, and is associated with a worse clinical prognosis, increased risk of suicide, and high relapse rates. The treatment of choice recommended by the guidelines is the combination of antidepressants with antipsychotics, or electroconvulsive therapy (ECT) in severe or refractory cases. The combination of selective serotonin reuptake inhibitors (SSRIs) with second-generation antipsychotics has greater efficacy and tolerability. Electroconvulsive therapy remains the most effective treatment in severe cases. Despite the focus on pharmacotherapy, psychotherapeutic interventions such as cognitive behavioral therapy (CBT) and psychoeducation have shown important benefits as adjuvants. In addition, emerging therapies, such as the use of psilocybin and cannabidiol, are being investigated, although there is still no robust evidence for their application in PD. There is an urgent need for more clinical studies evaluating maintenance treatments, integrated strategies, and long-term functional outcomes.

Keywords: Psychotic depression; Antidepressants; Antipsychotics; Combination therapy; Cognitive behavioral therapy.

INTRODUCTION

Psychotic depression (PD) is a severe subtype of major depressive disorder (MDD), characterized by the presence of delusions and/or hallucinations during a depressive episode (García-Gutiérrez et al., 2023). Affecting between 10% and 25% of patients with MDD, PD is associated with a significantly worse prognosis compared to non-psychotic depression, including a higher risk of suicide, greater functional impairment, longer hospitalizations, and a lower probability of complete remission (Oliva et al., 2022; García-Gutiérrez et al., 2023).

Historically, the treatment of PD has been a clinical challenge. Current guidelines and a robust evidence base recommend, as first-line treatment, the combination of an antidepressant with an antipsychotic or electroconvulsive therapy (ECT) (Oliva et al., 2022). Monotherapy with either class of drugs is considered less effective and is therefore not the preferred initial approach (García-Gutiérrez et al., 2023). Despite the proven efficacy of combination therapy and ECT, a significant proportion of patients do not respond adequately to initial treatment or experience adverse effects that limit adherence (Oliva et al., 2022).

This scenario drives the search for more effective and better tolerated therapeutic strategies. Recent advances have explored not only new pharmacological combinations but also the role of psychotherapeutic interventions as adjuncts to standard treatment. This review aims to synthesize the current evidence on pharmacological and psychotherapeutic treatments for psychotic depression, discussing both established approaches and emerging therapeutic innovations.

METHODOLOGY

This study was designed as a narrative review with the purpose of examining and synthesizing the current scientific literature on advances in the pharmacological and psychotherapeutic treatment of psychotic depression. A bibliographic search was conducted in the PubMed database using the descriptors "Psychotic Depression," "Diagnosis," and "Treatment," according to the Medical Subject Headings (MeSH) vocabulary. The search was optimized using the Boolean operators AND and OR. The inclusion criteria covered systematic reviews, meta-analyses, clinical trials, and relevant case reports published in the last five years that directly addressed therapeutic interventions for psychotic depression. Studies focusing exclusively on non-psychotic depression or other psychoses were excluded. The selection of articles took place in two phases: an initial screening through the analysis of titles and abstracts, followed by a full reading of the selected texts for the extraction and consolidation of data in a descriptive manner.

RESULTS

The results of the literature reviewed confirm the superiority of combined pharmacological therapy and point to the potential of adjuvant psychotherapeutic approaches and new therapeutic modalities.

STANDARD PHARMACOLOGICAL TREATMENT

The strongest evidence for the treatment of psychotic depression supports the combination of an antidepressant with an antipsychotic as first-line therapy (García-Gutiérrez et al., 2023; Oliva et al., 2022). Systematic reviews and meta-analyses consistently demonstrate that this combination is significantly more effective than monotherapy with either class of drugs alone (García-Gutiérrez et al., 2023). The combination of a selective serotonin reuptake inhibitor (SSRI) with a second-generation antipsychotic (SGA) is the most common and preferred strategy due to a more favorable tolerability profile compared to combinations of tricyclic antidepressants (TCAs) and first-generation antipsychotics (García-Gutiérrez et al., 2023). Fluoxetine and olanzapine, when administered alone, also have mood-stabilizing effects, and their combination is a recommended treatment option for treatment-resistant bipolar depression. In addition to their antidepressant and antipsychotic effects, the synergistic action of olanzapine and fluoxetine can significantly modulate some of the characteristic symptoms of BD (OLIVA, V. et al., 2022). A network meta-analysis identified the combination of venlafaxine and quetiapine as one of the most effective and well-tole-

rated (Oliva et al., 2022). The combination of sertraline and olanzapine is also a well-studied and effective option (García-Gutiérrez et al., 2023). For severe, refractory cases or when a rapid response is needed, electro r electroconvulsive therapy (ECT) remains the most effective treatment, considered the "gold standard" (Oliva et al., 2022).

PSYCHOTHERAPEUTIC APPROACHES

Research on specific psychotherapeutic interventions for psychotic depression is limited. However, adjunctive approaches show promise. One case study demonstrated that adding cognitive behavioral therapy (CBT) and psychoeducation to pharmacological treatment was beneficial for a patient with a partial response to medication (Kruizinga et al., 2020). The intervention helped the patient develop coping strategies for residual psychotic symptoms, improved insight into the illness, reduced delusional beliefs, and improved overall functioning (Kruizinga et al., 2020).

EMERGING THERAPIES

New treatment modalities for depressive disorders are being investigated, although they have not yet been specifically tested in psychotic depression. Psilocybin-assisted therapy, for example, has demonstrated rapid, robust, and sustained antidepressant effects in patients with major depressive disorder in randomized clinical trials (Davis et al., 2021). Although patients with a history of psychosis are typically excluded from these studies, the exploration of new mechanisms of action, such as serotonergic 2A receptor agonism, represents a future area of interest for severe and treatment-resistant depressive disorders (Davis et al., 2021).

In addition, García-Gutiérrez et al. (2020) highlight the therapeutic potential of cannabidiol (CBD), a compound derived from Cannabis sativa, which has anxiolytic, antidepressant, and antipsychotic effects, as well as a safe profile with no risk of abuse. These findings indicate that CBD may be a promising alternative in the management of psychiatric disorders, including depression, although specific studies in patients with psychotic depression are still needed.

GAPS AND FUTURE PERSPECTIVES

Despite the proposed therapeutic innovations, the literature still presents significant obstacles in addressing psychotic depression. Oliva et al. (2022) highlight that only a minority of large-scale randomized clinical trials have prioritized the evaluation of the efficacy of different pharmacological combinations, which limits the possibility of establishing robust standardized protocols. In addition, García-Gutiérrez et al. (2023) state that most studies have only short-term outcomes, with little research on maintenance treatment, relapses, and long-term functional impact. Emerging research on new pharmacological therapies, such as psilocybin (Davis et al., 2021), does not yet include populations with psychotic symptoms, indicating the need to establish targeted studies. Future research should address the development of predictive biomarkers for the development of personalized treatments and the integration of pharmacological, psychotherapeutic, and neuromodulatory strategies to optimize clinical and functional outcomes.

DISCUSSION

The current evidence base consolidates combined antidepressant and antipsychotic therapy as the cornerstone of pharmacological treatment for psychotic depression (García-Gutiérrez et al., 2023; Oliva et al., 2022). The superiority of this approach over monotherapy is clear, as it simultaneously targets the depressive and psychotic components of

the syndrome (García-Gutiérrez et al., 2023). The choice of the specific combination, preferably an SSRI with an ASG, should be individualized, taking into account the patient's adverse effect profile and comorbidities, with the aim of optimizing tolerability and treatment adherence (Oliva et al., 2022).

Despite the pharmacological focus on acute PD management, psychotherapeutic interventions should not be neglected. The case report by Kruizinga et al. (2020) suggests that CBT and psychoeducation can play a crucial adjuvant role, especially in addressing residual symptoms, improving understanding of the disease, and facilitating functional recovery. This finding points to a gap in the literature and the need for randomized clinical trials to formally evaluate the effectiveness of psychotherapy as an adjunct to standard PD treatment. The integration of these approaches may offer a more holistic and effective treatment in the long term.

Even with the therapies available, a proportion of PD patients do not achieve complete remission, highlighting the need for therapeutic innovation (Oliva et al., 2022). Research into new compounds, such as psilocybin-assisted therapy for MDD, opens up new perspectives (Davis et al., 2021). Although application in patients with psychotic symptoms requires extreme caution and further research, the study of new mechanisms of action is fundamental to the development of future therapies for the most severe and resistant forms of depression.

In addition to symptomatic treatment, the quality of life and psychosocial well-being of patients with psychotic depression have critical clinical outcomes. García-Gutiérrez et al. (2023) show that PD is related to significant deficits in occupational performance, interpersonal relationships, and functional autonomy. In this context, psychotherapeutic interventions, such as CBT associated with psychoeducation (Kruizinga et al., 2020), are significantly useful for reducing residual symptoms and improving social reintegration, even when used as a complement to pharmacological treatment.

In summary, the management of psychotic depression should be multimodal. The initial approach should be combined pharmacotherapy, with ECT reserved for more severe or refractory cases. The integration of adjuvant psychotherapeutic interventions, such as CBT, should be considered to optimize functional recovery and the management of residual symptoms, promoting better long-term outcomes.

CONCLUSION

Psychotic depression represents a significant clinical challenge, requiring a comprehensive and individualized therapeutic approach. Current evidence supports the combination of antidepressants with antipsychotics as first-line treatment, while electroconvulsive therapy remains the most effective intervention in severe or refractory cases. Although pharmacotherapy is the mainstay of treatment, psychotherapeutic interventions such as cognitive-behavioral therapy and psychoeducation have shown potential to improve functional outcomes and reduce residual symptoms, standing out as relevant adjunctive strategies.

The emergence of new therapeutic approaches, such as psilocybin and cannabidiol, points to a promising future, although scientific validation in the context of PD is still lacking. There are still significant gaps in the literature, especially regarding maintenance treatment, relapse prevention, and long-term functional impact. Given this, it is imperative to develop clinical trials that integrate pharmacological, psychotherapeutic, and neuromodulatory approaches, aiming not only at symptomatic remission but also at functional rehabilitation and improved quality of life for patients with psychotic depression.

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