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Generalized Anxiety Disorder: A Review of Current Literature in Saudi Arabia

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Abstract

Generalized anxiety disorder (GAD) is a neuropsychological disorder, under the class of anxiety disorders characterized by excessive and uncontrollable worrying for six or more months. GAD is a major hurdle for personal and social productivity and a financial burden on governmental health sectors; moreover, it is one of the common mental health problems in Saudi Arabia and globally with physical and psychological manifestations (e.g., muscle tension, sleeplessness, disoriented thoughts, etc.). Although, there is not a monofactor's direct causality of pathogenesis, there are multiple risk factors such as genetics, socioeconomic status, and life experiences that may contribute to the development of GAD. Nonetheless, the diagnosis is made using the criteria set by the diagnostic and statistical manual of mental disorders, 5th edition (DSM-5) or the international classification of diseases 11th revision (ICD-11), which covers the patient's past medical history and present social and environmental setting. The management of GAD includes a combination of psychiatric interventions (e.g., cognitive behavioral therapy) and different medications (e.g., selective-serotonin reuptake inhibitors) requiring thorough investigations and deep discussions with the patient to rule out other psychiatric conditions and to reach an optimal level of healthcare, preventing further deterioration. This article addresses the etiology, epidemiology, pathophysiology, diagnosis, and management of GAD in Saudi Arabia to present an integrated and updated review.

Keywords

Anxiety Disorders, Generalized Anxiety Disorder, Anxiety Attack

1. Introduction

Generalized anxiety disorder (GAD) is a neuropsychological disorder characterized by uncontrollable, extreme, and persistent worrying for the past six months or more. Subsequently, the pathogenesis impairs one or more of the physiological, psychological, and biological processes that manage the body's stress-reactivity which might disrupt the body's homeostasis. Although, there is not a singular cause of GAD, a combination of multiple risk factors might influence the development of the disorder. Nonetheless, the multifactorial pathogenesis of GAD increases the number of similar differential diagnoses, which makes it commonly misdiagnosed, such as the involvement of miRNAs as a cause of GAD and other stress anxiety disorders. Therefore, understanding the etiologies and the way to diagnose this disorder is crucial for early treatment and avoiding its complications. Furthermore, this disorder has many symptoms which might affect daily activities like work performance, academic progress, and interpersonal connections. Hence, this review addresses the etiology, epidemiology, pathophysiology, diagnosis, and management of GAD in Saudi Arabia to present an integrated view.

2. Etiology

GAD's development is influenced by a combination of factors (e.g., life stressors, physical or psychological conditions, genetics, substance use disorders, environmental factors, personality types, parenting styles, etc. (Francis, 2012; Munir & Takov 2020).

Studies have shown that GAD is a heritable condition with a genetic involvement (~30%). There are several genes inscribing certain factors that are correlated with GAD's pathogenesis (e.g., catechol-O-methyltransferase (COMT), 5-hydroxytryptamine transporter (5-HTT), 5-hydroxytryptamine 1A receptor (5-HT1A), etc.). However, these markers are not for diagnostic purposes and only demonstrate a possible risk as it can be influenced by environmental factors (Gosschalk, 2017).

The associations of life stressors have been established regardless of the cause and its intensity (e.g., health, finances, etc.). In addition, stressful life events are associated with increased probability of relapse even after full recovery. Moreover, chronic diseases, low cognitive source, and history of psychological disorders are also considered as risk factors. Furthermore, the most common personality type among patients with GAD is introvert (individuals characterized by being inward-looking and taking daily matters seriously on a spectrum of attitudes/behaviors) (Arul, 2016; ICD-11).

Additionally, factors that affect a child's development (e.g., education, health, secure attachments, etc.) are critical as GAD is commonly seen between low educated and poor self-perceived health individuals (i.e., such individuals might have unknown and unmanaged anxiety symptoms which may develop into different psychiatric disorders with other comorbidities later in life) (Moller, 2016;

Arul, 2016).

3. Epidemiology

Anxiety disorders are group of mental disorders that arise in several forms including phobic, social, obsessive-compulsive disorder (OCD), post-traumatic disorder (PTSD), or GAD. Globally, the prevalence of anxiety disorders varies from 2.5% to 7%, clarifying that 284 million people worldwide experienced an anxiety disorder in 2017 and approximately 63% of them were females (**Figure 1** and **Figure 2**) (Ritchie & Roser, 2022).

Many studies have been conducted globally to show that GAD is one of the most common anxiety disorders. For instance, in the United States, studies of representative samples (i.e., a large specimen, living and working there, etc.) have demonstrated a lifetime prevalence of 5.1% to 11.9%. In Europe, studies have shown a 12-month prevalence of 1.7% to 3.4%, and a lifetime prevalence of 4.3% to 5.9%. In primary care settings, GAD is known to be one of the most common mental disorders; also, it is associated with an increased use of health care services. In addition, a study of adult primary care patients in Denmark, Finland, Norway, and Sweden has shown that the rates of GAD were 4.1% to

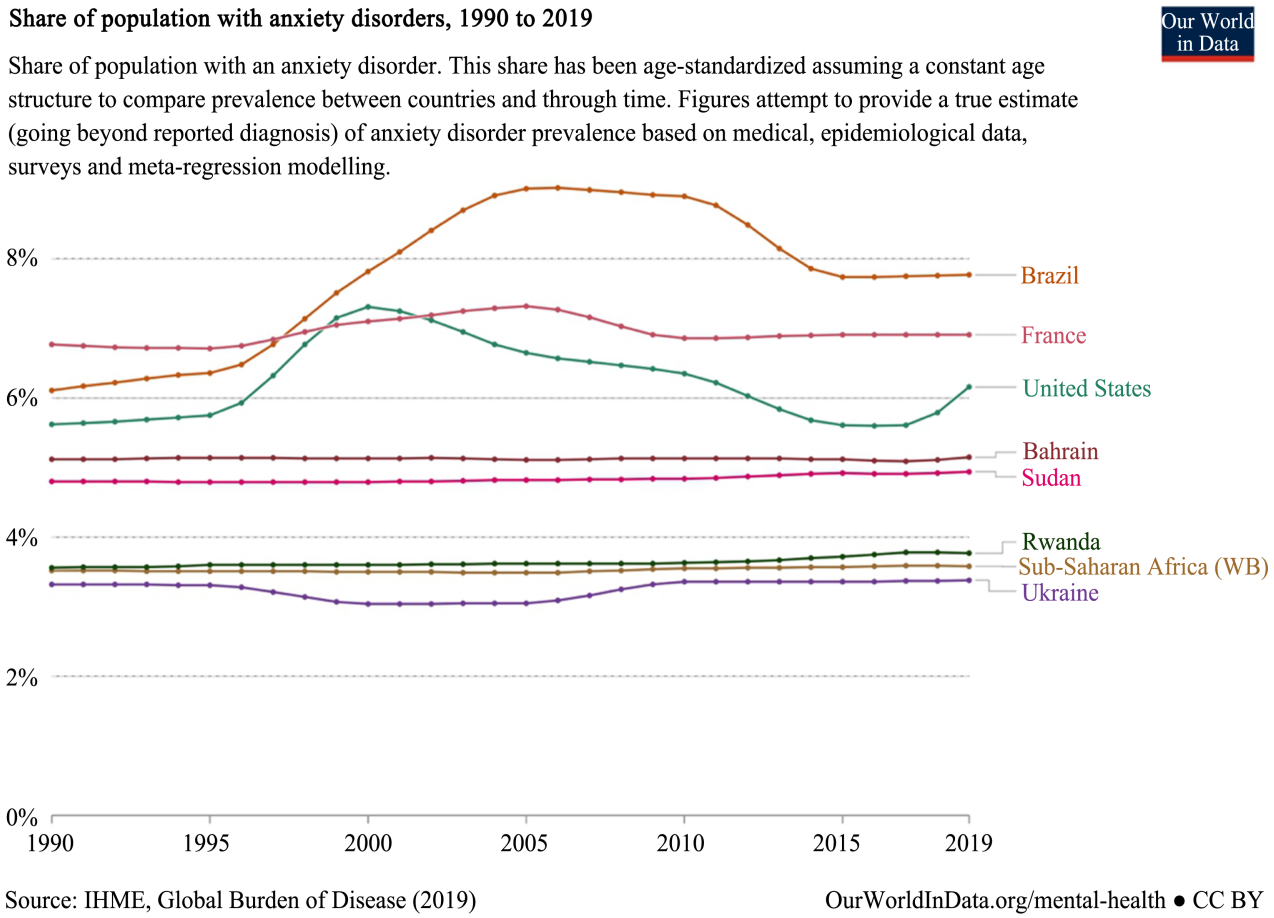

Figure 1. Prevalence of anxiety disorder.

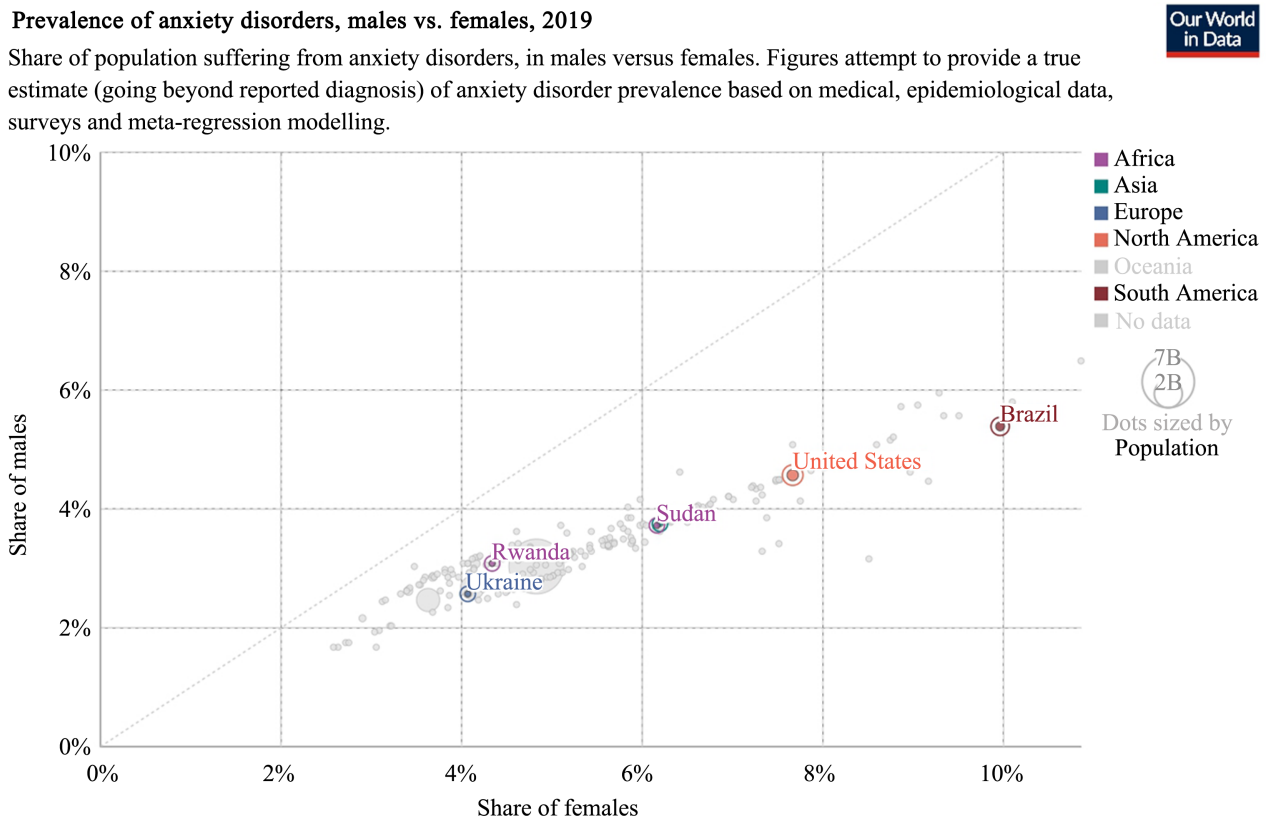

Figure 2. Gender distribution of anxiety disorders in different geographic regions.

6.0% among men, and 3.7% to 7.1% among women. Relatively, GAD is approximately twice as common in women as it is in men and among the elderly population, it is the most common anxiety disorder (Baldwin, 2019).

Therefore, we can comprehend the extent of the problem, as a disorder that will probably affect the upcoming generations of Saudi Arabia and the neighboring countries (e.g., Kuwait, Bahrain, Oman, etc.) and which requires an urgent attention.

4. Pathophysiology

Chronic psychological stress theory

The adaptation to short-term acute stressors (e.g., exams, work projects, social events, etc.) is a natural process. However, an increased exposure to acute stressors, may lead to chronic maladaptive stress reactions in which chronic stress will affect the body's homeostasis. Nonetheless, it will impact the patients' neuroendocrine, autonomic, and behavioral subsystems in responding to threats (actual or perceived) which will increase the allostatic load (i.e., an increase in all stress-related systems which may lead to several illnesses and can exacerbate others, such as acute myocardial infarction) (Fioranelli et al., 2018). Hence, an individual's resilience (ability to manage adverse life experiences) in dealing with

the stressors may get reduced by different factors (e.g., childhood trauma, genetics, parental abuse, etc.), increasing the likelihood of developing psychiatric difficulties or disorders.

Psycho-physiological aspect

Individuals with GAD have increased homeostatic dysregulation (e.g., low heart rate variability, high heart rate, and higher skin conductance level), in comparison to individuals with other anxiety disorders. The dysregulation is characterized by a chronic hyperarousal state at baseline physiological activity and demonstrates an exaggerated reactivity to fearful stimuli. Additionally, possible explanation for the hyperarousal state. Therefore, increasing the general physiological consequences of chronic exposure to the allostatic load (Patriquin & Mathew 2017; Grillon et al., 2017).

Neurobiological aspect

- Genetics

Generally, the genetic predisposition contributes ~30% - 50% and the non-genetic (environmental) factors ~50% - 70% to the development of anxiety disorders. In GAD, there are different mechanisms and genes that have shown pathogenic association.

The environmental factors have shown an increased association which is possibly mediated through epigenetic mechanisms (methylation, acetylation, etc.), altering the functionality of stress-related genes (e.g., methylation of the glucocorticoid receptor gene (NR3C1) promoter region) (Non et al., 2014); moreover, a world-wide study of different genomes, confirmed that anxious individuals have higher DNA methylation leading to dysfunctional regulation of stress-reactivity (Murphy et al., 2015).

There are other genes that if mutated, dysregulation of the downregulatory processes might occur, such as the 5-Hydroxytryptaminetransporter-linked polymorphic region (5HTTLPR), which is associated with neural patterns related to GAD. For instance, when individuals were shown fearful and angry faces, 5-HTTLPR short-allele carriers show bilateral hyperactivity of amygdala compared to 5-HTTLPR long-allele homozygotes. Concluding, that 5-HTTLPR short-allele carriers appear to be more sensitive to environmental factors, which may contribute to their excessive worrying and anxious thoughts with/without the presence of threat (Hariri et al., 2005; Hompes et al., 2013; Patriquin & Mathew, 2017).

- Neuroanatomy
  - Neocortical sites: The pre-frontal cortex (PFC) is important in maintaining affective regulation (e.g., downregulation of anxiety and worry) through mediating amygdalar fear/stress-related activity, demonstrating the necessity of their synaptic functionality. However, in GAD patients there is an uncoordinated activity in both (PFC and amygdala) and a reduced resting-state functional connectivity (Roy et al., 2013; Hilbert et al., 2014). In elaboration, the ventromedial area of the frontal lobe has shown an increased activity in regulating negative emotions (e.g., anxiety) and when there is a decreased con-

nectivity, there will be a dysregulation (Diekhof et al., 2011). Additionally, the frontolimbic connectivity has shown regulatory effects on the autonomic nervous system, suggesting a mechanism for the clinical manifestations (e.g., hyperarousal, decreased heart rate variability (HRV), etc.) (Makovac et al., 2016).

- The HPA-axis: The Hypothalamic-Pituitary-Adrenal-axis (HPA-axis) is a dynamic, neuroendocrine system in response to stressful stimuli, working on a negative-feedback loop.

Physiologically, an individual's exposure to stressors will trigger the initiation of many biological subsystems to manage it. Mainly, the HPA-axis, which works by:

- Cortical efferent to the amygdalar basolatral nucleus
- The basolateral nucleus then activates the central nucleus
- The central nucleus then sends efferent through the Stria terminalis (directly) and/or the brainstem's Raphe nuclei or locus coeruleus (indirectly) to the hypothalamic nuclei.
- The hypothalamic paraventricular nuclei (PVN) then release Corticotropic Releasing Hormone/Factor (CRH or CRF) into the hypothalamo-hypophyseal portal system to the anterior lobe of the pituitary gland.
- At the anterior lobe, Corticotrophs produce Pre-opiomelancortin (POMC) which is the precursor of Adrenocorticotrophic hormone (ACTH), released and cleaved peripherally.
- ACTH works on the adrenal glands' cortex (Zona fasciculata and reticularis), leading to the release of Glucocorticoids (cortisol).
- The glucocorticoids then perform several visceral functions to prepare the body in response to stress (increasing heart rate, glucose in the blood, and respiratory rate, etc.).
- The preparations are made, and a negative-feedback loop is simultaneously started. The glucocorticoids suppress the PVN and corticotrophs as a mechanism of auto-regulating the plasma levels.

Pathologically, there are many processes in the previous passage that take place before and after the activation of the HPA-axis. Although, there were findings suggesting a positive correlation between GAD psychometric instruments' measures of severity and cortisol levels, dysfunction of any process (e.g., negative-feedback loop impairment) or nuclei (e.g., Amygdalar hypertrophy) would increase an individual's risk of psychopathology and the effects of the Allostatic load, inevitably (Mantella et al., 2008).

- Neurotransmitters

The limbic system is a cortical, neuronal circuitry for emotional regulation that is hyperactive in GAD patients. Hence, a hypothesis of dysfunctional downregulation mediated by Gamma-aminobutyric acid (GABA) which is an inhibitory neurotransmitter having opposite effects of the symptoms observed in the clinical presentation (Nutt, 2001; Nemeroff, 2003). In elaboration, patients suffering from autonomic hyperactivity and psychosomatic symptoms have sub-

sided once benzodiazepines (GABAa agonists) were administered, supporting the hypothesis. On the other hand, Glutamate which is an excitatory neurotransmitter might also exacerbate the symptoms if it was not down-regulated properly or over produced. In support, GAD patients were given Riluzole (anti-glutamatergic agent) and symptoms subsided, suggesting other possible pathogenic pathways (Mathew et al., 2005; Pittenger et al., 2008).

In addition, the Serotonergic pathways play a major role in HPA-axis and autonomic regulation which might be dysregulated in GAD patients. Although, many would argue with such a hypothesis due to the proved efficacy of selective-serotonin reuptake inhibitors (SSRI), GAD might present with other comorbidities (e.g., major depressive disorder) which is also treated the same. Therefore, a hypothesis of serotonergic dysregulation is not proved yet when it comes to GAD patients.

Other neuropeptides, such as Cholecystokinin (CCK) and Neuropeptide Y (NPY) have demonstrated correlated anxiogenic/anxiolytic mechanisms, respectively. Firstly, the CCK system is mediated by two types of receptors (CCK-A and CCK-B) and was profoundly correlated with the Gastrointestinal tract (both receptors), though an abundance of CCK-B was found in the brain. In trials, CCK was found to works as an anxiogenic factor, potentiating anxiety in Rat-models which might suggest a similar effect on humans (Wang et al., 2005). Moreover, clinical trials are still in progress to formulate a CCK-antagonist having an anxiolytic efficacy and potency (34). Secondly, NPY is produced by pancreatic cells and neurons in cortical areas that are correlated with GAD pathogenesis (e.g., hypothalamus, amygdala, hippocampus, etc.), mediated by five receptors (Y1 - Y5), with Y1 and Y2 demonstrating anxiolytic effects (Griebel & Holsboer, 2012; Baldwin, 2019). Others claim, that NPY does not have an anxiolytic effect but the NPY-CRF suppressing interactions in major sites (e.g., amygdala, periaqueductal gray, etc.), with NPY having a suppressive effect causing a decrease in stress-related reactions (Sajdyk et al., 2004).

5. Diagnosis

Diagnosis of GAD can be made by using the DSM-5 diagnostic criteria. The criteria are correlated to the patient's social life and the consequent effects.

- DSM-5 criteria for general anxiety disorder: GAD is diagnosed by excessive and extreme anxiety occurring for the past six months for most of the days. The uncontrollable anxiety may interrupt with patient's social life (such as school, occupation). A person can be diagnosed as suffering from GAD if three or more of the following symptoms are presented:
  - Restlessness;
  - Easy fatiguability;
  - Concentration issues or mind going blank;
  - Irritability;
  - Tension of muscles;
  - Sleep disturbance.

When diagnosing GAD, the following points should also be taken care of:

- Sleep disturbance should not be caused by physiological effects of a substance or medical conditions.
- The patient should not be affected by other mental disorders such as panic disorder, OCD, Depression.
- Anxiety should cause remarkable distress or impairment in patients.

- ICD-11: Essential diagnostic criteria for GAD set by the WHO (World Health Organization) are called ICD-11 (international classification of diseases, 11th revision). It describes GAD as "anxiety that is generalized non-stop, but not because of any environmental conditions (e.g., substance use disorders)", mainly focusing on physiological stimulation (such as sweating and palpation). Symptoms may vary, but include persistent nervousness, tension of muscles, sweating, palpitation, dizziness, and epigastric discomfort (Hoge et al., 2012). A questionnaire, named GAD-7, is used as a screening tool for suspected GAD patients. The questionnaire outcome is helpful in measuring the severity of impact on the patient's social life for the past two weeks (**Figure 3**) and it is further explained in (**Table 1**).

Over the last 2 weeks, how often have you been bothered by the following problems?	*Not at all*	*Several days*	*More than half the days*	*Nearly every day*
(Use "✓" to indicate your answer)				
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Total score _____	= ___	+ ___	+ ___	+ ___

NOTE: *Total score for the 7 items ranges from 0 to 21. Scores of 5, 10, and 15 represent cutoffs for mild, moderate, and severe anxiety, respectively. Although designed primarily as a screening and severity measure for GAD, the GAD-7 also has moderately good operating characteristics for panic disorder, social anxiety disorder, and posttraumatic stress disorder. When screening for anxiety disorders, a recommended cutoff for further evaluation is a score of 10 or greater.*

GAD = generalized anxiety disorder.

Reprinted from Spitzer RL, Williams JB, Kroenke K, et al., with an educational grant from Pfizer Inc. Patient health questionnaire (PHQ) screeners. http://www.phqscreeners.com/overview.aspx?Screener=03_GAD-7. Accessed July 22, 2014.

Figure 3. Explanation of GAD 7 questionnaire (Locke et al., 2015).

Table 1. Severity of GAD ranged according to patient score in GAD-7.

Patient score in GAD-7	Severity of GAD
0 - 4	Minimal or no anxiety
5 - 9	Mild anxiety
10 - 14	Moderate anxiety
15 - 21	Severe anxiety

There are similarities in the clinical manifestations between GAD and other neuropsychological disorders. Therefore, evidential elimination of these disorders and their interconnected diagnostic criteria (i.e., a multi-perspective history, lab test, etc.) should be done through thorough investigations in the pre-diagnostic phase to rule out the following conditions (5th ed.; DSM-5 (2013)).

- Congenital and acquired medical conditions, such as pheochromocytoma in which a tumor of the renal medulla would increase the production of catecholamines (Epinephrine and Norepinephrine). Hence, the disrupted homeostatic state of the body leading to autonomic hyperactivity in which a presentation might satisfy GAD's diagnostic criteria. Consequently, Imaging (e.g., CT, MRI, etc.) and laboratory findings must be considered if there are indicators (Locke et al., 2015).
- Substance/medication induced anxiety disorder (e.g., caffeine induced) where administrating or withdrawing prescribed or recreational drugs might initiate or aggravate anxiety. A detailed conversation should be done with the patient about these things and their history to evaluate any possible causative substance abuse (Alegría et al., 2019). Nonetheless, assessing the patients for Antipsychotics drugs withdrawal leading to a major symptom Akathisia in which a patient would recurrently feel anxious, heavy, and uneasy in their own thought and body in which other diagnoses might also be considered.
- Social anxiety disorder (SAD) is where the patient's main concern is surrounding people's judgement on him/her in a social event (i.e., not necessarily a party or a talk, any place in which people gather such as mall and markets might trigger the anxiety) where in their thoughts they start a thought circuit where they are the center of judgment. However, in GAD the worry is about the whole event without the specificity of environmental factors (Mennin et al., 2000).
- Post-traumatic stress disorder (PTSD) is diagnosed if a stressor in the past three months can be identified resulting in an increased, persistent anxiety for six or more months, mostly around the traumatic event. For a GAD patient, continuous worry about everything since childhood or adolescence can be traced in their history, with no prior exposure to an altering stressor. However, certain stressors might increase their anxiety above their normal threshold, but it must not be mistaken as a traumatic event deviating us from the main diagnosis.

- Obsessive compulsive disorder (OCD) is defined as intrusive physical and mental complex urges in which a patient would feel consistent anxiety if the urge has not been done (e.g., a ritual done before bed by the patient or a caregiver). Whereas the defining feature for GAD is life-long worry and nervousness, not connected to intrusive urges and rarely relieved by any physical or mental activity. Although, in both disorders the manifestations start at a young age, prolonged patient observation is recommended, due to difficulty in diagnosing a child because certain actions might be misinterpreted.
- Depressive disorders and bipolar disorders have shown an incremental association with GAD and other anxiety disorders. Therefore, early diagnosis of any of these conditions will help in preventing a GAD patient accelerating towards bio-psychological deterioration as the presence of GAD alongside a depressive disorder as comorbidity would increase the patient's risk of suicidality (Rakel et al., 2016; Zbozinek et al., 2012).

6. Management

Clinically, after a GAD diagnosis is made, the appropriate course of the treatment is decided upon:

- The disorder's severity;
- Extent of impairment or distress;
- Patient preference;
- Whether the treatment of the disorder is necessary (e.g., in milder presentations with no significant function impairment, treatment may be withheld, initially. Nonetheless, proper monitoring is needed in the form of follow-up sessions every six months to determine the severity of symptoms) (Craske, 2020).

Therefore, the management of GAD is subdivided into psychotherapy and pharmacotherapy, and they both are considered as first-line treatment options, singularly or as a combination. Hence, the treatment plan should be developed based on several factors.

- The pharmacotherapeutic drugs':
  - Efficacy;
  - Drug to drug interactions;
  - Adverse effects;
  - Costs, etc.
- The patients':
  - Age;
  - Physical condition (e.g., pregnant women);
  - Preference, etc.

In addition, other comorbidities are also important to be investigated and diagnosed if present (e.g., major depressive disorder, substance abuse, personality disorders, etc.) (Bandelow et al., 2017).

Psychotherapy and other non-drug interventions

Evidence-based psychotherapy is extensively researched and has been proven to be effective in treating GAD. The first line of psychological treatment for the disorder is cognitive behavioral therapy (CBT). These are psycho-social interventions that have shown effectiveness in management of various other mental disorders also (e.g., eating disorders) and help patients to master a combination of skills to increase their quality of life (QOL). Hence, in some studies showing an increased clinical effectiveness than medications as the first line of treatment, if the patient cannot tolerate or refuses to take medications (Chand, Kuckel, & Huecker, 2022; Zhu et al., 2014).

There are three fundamental phases in the process of treating GAD. Attempting to treat GAD without the use of these phases would increase the patient's vulnerability to relapse (Wilkinson et al., 2011).

The phases are:

- Worry awareness training;
- Recognizing and overcoming unhelpful responses to uncertainty;
- Recognizing and challenging positive beliefs about worry.

At the beginning, the purpose of worry awareness training is to help the patients reflect on their worry by introducing them to the broad classification of worries which are real events' worry and hypothetical worry. These categories are not mutually exclusive, which means, real events can lead to hypothetical worry. Therefore, if the patient is predisposed to a real event worry, then the therapist needs to address the orientation of their negative problems. On the other hand, if the patient is generally worrying about hypothetical events, the therapist needs to use systemic exposure treatment to address cognitive avoidance (Wilkinson et al., 2011).

Intolerance of uncertainty is a set of negative physiological, emotional, and behavioral responses to uncertainty. Moreover, individuals with intolerance of uncertainty often engage in "cognitive avoidance" which can be addressed by the utilization of vivo and imaginal exposures. Therapists should address this by recognizing and overcoming unhelpful responses to uncertainty (Wilkinson et al., 2011; O'Donohue & Fisher, 2012).

The final key intervention is recognizing and challenging positive beliefs about worry. It can be effectively deployed by a range of cognitive therapeutic techniques (such as behavioral experiments and Socratic dialogues). These techniques help the patients in recognizing the negative impact of worry and to address their problems in various resolving ways (O'Donohue & Fisher, 2012).

In addition, other psychological interventions can be utilized as adjunct therapy to reach the desired results (e.g., psychodynamic therapy, applied relaxation, mindfulness, sleep hygiene education, exercise, bibliotherapy, etc.); moreover, some studies support the use of videoconferencing, internet, smartphones, or computer-based interventions which provide access to more patients (Firth, 2017; Berryhill, 2019).

Psychopharmacotherapy

The usual, global protocol includes the pharmacological intervention with CBT as the combination of both has a significant impact in boosting the potency of treatment (Strawn et al., 2018). Notably, prior to the administration of any given medication the patient must be informed about adverse effects, contraindications, interactions, and safety warnings. In addition, the risk of drugs misuse and a history of substance abuse should be investigated.

- First-line treatment:
  - Selective serotonin-reuptake inhibitor (SSRI's);
  - Serotonin-norepinephrine reuptake inhibitors (SNRI's);
  - Atypical antidepressant.

Primary options are escitalopram, duloxetine, and venlafaxine. Secondary options are buspirone, sertraline, fluoxetine, mirtazapine, and agomelatine. The tertiary option is paroxetine, but it is poorly tolerated with a relatively short half-life (Bandelow et al., 2017; Bystritsky, 2019; Gale, 2020).

- Second-line treatment:
  - Tricyclic antidepressant;
  - Antipsychotics;
  - Benzodiazepine;
  - Pregabalin (last).

Primary options are imipramine, quetiapine, clonazepam, and diazepam (Bandelow et al., 2017; Bystritsky, 2019; Gale, 2020).

- Third-line treatment:

The treatment of resistant GAD acquires switching to alternative drug, increasing the intensity of combining the pharmacotherapy with the psychological interventions (e.g., CBT), and/or combining two medications from different classes (i.e., if they are not contraindicated) with stopping ineffective treatment methods and trying different strategies until the most efficacious treatment method is found (Gale, 2020).

Because the second line of treatment for pregnant women and children is psychopharmacotherapy, careful selection of appropriate drug must be made, benefit/risk balance should be considered, and an expert's opinion should be sought. Nonetheless, SSRIs are primarily the drug of choice for pregnant women in first trimester and children after psychotherapy has been attempted (Ray & Stowe, 2014).

7. Generalized Anxiety Disorder's Impaction Saudi Arabia

Concerning the widespread of anxiety, several studies have been conducted in Saudi Arabia to measure the prevalence of GAD and prevent its complications. A systemic review collected data from 19 articles on anxiety disorders among college and school students. The data showed that the prevalence of anxiety reached up to 66% for female students and 44% for male students (Alahmadi, 2019). However, this study focused on students who were considered only a part of the Saudi community. Thus, another study has been conducted in Saudi Arabia to assess the prevalence of anxiety disorders, especially GAD, and they found

that GAD is present in 62.1% of the Saudi population, in which mild, moderate, and severe GAD affected 33.1%, 15.7%, and 13.3%, respectively (Aljurbua et al., 2021).

GAD has been correlated with many risk factors and comorbidities. For instance, females and young aged population are more prone to have GAD compared with others, this could be due to the numerous stressors that females and young people experience (e.g., academic progression, societal expectations, difficulties in communication), which make them vulnerable to GAD (Alyami et al., 2019; Samreen et al., 2020; Alamri et al., 2021). In addition, regarding the relation between GAD and comorbidities, it was reported that the prevalence of GAD is higher in patients with Systemic lupus erythematosus, thyroid dysfunction, end-stage renal disease, or anemia in Saudi Arabia, which could be secondary to intense fear and worry about the diseases' flare up or complications, resulting in continuous anxiety (Turkistani et al., 2014; Aljurbua et al., 2021). Moreover, it has been reported that patients who suffer from anxiety disorder are more likely to develop Major depressive disorder which may lead to an increase in suicidality (e.g., thoughts or plans) (Ibrahim et al., 2013; Samreen et al., 2020; Aljurbua et al., 2021).

8. Conclusion

The Saudi Arabian and global data have shown an increased prevalence of GAD which makes as one of the most common anxiety disorders and showcases a socioeconomic burden. Although, the underlying pathophysiological mechanisms are still unclear. Nonetheless, the diagnostic criteria and management protocols are based on different comprehensive papers, and we advise practitioners to check their local protocols. Lastly, we hope that such a global, mental health problem gets attention for futuristic research and new therapies to give the patients a chance to reach optimal quality of life.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

Alahmadi, A. M. (2019). Prevalence of Anxiety among College and School Students in Saudi Arabia: A Systematic Review. *Journal of Health Informatics in Developing Countries, 13,* 1-15. https://www.jhidc.org/index.php/jhidc/article/view/237

Alamri, H. S., Algarni, A., Shehata, S. F. et al. (2021). Prevalence of Depression, Anxiety, and Stress among the General Population in Saudi Arabia during Covid-19 Pandemic. *International Journal of Environmental Research and Public Health, 17,* 9183. https://doi.org/10.3390/ijerph17249183

Alegría, A., Hasin, D., Nunes, E. et al. (2019). Comorbidity of Generalized Anxiety Disorder and Substance Use Disorders: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Clinical Psychiatry, 71,* 1187-1195. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2951633

Aljurbua, F. I., Selaihem, A., Alomari, N. A., & Alrashoud, A. M. (2021). A Cross-Sectional Study on Generalized Anxiety Disorder and Its Socio-Demographic Correlates among the General Population in Saudi Arabia. *Journal of Family Medicine and Primary Care, 10,* 3644. https://doi.org/10.4103/jfmpc.jfmpc_847_21

Alyami, H. S., Naser, A. Y., Dahmash, E. Z. et al. (2019). Depression and Anxiety during 2019 Coronavirus Disease Pandemic in Saudi Arabia: A Cross-Sectional Study. *International Journal of Clinical Practice*. https://doi.org/10.1101/2020.05.09.20096677

Arul, A. S. (2016). Study of Life Events and Personality Dimensions in Generalized Anxiety Disorder. *Journal of Clinical and Diagnostic Research: JCDR, 10,* VC05-VC09. https://doi.org/10.7860/JCDR/2016/18123.7652

Baldwin, D. (2019). *Generalized Anxiety Disorder in Adults: Epidemiology, Pathogenesis, Clinical Manifestations, Course, Assessment, and Diagnosis*. UpToDate. https://www.uptodate.com/contents/generalized-anxiety-disorder-in-adults-epidemiology-pathogenesis-clinical-manifestations-course-assessment-and-diagnosis#H448541483

Bandelow, B., Michaelis, S., & Wedekind, D. (2017). Treatment of Anxiety Disorders. *Dialogues in Clinical Neuroscience, 19,* 93-107. https://doi.org/10.31887/DCNS.2017.19.2/bbandelow

Berryhill, M. B. (2019). Video Conferencing Psychological Therapy and Anxiety: A Systematic Review. *Family Practice, 36,* 53-63.

Bystritsky, A. (2019). Uptodate. https://www.uptodate.com/contents/pharmacotherapy-for-generalized-anxiety-disorder-in-adults

Chand, S. P., Kuckel, D. P., & Huecker, M. R. (2022) Cognitive Behavior Therapy. StatPearls Publishing, Treasure Island. https://www.ncbi.nlm.nih.gov/books/NBK470241/

Craske, M. (2020). *Approach to Treating Generalized Anxiety Disorder in Adults*. UPTODATE.

Diekhof, E. K., Geier, K., Falkai, P., & Gruber, O. (2011). Fear Is Only as Deep as the Mind Allows: A Coordinate-Based Meta-Analysis of Neuroimaging Studies on the Regulation of Negative Affect. *Neuroimage, 58,* 275-285. https://doi.org/10.1016/j.neuroimage.2011.05.073

DSM-5 (2013). Generalized Anxiety Disorder. *Diagnostic and Statistical Manual of Mental Disorders* (5th ed., pp. 222-226). American Psychiatric Publishing.

Fioranelli, M., Bottaccioli, A. G., et al. (2018) Stress and Inflammation in Coronary Artery Disease: A Review Psycho-Neuro-Endocrine-Immunology-Based. *Frontiers in Immunology, 9,* 2031. https://doi.org/10.3389/fimmu.2018.02031

Firth, J. (2017). Can Smartphone Mental Health Interventions Reduce Symptoms of Anxiety? A Meta-Analysis of Randomized Controlled Trials. *Journal of Affective Disorders, 218,* 15-22. https://doi.org/10.1016/j.jad.2017.04.046

Francis, J. L. (2012). Life Stress and GAD. *Depression and Anxiety, 29,* 5. https://doi.org/10.1002/da.20919

Gale, C. (2020). *Generalised Anxiety Disorder*. https://bestpractice-bmj-com.sdl.idm.oclc.org/topics/en-gb/120

Gosschalk, M. G. (2017). Genetics of Generalized Anxiety Disorder and Related Traits. *Dialogues in Clinical Neuroscience, 19,* 159-168. https://doi.org/10.31887/DCNS.2017.19.2/kdomschke

Griebel, G., & Holsboer, F. (2012). Neuropeptide Receptor Ligands as Drugs for Psychiatric Diseases: The End of the Beginning? *Nature Reviews Drug Discovery, 11,* 462-478.

https://doi.org/10.1038/nrd3702

Grillon, C., O'Connell, K., Lieberman, L. et al. (2017). Distinct Responses to Predictable and Unpredictable Threat in Anxiety Pathologies: Effect of Panic Attack. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging, 2,* 575-581. https://doi.org/10.1016/j.bpsc.2016.08.005

Hariri, A., Drabant, E., Munoz, K. et al. (2005). A Susceptibility Gene for Affective Disorders and the Response of the Human Amygdala. *Archives of General Psychiatry, 62,* 146. https://doi.org/10.1001/archpsyc.62.2.146

Hilbert, K., Lueken, U., & Beesdo-Baum, K. (2014). Neural Structures, Functioning and Connectivity in Generalized Anxiety Disorder and Interaction with Neuroendocrine Systems: A Systematic Review. *Journal of Affective Disorders, 158,* 114-126. https://doi.org/10.1016/j.jad.2014.01.022

Hoge, E. A., Ivkovic, A., & Fricchione, G. L. (2012). Generalized Anxiety Disorder: Diagnosis and Treatment. *BMJ: British Medical Journal, 345,* e7500. https://doi.org/10.1136/bmj.e7500

Hompes, T., Izzi, B., Gellens, E. et al. (2013). Investigating the Influence of Maternal Cortisol and Emotional State during Pregnancy on the DNA Methylation Status of the Glucocorticoid Receptor Gene (NR3C1) Promoter Region in Cord Blood. *Journal of Psychiatric Research, 47,* 880-891. https://doi.org/10.1016/j.jpsychires.2013.03.009

Ibrahim, N., Dania, A. K., Lamis, E. K. et al. (2013). Prevalence and Predictors of Anxiety and Depression among Female Medical Students in King Abdulaziz University, Jeddah, Saudi Arabia. *Iranian Journal of Public Health, 42,* 726.

ICD-11 (2018). *Generalized Anxiety Disorder*. https://icd.who.int/en

Locke, A., Kirst, N., & Shultz, C. (2015). Diagnosis and Management of Generalized Anxiety Disorder and Panic Disorder in Adults. *American Family Physician, 91,* 617-624. https://www.aafp.org/afp/2015/0501/p617.html

Makovac, E., Meeten, F., Watson, D. R., et al. (2016) Alterations in Amygdala-Prefrontal Functional Connectivity Account for Excessive Worry and Autonomic Dysregulation in Generalized Anxiety Disorder. *Biological Psychiatry, 80,* 786-795. https://doi.org/10.1016/j.biopsych.2015.10.013

Mantella, R. C., Butters, M. A., Amico, J. A. et al. (2008). Salivary Cortisol Is Associated with Diagnosis and Severity of Late-Life Generalized Anxiety Disorder. *Psychoneuroendocrinology, 33,* 773-781. https://doi.org/10.1016/j.psyneuen.2008.03.002

Mathew, S. J., Amiel, J. M., Coplan, J. D. et al. (2005). Open-Label Trial of Riluzole in Generalized Anxiety Disorder. *American Journal of Psychiatry, 162,* 2379-2381. https://doi.org/10.1176/appi.ajp.162.12.2379

Mennin, D., Heimberg, R., & Jack, M. (2000). Comorbid Generalized Anxiety Disorder in Primary Social Phobia. *Journal of Anxiety Disorders, 14,* 325-343. https://doi.org/10.1016/S0887-6185(00)00026-8

Moller, E. L. (2016). Parenting Behaviors and Anxiety Meta-Analysis. *Clinical Psychology Review*.

Munir, S., & Takov, V. (2020). *Generalized Anxiety Disorder (GAD)*. StatPearls Publishing.

Murphy, T. M., O'Donovan, A., et al. (2015) Anxiety is Associated with Higher Levels of Global DNA Methylation and Altered Expression of Epigenetic and Interleukin-6 Genes. *Psychiatric Genetics, 25,* 71-78. https://doi.org/10.1097/YPG.0000000000000055

Nemeroff, C. B. (2003). The Role of GABA in the Pathophysiology and Treatment of An-

xiety Disorders. *Psychopharmacology Bulletin, 37,* 133-146.

Non, A. L., Binder, A. M., Kubzansky, L. D., & Michels, K. B. (2014) Genome-Wide DNA Methylation in Neonates Exposed to Maternal Depression, Anxiety, or SSRI Medication during Pregnancy. *Epigenetics, 9,* 964-972. https://doi.org/10.4161/epi.28853

Nutt, D. J. (2001). Neurobiological Mechanisms in Generalized Anxiety Disorder. *Journal of Clinical Psychiatry, 62,* 22-28.

O'Donohue, W., & Fisher, J. (2012). *Cognitive Behavior Therapy* (pp. 86-88). Wiley.

Patriquin, M., & Mathew, S. (2017). The Neurobiological Mechanisms of Generalized Anxiety Disorder and Chronic Stress. *Chronic Stress (Thousand Oaks), 1.* https://doi.org/10.1177/2470547017703993

Pittenger, C., Coric, V., Banasr, M. et al. (2008). Riluzole in the Treatment of Mood and Anxiety Disorders. *CNS Drugs, 22,* 761-786. https://doi.org/10.2165/00023210-200822090-00004

Rakel, R., Rakel, D., & Ahmed, S. (2016). *Textbook of Family Medicine* (9th ed.). Elsevier/Saunders.

Ray, S., & Stowe, Z. N. (2014). The Use of Antidepressant Medication in Pregnancy. *Best Practice & Research Clinical Obstetrics & Gynaecology, 28,* 71-83. https://doi.org/10.1016/j.bpobgyn.2013.09.005

Ritchie, H., & Roser, M. (2022). *Mental Health*. Our World in Data. https://ourworldindata.org/mental-health#anxiety-disorders

Roy, A. K., Fudge, J. L., Kelly, C. et al. (2013). Intrinsic Functional Connectivity of Amygdala-Based Networks in Adolescent Generalized Anxiety Disorder. *The Journal of the American Academy of Child & Adolescent Psychiatry, 52,* 290-299.e2. https://doi.org/10.1016/j.jaac.2012.12.010

Sajdyk, T. J., Shekhar, A., & Gehlert, D. R. (2004). Interactions between NPY and CRF in the Amygdala to Regulate Emotionality. *Neuropeptides, 38,* 225-234. https://doi.org/10.1016/j.npep.2004.05.006

Samreen, S., Siddiqui, N. A., & Mothana, R. A. (2020). Prevalence of Anxiety and Associated Factors among Pharmacy Students in Saudi Arabia: A Cross-Sectional Study? *BioMed Research International, 2020,* Article ID: 2436538. https://doi.org/10.1155/2020/2436538

Strawn, J., Geracioti, L., Rajdev, N. et al. (2018). Pharmacotherapy for Generalized Anxiety Disorder in Adult and Pediatric Patients: An Evidence-Based Treatment Review. *Expert Opinion on Pharmacotherapy, 19,* 1057-1070. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6340395

Turkistani, I., Nuqali, A., Badawi, M. et al. (2014). The Prevalence of Anxiety and Depression among End-Stage Renal Disease Patients on Hemodialysis in Saudi Arabia. *Renal Failure, 36,* 1510-1515. https://doi.org/10.3109/0886022X.2014.949761

Wang, H., Wong, P. T., Spiess, J., & Zhu, Y. Z. (2005). Cholecystokinin-2 (CCK2) Receptor-Mediated Anxiety-Like Behaviors in Rats. *Neuroscience & Biobehavioral Reviews, 29,* 1361-1373. https://doi.org/10.1016/j.neubiorev.2005.05.008

Wilkinson, A., Meares, K., & Freeston, M. (2011). *CBT for Worry and Generalised Anxiety Disorder*. Sage. https://doi.org/10.4135/9781446289105

Zbozinek, T., Rose, R., Wolitzky-Taylor, K. et al. (2012). Diagnostic Overlap of Generalized Anxiety Disorder and Major Depressive Disorder in a Primary Care Sample. *Depress Anxiety, 29,* 1065-1071. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3629816

Zhu, Z., Zhang, L., Jiang, J. et al. (2014). Comparison of Psychological Placebo and Wait-

ing List Control Conditions in the Assessment of Cognitive Behavioral Therapy for the Treatment of Generalized Anxiety Disorder: A Meta-Analysis. *Shanghai Archives of Psychiatry, 26,* 319-331.