A Comprehensive Overview on the Generalized Anxiety Disorder – Etiology and Treatment

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Abstract. Generalized Anxiety Disorder (GAD) is a mental disorder that affects people across the lifespan. The study of GAD has evolved over time, with advancements in research methodologies and treatments. This paper provides an examination of the current understanding of GAD, including etiological factors and evidence-based treatments. Advances in neuroimaging technologies have contributed to a greater understanding of the neurological underpinnings of GAD, while psychotherapeutic interventions have emerged as effective treatment strategies. Moreover, GAD is associated with traits such as avoidance of perceived harm, neuroticism levels, and introversion preference. Studies have also explored the etiology of GAD from a genetic perspective. Future research should focus on validating the efficacy of treatments and exploring novel therapeutic combinations. Additionally, investigating the role of early life events, societal stressors, and cognitive biases in the development of GAD may provide insights into improving management and treatment strategies. This study provides further insights into the etiology of GAD and its treatment.

1 Introduction

Generalized Anxiety Disorder (GAD) is disorder that is characterized by excessive and uncontrolled worry, leading to significant difficulties in daily life. Looking at the prevalence of this disease, women may be twice as likely as men to have generalized anxiety disorder. Prevalence tends to peak in middle age and decrease with older age. In recent years, there has been an increasing focus on studying the etiology and treatments of GAD due to its impact on individuals well-being and society.

Throughout human history, anxiety-related disorders have been recognized under different frameworks. From concepts like Humorism by Hippocrates to Freud's psychoanalytic theories, the understanding and treatment of anxiety disorders have evolved over time. Despite changes in terminology and theories, the central theme of distress and dysfunction caused by worry has remained consistent across eras, highlighting the enduring significance of anxiety disorders in the human experience.

Contemporary research on GAD employs methodologies, including investigations into the neurology that explores underlying brain circuits as well as psychotherapeutic interventions aimed at modifying maladaptive thought. Advances in neuroimaging techniques have revolutionized the researchers' understanding of how GAD affects the brain, revealing interactions between factors, environmental stressors, and disruptions in neural circuits. Meanwhile, psychological treatments emerged as key strategies for managing symptoms and improving functioning.

Given the information presented, this paper aims to offer an examination of what's currently known about generalized anxiety disorder (GAD). By exploring the factors that contribute to GAD development and potential treatments, this review seeks to provide insights for clinicians, researchers, and policymakers. The goal is to promote an understanding of GAD and facilitate progress in developing interventions that can alleviate the impact of this widespread mental health issue.

2 Generalized anxiety disorder (GAD)

2.1. Definition and diagnostic criteria

GAD, as defined by the DSM-5, is characterized by persistent and excessive worry or anxiety about specific events or daily activities for a minimum duration of six months. The level of tension and frequency of worry are disproportionate to the actual likelihood or impact of the anticipated situations. People with this disorder find it difficult to control their worrying thoughts and prevent them from interfering with their concentration and ability to focus on tasks.

The anxiety is associated with at least three of the following six symptoms: feeling restless or on edge, easily fatigued, issues concentrating, irritability, muscle tension, and sleep problems. Significantly, the worrying or physical symptoms would cause meaningful distress

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and cannot be attributed to substance use or a medical condition, ultimately leading to problems in social functioning for the patient.

According to the DSM-5, in the U.S., around 1% of adolescents and near 3% of adults experience an anxiety disorder in a 12-month period based on prevalence. The prevalence ranges from 0.4% to 3.6% in other countries. The lifetime risk is about 9% [1].

Many individuals diagnosed with GAD often report feeling anxious and stressed for most of their lives. Onset typically occurs around the age 30. Compared to other anxiety disorders, this one typically manifests at a later age. Symptoms like worrying thoughts and anxiety may appear early on but develop over time into an anxious temperament. Generalized anxiety disorder usually emerges during adolescence or later in adulthood. The symptoms of this disorder tend to persist over time, with periods of worsening symptoms and temporary relief that fluctuate between subclinical states. While full remission is unlikely, the manifestation of anxiety remains relatively stable throughout a person's life. It is important to note that the specific concerns individuals have can differ based on their age group. Adolescent anxiety may revolve around academics and social interactions; midlife worries may center on career progression and family obligations; and old age may mostly involve health concerns.

2.2 Differences between GAD and other anxiety disorders

Social anxiety disorder (SAD) refers to feelings of nervousness in any social situation, including smaller or one-on-one interactions. Generalized anxiety disorder causes feelings of anxiety or excessive worrying about daily events or the future, both in and outside of social settings. Those with GAD tend to worry more about minor daily tasks like finances or general life issues. Individuals struggling with SAD will worry more about meeting with others or putting themselves in social environments. At the same time, social concern is common in GAD, but it centers more on ongoing relationships without fear of negative judgment.

Although certain symptoms of GAD overlap with panic disorder, such as excessive anxiety, these are distinct mental health conditions. Panic disorder (PD) is characterized by frequent, unexpected panic attacks that occur in the absence of an apparent threat. ' Symptoms of PD often appear rapidly, peak in 10 minutes, and then decrease. Conversely, Generalized Anxiety Disorder (GAD) mostly concerns itself with ordinary life circumstances such as employment and health conditions, in contrast to PD, when worry arises spontaneously and revolves on the timing of the next panic episode.

3 Research on the etiology of GAD

3.1 Genetic and biological Factors

As a common and debilitating anxiety illness, generalized anxiety disorder (GAD) is noteworthy for its association with several types of psychopathology. It is also known for its clinical heterogeneity, as sufferers may exhibit a wide range of symptom profiles. Moreover, a significant proportion of individuals with GAD also suffer from at least one additional psychiatric condition, such as major depressive disorder (MDD). The study conducted by researchers revealed an increase in gray matter volume (GMV) in the amygdala and prefrontal cortex (PFC) among individuals diagnosed with Generalized Anxiety Disorder (GAD), accompanied by a decrease in (GMV) in the hippocampus. The measures of cortical thickness (CT) and surface area exhibited comparable levels of inconsistency. The presence of clinical heterogeneity may perhaps account for this observed inconsistency. Conflicting results may arise due to the presence of small sample sizes and analytical variation between distinct research studies. These issues are resolved through the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) collaboration, which facilitates the aggregation of neuroimaging data from numerous research locations. This is often accomplished through meta-analyses. Researchers collected data from 28 research sites in the USA, Europe, and Brazil to perform a pre-registered data analysis [2]. The researchers examined variations in various brain area among 1020 persons diagnosed with GAD and 2999 healthy individuals, taking into account the influence of age and sex. Concurrently, individuals with GAD are suggested to exhibit distinct subcortical volumes in the amygdala and hippocampus, as well as variations in CT and surface area in the PFC, in comparison to individuals without the disorder. Additionally, they postulated that the correlation between GAD and structural measurements would vary based on the age of the participants.

The main analysis revealed that GAD did not have an impact on brain structure, and there were no interactions observed between GAD, age, or sex. Males with GAD had a higher volume in the right ventral diencephalon compared to controls, while female with GAD did not demonstrate any differences. This study found that brain structure might not significantly related to GAD, probably reflecting heterogeneity, or that structural changes are not a substantial factor of its pathogenesis [2]. By utilizing a large sample size, the statistical power of the study is increased, and the findings become more generalizable. Additionally, the confidence in the results is bolstered, and the findings are strengthened through the secondary analysis. However, it is worth mentioning that the study recognizes the clinical heterogeneity of GAD, which may have contributed to the absence of substantial results. The results may have been influenced by the variability in symptom severity, duration, and comorbidities observed among individuals diagnosed with GAD. Future research should concentrate on

describing the phenotypic variability of GAD. Investigating various GAD subtypes and taking into account the intensity, length, and co-occurring conditions as possible contributing factors could be part of this.

Examining the etiology of mental disorders through brain structure analysis is undeniably a significant field of study. However, genetic factors also persistently contribute to the advancement of knowledge regarding generalized anxiety disorder (GAD). The norepinephrine transporter (NET) regulates the amounts of norepinephrine in synapses to facilitate noradrenergic signaling and contributes to the anxiety development [3]. In Chang's study, researchers investigate whether age-specific associations exist between genetic variants in the NET gene and an increased risk of developing GAD, which is considered to be among the most incapacitating anxiety disorders. This study involved the genotyping of 2,317 Han-Chinese people to identify three commonly occurring single-nucleotide polymorphisms (SNPs) in the promoter (rs168924: A/G; rs2242446: T/C) and 5′-untranslated region (5′-UTR) (rs2397771: G/C) of the NET gene. To address confounding variables, sex, stress, and mental comorbidities were taken into consideration. The researcher identified an interaction between age and NET haplotypes and genotypes in relation to the risk of GAD. Younger participants who were homozygous for the minor allele G at rs168924 had the lowest occurrence of GAD. In contrast, older respondents showed the opposite trend, with those who were homozygous G/G having the highest frequency of GAD. Youth with two copies of the GGT haplotype consisting of rs2397771, rs168924, and rs2242446 had the lowest GAD rate. Individuals with two copies of the same haplotype showed the greatest susceptibility to GAD in elders [3]. The results reveal that there are age-specific relationships between potentially functional SNPs in the NET promoter and 5′-UTR with an elevated risk of GAD.

Utilizing standardized measures and methodologies to assess stress levels improves the study's reliability and validity. Furthermore, this approach provides for a more nuanced understanding of the association between genetic variables and GAD, taking into account the potential role of age. Nevertheless, this research was restricted to examining the promoter and 5′-UTR of the NET gene, which contained only three common SNPs. The omission of other genetic variants may restrict the study of the cumulative effects and comprehensive genetic profile of NET gene polymorphisms, despite the interest in these variants.

Inflammation is widely recognized as being involved in the development of mental disease. Researchers performed analysis on the relationship between peripheral indicators of inflammation and GAD, analyzing 16 cytokines. Elevated levels of C reactive protein, interferon-γ, and tumor necrosis factor-αwere consistently seen in individuals with GAD in multiple trials compared to the control group [4]. Preliminary data indicates the presence of an inflammatory response in GAD; however, it is uncertain if inflammatory cytokines contribute to its development. GAD is not as extensively researched in the field of neuroinflammation as other mental diseases, necessitating more longitudinal investigations.

3.2 Psychological and social factors

While not every individual with generalized anxiety disorder has a biological predisposition to the condition, psychological elements are also crucial. When it comes to health, the significance of personality on mental disorders has been acknowledged. Reinforcement sensitivity theory (RST) contribute to the understanding of personality, which has contributed to studying how personality relates to health concerns. By exploring personality traits, the present study can gain insights into the underlying mechanisms behind anxiety disorders. Traits such as a tendency to avoid perceived harm, levels of neuroticism, and a preference for introversion have been associated with generalized anxiety disorder, in which GAD can positively associated with harm avoidance and neuroticism. These associations have implications for both diagnosing and treating anxiety disorders, emphasizing the importance of recognizing how personalities contribute to the nature of GADs [5].

In the current study, 78 GAD patients, 76 people with SAD, 72 people with PD, and 85 healthy people took part. GAD patients scored higher on the revised Behavioral Inhibition System (r-BIS) scale compared to the other groups, according to the r-RST findings. All individuals exhibited differences in the updated reinforcement sensitivity hypothesis, according to Afshari [5]. The r-RST proposes that variations in the responsiveness of the Behavioral Inhibition System (BIS) are responsible for differences in both the trait anxiety/neuroticism personality dimension and susceptibility to anxiety disorders, such as GAD. The Behavioral Inhibition System (BIS) induces fear and suppresses contradictory actions, resulting in a tendency towards risk avoidance. Increased BIS activity is linked to situations of conflict may affect the onset of GAD. GAD is closely linked to other anxiety disorders, including SAD and PD, which are also connected to neuroticism and introversion. The study indicates that personality factors, including neuroticism and harm avoidance, are involved in the development of GAD. Studying BIS reactivity and its influence on anxiety and avoidance behaviors helps enhance comprehension of the connection between personality and GAD.

In addition to the analysis of individual factors, there may also be multiple factors interacting in the etiology of GAD. A study analyzed microRNA (miRNA) expression in patients with GAD and observed a decrease in miR-1301 expression [6]. Furthermore, miR-4484, miR-4674, miR-501-3p, miR-663, and miR-4505 showed increased expression in patients with GAD. The study discovered a notable inverse relationship between the expression level of miR-1301 and both the total

social support (SS) score and the score of SS use. Individuals with stronger SS exhibit reduced levels of miR-1301 expression [6].

4 Treatment of GAD

4.1 Pharmacological treatment

Understanding and managing generalized anxiety disorder is crucial for its prognosis and treatment. Effective treatment approaches do not only improve the well-being of individuals; they also have positive impacts on society as a whole. The future prospects for those with GAD greatly depend on effective treatment. By initiating treatment-tailored strategies for each individual, significant relief from symptoms and an improvement in quality of life can be achieved. On the other hand, without treatment, GAD can become a long-term problem with persistent symptoms that may worsen over time.

Discovering effective treatments to control GAD is a top priority. Pharmaceuticals like selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), and benzodiazepines have been proven effective in alleviating GAD symptoms. Baldwin et al. [7] highlight the supported pharmacological treatments that help reduce anxiety symptoms, providing a foundation for therapeutic measures. A meta-analysis conducted by Stein et al. [8] pooled data that assessed the short-termefficacy of agomelatine 25–50 mg, which confirms the effectiveness of agomelatine and improving functioning in individuals diagnosed with generalized anxiety disorder.

Furthermore, another study suggests that modifying the transmission of neurotransmitters can have an impact on neural circuits associated with generalized anxiety disorder [9]. BNC210 is a specific compound that inhibits the α7 nAChR. Researchers studied the impact of a new compound, BNC210, which acts on the α7 nAChR-negative allosteric modulator, on brain circuits related to anxiety in persons with generalized anxiety disorder (GAD) through fMRI scans. The study shows that a small amount of BNC210 decreases amygdala reactions to fearful faces and decreases the functional connectivity of the anterior cingulate in individuals with GAD [9]. This indicates that cholinergic neurotransmission is important for these networks, and drugs that target this system could be helpful in treating anxiety disorders.

4.2 Psychotherapy

Cognitive-behavioral therapy (CBT) is highly regarded as an effective method for treating GAD, which shows its success in mitigating anxiety symptoms via cognitive restructuring and behavioral strategies. This form of psychotherapy serves as a valuable complement to pharmacological treatments, targeting the cognitive and emotional roots of the disorder. Additionally, newer treatment approaches (e.g., CBM errors) are emerging, providing further optimism and alternatives for those with GAD.

Although CBT is an effective treatment for GAD, the clinical course of GAD is usually long and generally worsens with treatment. This is why long-term predictors of outcomes are particularly important. In order to enhance treatment for GAD, researchers aimed to investigate factors that can predict the degree of worry six months after CBT . They also sought to determine the extent to which anxiety decreases from the time of intake and post-treatment to the six-month follow-up. The findings indicate a sustained reduction in worry levels for a duration of six months following the completion of treatment. Significantly less worry is experienced during the intake and post-treatment phases as well as the six-month follow-up, indicating that anxiety in people with GAD may not stop even after therapy ends [10]. This certainly demonstrates the effective viability of CBT as a management tool for GAD and the importance of maintaining its long-term regimen.

Comparisons with other therapies are also important for research on the development of GAD management. Metacognitive therapy (MCT) and CBT are efficacious interventions for GAD. The researchers conducted a follow-up study on patients who had previously taken part in prior studies comparing the effectiveness of MCT and CBT. During the 9-year follow-up period, data was received from 39 out of the initial 60 patients. This research examined the potential enduring impacts of CBT and MCT on individuals diagnosed with GAD. The findings of the research indicated an engagement rate of 65% within the initial sample. The CBT had a long-term recovery rate of 38%, whereas the MCT had a greater recovery rate of 57% [11]. It can be seen that both CBT and MCT have long-term efficacy and that the superiority of MCT after treatment may become stronger during long-term follow-up, and recovery appears to be more stable in MCT patients compared to those receiving CBT.

Despite its efficacy as a primary evidence-based psychotherapy for GAD, a significant number of patients are unable to access CBT due to financial constraints, social stigma, or practical challenges. Likewise, the accessibility, tolerability, and efficacy of pharmacotherapy may be limited. The need for alternative interventions, such as mindfulness and yoga, is on the rise among patients. While these interventions have not demonstrated performance beyond that of psychotherapy, they have demonstrated their effectiveness in helping to improve symptoms in patients with GAD. So, as a complement to pharmacological and psychological treatments, these interventions will be effective in helping the recovery and prognosis of patients with GAD.

5 Discussion and suggestions

This in-depth exploration of GAD sheds light on the nature of this health condition, showcasing the significant progress made in understanding its causes

and treatment options. The widespread occurrence of GAD and its impact on society underscore the importance of research and the development of interventions. Noteworthy advancements in brain imaging technology and research into biological factors have deepened the researchers' knowledge of GAD, with cognitive behavioral therapy (CBT) and mindfulness techniques proving to be treatments.

The value of this study lies in its potential to inform practices and policy decisions, stressing the significance of intervention and tailored treatment plans. As society addresses the increasing prevalence of health issues, this analysis forms the basis for tackling GAD through a blend of medication, therapy, and alternative remedies.

Future studies should concentrate on validating the effectiveness of treatments while exploring how different therapeutic approaches can be combined. The synergy between CBT and metacognitive therapy (MCT) mindfulness practices, along with medication, offers an approach to managing GAD. Furthermore, assessing the long-term impacts of these therapies is essential for gauging their lasting efficacy. On this basis, researchers can use neurological evidence to validate GAD treatment in future studies.

The influence of factors and environmental pressures on the development of GAD suggests that upcoming studies should also take into account how early life events and societal stressors play a role. These include family environment, parenting styles, socioeconomic status, and cognitive biases, which may work together to shape an individual's response to stress. This also suggests that future management and treatment strategies for GAD should include multiple perspectives and multidisciplinary supervision in order to improve the prognosis and treatment of patients with GAD.

To sum up, this analysis emphasizes the significance of research on the causes and treatment of GAD, emphasizing the need for personalized approaches. To deepen the knowledge of this disorder, there is a growing opportunity to enhance the quality of life for those impacted by GAD, bringing hope, management, and treatment options.

6 Conclusion

The study of generalized anxiety disorder (GAD) highlights its influence on people and society, stressing the importance of approaches to comprehending and addressing it. Progress in genetics, brain imaging, and treatment options brings hope for studies and medical care. By giving importance to combining medication with therapy while also investigating the impact of mindfulness, researchers are progressing towards creating tailored and efficient methods for handling GAD and achieving results.

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