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CLINICAL AND THERAPEUTIC ASPECTS OF GENERALIZED ANXIETY DISORDER: A SYSTEMATIC REVIEW

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ABSTRACT

Objective: The general objective of this study is to analyze the scientific production on Generalized Anxiety Disorder (GAD), seeking to identify the main clinical aspects, etiological mechanisms and treatment methods of this condition. Methodology: This is a systematic review that aims to understand the main factors associated with GAD. The research was guided by the question: "What are the main clinical aspects and what diagnostic and therapeutic resources are used in the management of generalized anxiety disorder?" To do this, searches were performed in the PubMed database using the descriptors: Generalized Anxiety Disorder, Comorbidity, Anxiety Symptoms, and Pharmacological Treatment, combined with the Boolean term "AND". Initially, 312 articles were identified, of which 23 met the inclusion criteria, resulting in the analysis of 17 relevant studies. Results: GAD is a common and multifaceted condition, often associated with comorbidities such as depression and substance use disorders. Treatment options include selective serotonin reuptake inhibitors (SSRIs) and Cognitive Behavioral Therapy (CBT). The review highlights the importance of an integrated approach that includes pharmacological and psychotherapeutic interventions for more effective management. Conclusion: In-depth understanding of GAD is critical to improving clinical practices and patient outcomes, necessitating a holistic and ongoing approach.

Keywords: Generalized Anxiety Disorder, Treatment, Comorbidities.

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INTRODUCTION

Anxiety is an emotional response to a potential future threat or danger, causing affective, somatic, and behavioral symptoms. While anxiety considered normal is adaptive to alert and prepare the body for the potential threat, anxiety is considered pathological when it becomes maladaptive, permanent and uncontrollable, negatively affecting daily life, it can manifest as anxiety disorders, including Generalized Anxiety Disorder (GAD), Panic Disorder and Phobias (GARAKANI et al., 2020) (TAFET; NEMEROFF, 2020). Anxiety is one of the most common psychiatric conditions, affecting millions of people worldwide and contributing significantly to global disability According to the World Health Organization, there are an estimated 264 million people in the world who suffer from anxiety disorders, representing a 15% increase since 2005. Anxiety can lead to absences from work and school and have a higher cost than other psychiatric disorders. The prevalence of these disorders has been increasing, highlighting the need for effective treatment strategies (GARAKANI et al., 2020).

The World Health Organization considers GAD a public health problem in Brazil. GAD affects 18 million Brazilians, or 9.3% of the population. Between 55 and 60% of patients with GAD are women (BALDAÇARA et al., 2024). In the Western world, the lifetime prevalence of this disorder represents approximately 20–30% in the general population, making neuropsychiatric disorders more frequent. The overall prevalence of GAD was reported to be 4.5%, being lower in low- and middle-income countries (2.8%) than in high-income countries (5.3%) (SARTORI; SINGEWALD, 2019) (BALDAÇARA et al., 2024). Based on clinical observation criteria, the current version of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) categorizes anxiety disorders into generalized anxiety disorder (GAD), phobias, social anxiety disorder (SAD), post-traumatic stress disorder (PTSD), panic disorder (PD) with/without agoraphobia, and obsessive-compulsive disorder (OCD) (SARTORI; SINGEWALD, 2019).

Anxiety disorders cause great distress to patients, as well as represent a huge burden on their families and social resources, and they contribute to the development of depression, substance abuse, physical illness, and other adverse outcomes. In 2010, health care utilization, sick leave, retirement, and reduced productivity at work cost approximately €75 billion in Europe. underlining the enormous financial burden caused by anxiety disorders (SARTORI; SINGEWALD, 2019).

There is also evidence to suggest that patients with anxiety disorders, in particular generalized anxiety disorder (GAD), have high rates of recurrence and/or have persistent anxiety symptoms, especially if they have comorbid Major Depressive Disorder (MDD).

There may be several explanations for the potentially refractory nature of these disorders, including misdiagnosis, poor treatment adherence, substance use, or other comorbidities, although this suggests that conventional treatments may not be effective for all patients and that alternative pharmacotherapies should be developed (GARAKANI et al., 2020).

Variations in the serotonin transporter gene (5-HTT) may predispose children and adolescents to develop GAD (Tsuang et al., 2004). However, the neurochemical basis of GAD in children and adolescents is likely more comprehensive and complex with contributions from the serotonin, norepinephrine, glutamate, and GABA systems. This complexity creates clinical challenges in precision medicine approaches to personalise treatment in young people with GAD, but it also presents immense research opportunities to develop new pharmacological treatments. Neurodevelopmental considerations are important when considering the pathophysiology of anxiety, as the glutamatergic and GABAergic neurotransmitter systems also undergo substantial changes, potentially facilitating further heterogeneity in the clinical picture, pathophysiology, and pharmacological response in GAD (SÁIZ et al., 2022).

This systematic review article aims to compile and analyze the scientific evidence on the management of Generalized Anxiety Disorder (GAD). The objective is to provide a comprehensive and up-to-date view, which synthesizes existing knowledge and identifies gaps in research, guiding future investigations and clinical practices. In-depth analysis of the evidence is intended to be a useful resource for healthcare professionals, researchers, and academics, contributing to the improvement of therapeutic approaches.

METHODOLOGY

This is a systematic review that seeks to understand the main aspects of the clinical manifestations resulting from generalized anxiety disorder, as well as to demonstrate the main methods used in the diagnosis and treatment of the condition, aiming to ensure a greater clinical elucidation of this pathology. For the development of this research, a guiding question was elaborated through the PVO (population, variable and objective) strategy: "What are the main aspects that permeate generalized anxiety disorder, as well as what are the diagnostic and therapeutic resources used in clinical practice?"

The searches were carried out through searches in the PubMed Central (PMC) databases. Four descriptors were used in combination with the Boolean term "AND": Generalized Anxiety Disorder, Comorbidity, Anxiety Symptoms and Pharmacological Treatment. The search strategy used in the PMC database was: Generalized Anxiety Disorder AND Comorbidity AND Anxiety Symptoms and Generalized Anxiety Disorder AND

Pharmacological Treatment. From this search, 312 articles were found, which were later submitted to the selection criteria. The inclusion criteria were: articles in English, Portuguese and Spanish; published in the period from 2019 to 2024 and that addressed the themes proposed for this research, in addition, review, observational and experimental studies, made available in full. The exclusion criteria were: duplicate articles, available in the form of abstracts, that did not directly address the proposal studied and that did not meet the other inclusion criteria.

After associating the descriptors used in the searched databases, a total of 312 articles were found. After applying the inclusion and exclusion criteria, 23 articles were selected from the PubMed database, and a total of 17 studies were used to compose the collection.

DISCUSSION

Anxiety disorders are the most prevalent class of mental disorder in most Western societies and are a leading cause of disability. The onset of anxiety disorders usually occurs in early adulthood. So, they seem to follow a chronic course, characterized by periods of remission and relapse; The stability of the disease over time varies between studies and specific diagnoses. According to the DSM-5, anxiety disorders include specific phobias, social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder (post-traumatic stress disorder and obsessive-compulsive disorders no longer fall into this group and were not considered. The DSM-5 diagnostic criteria for anxiety are similar to those of the other standard classification system, the International Classification of Diseases, tenth edition (ICD-10).

In both systems, anxiety disorders are a spectrum of multidimensional phenotypes that share clinical features such as excessive and stable anxiety; physiological symptoms, such as tachycardia and chest tightness; and typical behavioral responses, such as avoiding perceived threats, places, or situations, which impair people's psychological well-being and quality of life (OMAER et al., 2024).

During the last two decades, there has been a strong push for a better understanding of the complex mechanisms involving neuroanatomical, neurochemical, genetic and epigenetic processes that regulate anxiety and fear in both healthy and sick states, in the belief that this knowledge would facilitate the identification of new treatments. A fundamental idea about the developmental mechanisms of anxiety disorders is that there are scrambled brain connections, chemical imbalances, and imbalanced processes in relevant neurocircuits, for example between those that promote aversive responding,

favoring learning, and fear maintenance versus those that inhibit aversive processing and favor inhibitory learning (extinction). These alterations are produced by endogenous (e.g., genetic) and exogenous (e.g., environmental, epigenetic) factors (SARTORI; SINGEWALD, 2019).

Changes in the structure, function, and connectivity of the amygdala, mPFC, anterior cingulate cortex, and insula, as well as, more recently, the nucleus of the stria terminalis bed, due to advances in imaging techniques are suggested to contribute to the development and maintenance of anxiety disorders in humans. Other maladaptations in other areas, including the thalamus and striatum, have been observed in a specific way of anxiety disorder. In particular, pathologically increased fear/anxiety appears to be commonly associated with increased amygdala activation in response to negative events (SARTORI; SINGEWALD, 2019).

Hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis is associated with increased cortisol levels, which can interfere with cognitive and emotional functions. This hyperactivity can be triggered by genetic factors, prolonged exposure to stress, or other environmental factors. The impact of this dysregulation is observed in several anxiety disorders, such as generalized anxiety disorder (GAD), panic disorder, and post-traumatic stress disorder (PTSD). The text also addresses the role of corticotropin receptors (CRH) in the brain and their interaction with the neurotransmitters serotonin and noradrenaline, which are fundamental in the regulation of mood and stress response (TAFET; NEMEROFF, 2020).

The endocannabinoid system is composed of cannabinoid receptors (CB1 and CB2), endogenous ligands (such as anandamide and 2-AG), and enzymes responsible for their synthesis and degradation. This system is responsible for regulating several physiological functions, such as mood, appetite, and memory, in addition to playing a central role in modulating stress and anxiety. The activation of CB1 receptors in the central nervous system is especially relevant for the regulation of anxiety, as it can inhibit the release of excitatory neurotransmitters such as glutamate, promoting a calming effect. Chronic stress is a crucial factor in the dysregulation of the endocannabinoid system. The hypothalamic-pituitary-adrenal (HPA) axis, which is the primary mediator of the stress response, interacts with the endocannabinoid system. Under normal conditions, endocannabinoids help modulate the stress response, preventing an over-response. However, in situations of chronic stress, endocannabinoid signaling is compromised, which can result in an increase in anxiety levels (HALLER ; 2023).

Pharmacological treatments for anxiety include a variety of medications that act on different neurochemical systems. Benzodiazepines, such as diazepam and lorazepam, are often prescribed for quick relief of anxiety symptoms, but their long-term use is limited due to the risk of addiction and tolerance. These drugs act as GABA receptor agonists, promoting a sedative and anxiolytic effect. However, prolonged use can lead to physical and psychological dependence, as well as side effects such as excessive sedation and cognitive impairment (SÁIZ et al., 2022).

Selective serotonin reuptake inhibitors (SSRIs), such as sertraline and fluoxetine, are considered the first-line treatment for anxiety disorders, increasing the availability of serotonin in the brain (SÁIZ et al., 2022). These drugs are generally well tolerated and have a favorable safety profile compared to benzodiazepines (SÁIZ et al., 2022). Serotonin and norepinephrine reuptake inhibitors (SNRIs), such as venlafaxine and duloxetine, have also been shown to be effective, acting on both serotonin and norepinephrine to improve anxiety and depressive symptoms (SÁIZ et al., 2022).

Vilazodone, approved by the FDA in 2011, is a serotonin reuptake inhibitor that also acts as a partial agonist of the 5-HT1A receptor, showing efficacy in the treatment of major depression and GAD. Studies show that vilazodone can raise serotonin levels more potently than traditional SSRIs, with anxiolytic properties that improve anxiety scores in the first few weeks of treatment. However, adverse effects such as nausea and diarrhea may lead to a higher rate of treatment interruption, underscoring the need for further trials to confirm its role in GAD (SARTORI; SINGEWALD, 2019).

The recommended duration of treatment can vary, but can be as short as 3–6 months, or up to 1–2 years or even longer. Although there may be concern about tachyphylaxis, there is limited evidence of adverse outcomes with chronic use of SSRIs or SNRIs. These medications also tend to be well-tolerated, with adverse effects that are usually manageable or short-lived, such as nausea, headache, dry mouth, diarrhea, or constipation. Sexual dysfunction tends to be a more durable and problematic adverse effect of SSRIs and SNRIs, but it can be controlled with adjunctive treatments. There is a possibility that patients may develop antidepressant-induced nervousness or anxiety, potentially due to the initial increase in serotonin, although this anxiety may be alleviated by slower titration or adjunctive use of benzodiazepines (GARAKANI et al., 2020).

Tricyclic antidepressants (TCAs), which act as serotonin and norepinephrine transporter reuptake inhibitors, were one of the first classes of medications used for anxiety disorders. Despite comparable efficacy to SSRIs, they are now less frequently prescribed

due to concerns about side effects, including weight gain, dry mouth, sedation, urinary hesitancy or retention, arrhythmias, and risk of overdose mortality (GARAKANI et al., 2020).

Other therapeutic agents, such as brexpiprazole and cyclobenzaprine, have also been explored for the treatment of anxiety (SARTORI; SINGEWALD, 2019). Brexpiprazole, an atypical antipsychotic, acts on multiple receptors, including those for dopamine and serotonin, and has been investigated for disorders such as PTSD, although data on its safety and efficacy in different settings remain limited (SARTORI; SINGEWALD, 2019). Cyclobenzaprine, traditionally used as a muscle relaxant, was reformulated to a sublingual version to improve sleep quality and reduce nightmares in people with trauma, suggesting significant therapeutic potential in sleep regulation and mitigation of disorders associated with anxiety (SARTORI; SINGEWALD, 2019). In addition, new therapeutic agents, such as neurosteroids, neuropeptides and phytochemicals, have shown some potential, although they face challenges due to flawed study designs (GARAKANI et al., 2020).

Anxiety and distress are conditions often faced by adults, with many seeking pharmacological treatment for quick symptom relief. In this context, minor tranquilizers, such as benzodiazepines, pregabalin, and quetiapine, have been widely used. A recent systematic review and network meta-analysis evaluated the efficacy of these medications in the short-term treatment for new-onset anxiety and distress symptoms, highlighting both the benefits and limitations associated with these interventions (MUNKHOLM et al., 2024).

The results of the meta-analysis indicate that, with a low certainty level, minor tranquilizers prove to be superior to placebo in reducing anxiety symptoms. The use of the Hamilton Anxiety Scale (HAM-A) as an outcome measure revealed that both benzodiazepines and pregabalin and quetiapine provide significant relief to patients. However, the analysis found no statistically significant differences in efficacy between the three drugs when compared directly, which suggests that treatment choice should consider individual clinical factors and patient preferences (MUNKHOLM et al., 2024).

A critical aspect of the review was the paucity of data on serious adverse events and the inconsistency in the collection of information on side effects. Although no relevant differences in tolerability between drugs have been identified, the lack of adequate systematization may hide significant risks. Benzodiazepines, while effective, are known for their addictive potential, especially in long-term treatments. On the other hand, quetiapine, even at low doses, may be associated with adverse metabolic effects, although available data are limited due to the short duration of trials (MUNKHOLM et al., 2024).

The review emphasizes the need for a holistic approach in the treatment of anxiety, considering not only efficacy but also patient preferences and the possibility of non-

pharmacological interventions, which are often overlooked in clinical trials. The scarcity of data on patients with adjustment disorders represents an important gap in the literature, suggesting that future research should be directed to this specific population (MUNKHOLM et al., 2024).

Cognitive Behavioral Therapy (CBT) is recognized as the most effective psychotherapeutic approach for GAD, outperforming other modalities in terms of positive short-term outcomes. CBT helps patients identify and modify patterns of thought and behavior that contribute to anxiety. Studies indicate that CBT is beneficial not only in adults, but also in children and adolescents. Psychodynamic therapy has also been shown to be effective, although with slightly less robust evidence. The duration of psychotherapy generally varies between 8 and 12 weeks, but the literature does not provide clear guidelines on the time needed to maintain the therapeutic effects in the long term (BALDAÇARA et al., 2024). Individualization of treatment is crucial, considering that each patient may respond differently to interventions (BALDAÇARA et al., 2024). In addition, mindfulness-based approaches and muscle relaxation training have shown considerable benefits (ZHU et al., 2023).

Complementary methods, such as physical exercise, have been shown to reduce GAD symptoms. A recent meta-analysis of 13,574 participants found that exercise alone can reduce symptoms of GAD. Another meta-analysis in college students with GAD (49 students: 75% women; age: 20 years) concluded that exercise significantly reduced GAD symptoms. It should be noted that exercise programs, which are widely available and have no side effects, can be an alternative to pharmacological treatment or cognitive-behavioral therapy (BALDAÇARA et al., 2024). Aromatherapy, using essential oils such as lavender, bergamot, ylang ylang, patchouli, rose, and spikenard, can also be effective in relieving anxiety symptoms (2). These oils can be used in a variety of ways, such as direct inhalation, diffusion into the environment, or topical application diluted in a carrier oil, providing additional relief from anxiety symptoms when integrated into conventional medical treatment (2).

Silexan has gained attention as a natural and effective alternative in the management of anxiety disorders. This compound is derived from Lavandula angustifolia (lavender), and studies indicate that it may have anxiolytic properties and improve physical symptoms associated with anxiety without the common side effects of traditional medications such as benzodiazepines. Anxiety disorders, such as generalized anxiety disorder (GAD), panic disorder, and social anxiety disorder, often present with a combination of psychological and somatic symptoms. The physical health of patients with

chronic anxiety can also be impaired due to the ongoing impact of stress on the body, resulting in fatigue, insomnia, muscle aches, and other symptoms (VON KÄNEL et al., 2021).

Insomnia and sleep disturbances are common symptoms in patients with anxiety. Silexan has been shown to be effective in improving sleep quality, with patients reporting a reduction in sleep latency (time to fall asleep) and an improvement in sleep duration and depth. Insomnia, often associated with psychiatric conditions such as anxiety and depression, should also be treated in an integrated manner, considering insomnia as a comorbid disorder Cognitive-behavioral therapy for insomnia (CBT-I) has shown significant benefits when applied to insomnia and anxiety disorders, with studies demonstrating that concurrent treatment can result in better clinical outcomes (MORIN et al., 2023) (VON KÄNEL et al., 2021). In addition, Silexan has demonstrated beneficial effects in restoring energy levels and reducing feelings of fatigue, with patients reporting increased mood throughout the day (VON KÄNEL et al., 2021).

Studies on anxiety disorders have shown varying results. In general, many have not found a significant association between cannabis use and the development of new anxiety diagnoses. However, some studies have identified that cannabis use may be linked to an increase in anxiety symptoms, especially when factors such as the use of other substances are adjusted. Research is even scarcer when it comes to the therapeutic efficacy of cannabinoids in anxiety disorders, with few studies demonstrating clear benefits (ZIKA; BECKER, 2021).

The endocannabinoid system, a network of natural receptors and ligands in the body, plays an essential role in regulating emotions and stress response, and interaction with cannabis compounds such as THC and CBD has been shown to have diverse effects on mood and anxiety. Cannabis can have both positive and negative effects on mood and anxiety disorders. THC (Δ9-tetrahydrocannabinol), the main psychoactive component of cannabis, may have anxiolytic effects at low doses, but it may also induce anxiogenic effects at higher doses, exacerbating symptoms of anxiety and panic in some individuals. In contrast, CBD (cannabidiol), another non-psychoactive component of cannabis, has consistently shown anxiolytic effects in clinical studies, without the side effects associated with THC (BOTSFORD; YANG; GEORGE, 2020).

Migraine is a very common neurological disorder and contributes to productive disability worldwide, being more frequent in women of childbearing age than in men. Previous studies have often demonstrated the comorbidity of migraine and other psychiatric disorders. It found that the prevalence of migraine with anxiety ranged between 16 and

83%, with a median of 43%. According to population studies, the incidence of migraine with anxiety is prevalent among one-third of migraine sufferers, which is consistent with many of the previous studies. The results showed that the prevalence of women with migraine was significantly higher than that of men, which is well established in previous studies. However, the prevalence of migraine with anxiety was much higher among men compared to women. Despite the different study scenarios, regions, age, and other individual characteristics, the evidence of higher prevalence in men was consistent (KARIMI et al., 2020).

The COVID-19 pandemic has brought to the fore many challenges related to mental health, including anxiety and depression. Studies reveal that an imbalance in the gut microbiota can lead to abnormalities in the gut-brain axis, resulting in an increased activation of the HPA axis and changes in neurotransmitter levels (ZHU et al., 2023). During the COVID-19-related lockdown, there was a significant increase in the prevalence of gastrointestinal symptoms, associated with dysfunction of the gut-brain axis and changes in the neuroimmune and endocrine systems. Pharmacological and psychological interventions, such as CBT, have shown significant benefits in reducing anxiety symptoms during the pandemic (ZHU et al., 2023).

Anxiety disorders often occur with substance use disorders (SUD), posing a considerable challenge to clinical practice. Evidence for the management of TUS in patients with anxiety is limited, with treatments such as sertraline, desipramine, paroxetine, buspirone, naltrexone, and disulfiram being explored. Desipramine, for example, may be preferable to paroxetine in reducing anxiety symptoms in patients with PTSD and alcohol consumption, although the recommendation is weak. The lack of clinical trials that include other types of substances besides alcohol is a significant limitation in the current literature (BALDAÇARA et al., 2024).

It is widely recognized that mood and anxiety disorders often occur together — the presence of one of these two disorders increases the risk of later developing another (comorbid) disorder. Comorbidity refers to the presence of one or more disorders in relation to an index disorder, either in the same period of time (concomitant comorbidity) or at different stages of the life cycle (cumulative comorbidity). The presence of comorbidity between these two disorders is important because anxiety and depressive disorders dependently contribute to a significant portion of the global burden of disease, with depression being the second largest contributor to years lived with disability in people aged 15 to 44 years. In addition, comorbidity between mood and anxiety disorders is associated with greater symptom severity, increased substance use, and suicidal risk. For example, a cohort study found that among those between the ages of 11 and 32, anxiety occurs

simultaneously in 37% of depression cases, while depression occurs in 32% of anxiety cases. Cumulatively, 72% of lifetime anxiety cases had a history of depression, and 48% of lifetime depression cases had anxiety disorders (SAHA et al., 2021).

The treatment of anxiety is a complex endeavor that requires a multidisciplinary approach. The combination of pharmacological and psychotherapeutic treatments, along with complementary approaches, can provide significant improvements in patients' quality of life. Ongoing research and clinical trials are key to integrating these approaches and developing effective practical guidelines (MORIN et al., 2023). The individualization of treatment, considering the specific characteristics of each patient, is essential to achieve the best results (BALDAÇARA et al., 2024).

CONCLUSION

It is concluded that anxiety disorders, due to their high prevalence and complexity, present considerable challenges for both diagnosis and treatment. While there are effective therapeutic options, such as SSRIs, SNRIs, and benzodiazepines, each treatment must be carefully evaluated for side effects and risk of addiction.

In addition, psychotherapeutic approaches, such as Cognitive-Behavioral Therapy, demonstrate promising results in modifying the patterns of thought and behavior associated with anxiety. With the advancement of understanding of the underlying neurobiological mechanisms, including the role of the HPA axis and the endocannabinoid system, it is expected that new treatments may emerge, offering safer and more personalized options. It is critical, however, to take a holistic approach that also includes complementary therapies and the treatment of comorbidities, such as depression and substance use disorders, to provide more complete and lasting relief to patients.

REFERENCES

1. BALDAÇARA, L., de Andrade, L. F., Oliveira, G. R., & Schuch, J. B. (2024). Brazilian Psychiatric Association treatment guidelines for generalized anxiety disorder: Perspectives on pharmacological and psychotherapeutic approaches. Brazilian Journal of Psychiatry, 46, e20233235.

2. BOTSFORD, S. L., YANG, S., & GEORGE, T. P. (2020). Cannabis and cannabinoids in mood and anxiety disorders: Impact on illness onset and course, and assessment of therapeutic potential. The American Journal on Addictions, 29(1), 9-26.

3. FARRAR, A. J., & FARRAR, F. C. (2020). Clinical aromatherapy. Nursing Clinics, 55(4), 489-504.

4. GARAKANI, A., Kahn, A. J., & Henter, I. D. (2020). Pharmacotherapy of anxiety disorders: Current and emerging treatment options. Frontiers in Psychiatry, 11, 595584.

5. HALLER, J. (2023). Anxiety modulation by cannabinoids—the role of stress responses and coping. International Journal of Molecular Sciences, 24(21), 15777.

6. KARIMI, L., Afshar, H., & Heshmat, R. (2020). The prevalence of migraine with anxiety among genders. Frontiers in Neurology, 11, 569405.

7. López-Muñoz, F., & Alamo, C. (2020). Minor tranquillizers for short-term treatment of newly onset symptoms of anxiety and distress: A systematic review with network meta-analysis of randomized trials.

8. MORIN, C. M., Reeve, A., & Kutz, I. (2023). What should be the focus of treatment when insomnia disorder is comorbid with depression or anxiety disorder? Journal of Clinical Medicine, 12(5), 1975.

9. SAHA, S., Karam, A., & Karam, R. (2021). Co-morbidity between mood and anxiety disorders: A systematic review and meta-analysis. Depression and Anxiety, 38(3), 286-306.

10. SÁIZ, P. A., González-Pinto, A., & de la Fuente-Tomas, L. (2022). Clinical practice guideline on pharmacological and psychological management of adult patients with an anxiety disorder and comorbid substance use. Adicciones, 34(2), 157-167.

11. SARTORI, S. B., & SINGEWALD, N. (2019). Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacology & Therapeutics, 204, 107402.

12. SONMEZ, A. I., Kadioglu, O., & Kuru, T. (2020). Novel pharmacological treatments for generalized anxiety disorder: Pediatric considerations. Depression and Anxiety, 37(8), 747-759.

13. TAFET, G. E., & NEMEROFF, C. B. (2020). Pharmacological treatment of anxiety disorders: The role of the HPA axis. Frontiers in Psychiatry, 11, 443.

14. VERGALLITO, A., Marzola, E., & Fabbri, A. (2021). Effectiveness of noninvasive brain stimulation in the treatment of anxiety disorders: A meta-analysis of sham or behaviour-controlled studies. Journal of Psychiatry and Neuroscience, 46(6), E592-E614.

15. VON KÄNEL, R., Preckel, J., & Mergl, R. (2021). Therapeutic effects of Silexan on somatic symptoms and physical health in patients with anxiety disorders: A meta-analysis. Brain and Behavior, 11(4), e01997.

16. ZHU, C., & Chen, H. (2023). Depression and anxiety during the COVID-19 pandemic: Epidemiology, mechanism, and treatment. Neuroscience Bulletin, 39(4), 675-684.

17. ZIKA, M. A., & BECKER, L. (2021). Physical activity as a treatment for social anxiety in clinical and non-clinical populations: A systematic review and three meta-analyses for different study designs. Frontiers in Human Neuroscience, 15, 653108.