Section A-Research paper

General Points about Different Mental Disorders

Esraa Moustafa Abd El Aleem, Nagy Fawzy Mohamed Selim, Ahmed Mohamed Abdallah, Shimaa Ibrahim Amin

Department of psychiatry, Faculty of Medicine, Zagazig University, Egypt

Email: noresraa22@gmail.com

Abstract

Background: Post-traumatic stress disorder (PTSD) is a severe psychiatric disorder that develops in the months and years following exposure to severe trauma. The risk of developing PTSD after a traumatic event varies by trauma typeand is highest following exposure to sexual violence (11.4%), particularly rape (19.0%). Major depressive disorder (MDD) is considered a serious public health issue that adversely impacts an individual's quality of life and contributes significantly to the global burden of disease. Globally, more than 264 million people of all ages suffer from depression. Depression has been a leading cause of disability worldwide and is a major contributor to overall global burden of disease. Generalized anxiety disorder (GAD) is a common and disabling psychiatric disorder that can cause substantial dysfunction affecting daily physical, psychological, and social functioning. GAD is characterized by persistent, excessive and unrealistic worry about everyday things difficult to control accompanied by nonspecific physical and psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbances).

Keywords: Mental Disorders

post traumatic stress disorder (PSTD)

Post-traumatic stress disorder (PTSD) is a severe psychiatric disorder that develops in the months and years following exposure to severe trauma. The risk of developing PTSD after trauma is multi-factorial, and involves genes and the environment Although at least 30–40% of this risk is heritable **(1)**, it is also influenced by past personal history, including prior adult and childhood trauma, and psychological factors that might differentially mediate the regulation of fear and emotion.

Epidemiology of PTSD

The prevalence of traumatic events in the lives of individuals ranges from 61% to 80%**.** After the trauma, posttraumatic stress disorder occurs in approximately 5% to 10% of the population and is higher in women than in men to be approximately twice that found in men**.** In addition to being more prevalent, PTSD in women also tends to be more severe and chronic and have higher comorbidity rates ,although women generally respond better to treatment than men **(2).**

Risk factors and pathology

The risk of developing PTSD after a traumatic event varies by trauma typeand is highest following exposure to sexual violence (11.4%), particularly rape (19.0%). Men are more likely to experience a traumatic event (of any type), but women are more likely to experience the kind of high-impact traumatic event that can lead to PTSD, such as interpersonal violence and sexual assault **(3).**

Diagnostic criretia according DSM-5

The diagnostic criteria for the diagnosis of PTSD according to DSM-5 include

A. Exposure to actual or threatened death, serious injury, or sexual violence in one (or more) of the following ways:

1. Directly experiencing the traumatic event(s).
2. Witnessing, in person, the event(s) as it occurred to others.

3. Learning that the traumatic event(s) occurred to a close family member or close friend. In cases of actual or threatened death of a family member or friend, the event(s) must have been violent or accidental.
4. Experiencing repeated or extreme exposure to aversive details of the traumatic event(s) (e.g., first responders collecting human remains; police officers repeatedly exposed to details of child abuse).
Note: Criterion A4 does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related. B. Presence of one (or more) of the following intrusion symptoms associated with the traumatic event(s), beginning after the traumatic event(s) occurred:
1. Recurrent, involuntary, and intrusive distressing memories of the traumatic event(s). Note: In children older than 6 years, repetitive play may occur in which themes or aspects of the traumatic event(s) are expressed.
2. Recurrent distressing dreams in which the content and/or effect of the dream are related to the traumatic event(s). Note: In children, there may be frightening dreams without recognizable content.
3. Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring. (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.) Note: In children, trauma-specific reenactment may occur in play.
4. Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
5. Marked physiological reactions to internal or external cues that symbolize or resemble an aspect of the traumatic event(s).
C. Persistent avoidance of stimuli associated with the traumatic event(s), beginning after the traumatic event(s) occurred, as evidenced by one or both of the following:
1. Avoidance of or efforts to avoid distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
2. Avoidance of or efforts to avoid external reminders (people, places, conversations, activities, objects, situations) that arouse distressing memories, thoughts, or feelings about or closely associated with the traumatic event(s).
D. Negative alterations in cognitions and mood associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Inability to remember an important aspect of the traumatic event(s) (typically due to dissociative amnesia and not to other factors such as head injury, alcohol, or drugs).
2. Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world (e.g., "I am bad," "No one can be trusted," "The world is completely dangerous," "My whole nervous system is permanently ruined").
3. Persistent, distorted cognitions about the cause or consequences of the traumatic event(s) that lead the individual to blame himself/herself or others.
4. Persistent negative emotional state (e.g., fear, horror, anger, guilt, or shame).
5. Markedly diminished interest or participation in significant activities.
6. Feelings of detachment or estrangement from others.
7. Persistent inability to experience positive emotions (e.g., inability to experience happiness, satisfaction, or loving feelings). E. Marked alterations in arousal and reactivity associated with the traumatic event(s), beginning or worsening after the traumatic event(s) occurred, as evidenced by two (or more) of the following:
1. Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects.
2. Reckless or self-destructive behavior.
3. Hypervigilance.
4. Exaggerated startle response.
5. Problems with concentration.
6. Sleep disturbance (e.g., difficulty falling or staying asleep or restless sleep).

F. Duration of the disturbance (Criteria B, C, D, and E) is more than 1 month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. 303 H. The disturbance is not attributable to the physiological effects of a substance (e.g., medication, alcohol) or another medical condition.

Specify whether: With dissociative symptoms: The individual's symptoms meet the criteria for posttraumatic stress disorder, and in addition, in response to the stressor, the individual experiences persistent or recurrent symptoms of either of the following:

1. Depersonalization: Persistent or recurrent experiences of feeling detached from, and as if one were an outside observer of, one's mental processes or body (e.g., feeling as though one were in a dream; feeling a sense of unreality of self or body or of time moving slowly).

2. Derealization: Persistent or recurrent experiences of unreality of surroundings (e.g., the world around the individual is experienced as unreal, dreamlike, distant, or distorted).

Note: To use this subtype, the dissociative symptoms must not be attributable to the physiological effects of a substance (e.g., blackouts, behavior during alcohol intoxication) or another medical condition (e.g., complex partial seizures).

Specify if: With delayed expression: If the full diagnostic criteria are not met until at least 6 months after the event (although the onset and expression of some symptoms may be immediate).

Pathophysiology

1) Neuroendocrinology

During traumatic experiences, the high levels of stress hormones secreted suppress hypothalamic activity that may be a major factor toward the development of PTSD**.(4)**

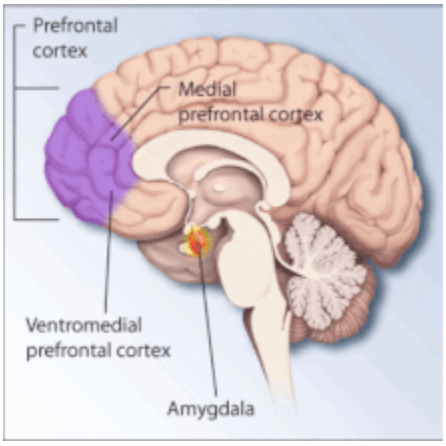
HPA axis abnormalities are likely predicated on strong negative feedback inhibition of cortisol, itself likely due to an increased sensitivity of glucocorticoid receptors.**(4)**

It is thought that the locus coeruleus-noradrenergic system mediates the over-consolidation of fear memory. High levels of cortisol reduce noradrenergic activity, and because people with PTSD tend to have reduced levels of cortisol, it has been proposed that individuals with PTSD cannot regulate the increased noradrenergic response to traumatic stress**. (5)**

Intrusive memories and conditioned fear responses are thought to be a result of the response to associated triggers. Neuropeptide Y (NPY) has been reported to reduce the release of norepinephrine and has been demonstrated to have anxiolytic properties in animal models. Studies have shown people with PTSD demonstrate reduced levels of NPY, possibly indicating their increased anxiety levels**. (9)**

Dopamine levels in a person with PTSD can contribute to symptoms: low levels can contribute to anhedonia, apathy, impaired attention, and motor deficits; high levels can contribute to psychosis, agitation, and restlessness**. (6)**

2)Neuroanatomy



Regions of the brain associated with stress and post-traumatic stress disorder **(6)**

A meta-analysis of structural MRI studies found an association with reduced total brain volume, intracranial volume, and volumes of the hippocampus, insula cortex, and anterior cingulate. Much of this research stems from PTSD in those exposed to the Vietnam War. **(7)**

People with PTSD have decreased brain activity in the dorsal and rostral anterior cingulate cortices and the ventromedial prefrontal cortex, areas linked to the experience and regulation of emotion.**(8)**

The amygdala is strongly involved in forming emotional memories, especially fear-related memories. The amygdalocentric model of PTSD proposes that the amygdala is very much aroused and insufficiently controlled by the medial prefrontal cortex and the hippocampus, in particular during extinction.This is consistent with an interpretation of PTSD as a syndrome of deficient extinction ability.The basolateral nucleus (BLA) of the amygdala is responsible for the comparison and development of associations between unconditioned and conditioned responses to stimuli, which results in the fear conditioning present in PTSD. The BLA activates the central nucleus (CeA) of the amygdala, which elaborates the fear response, (including behavioral response to threat and elevated startle response). Descending inhibitory inputs from the medial prefrontal cortex (mPFC) regulate the transmission from the BLA to the CeA, which is hypothesized to play a role in the extinction of conditioned fear responses. During high stress, the hippocampus, which is associated with placing memories in the correct context of space and time and memory recall, is suppressed. According to one theory this suppression may be the cause of the flashbacks that can affect people with PTSD. When someone with PTSD undergoes stimuli similar to the traumatic event, the body perceives the event as occurring again because the memory was never properly recorded in the person's memory.**(9)**

3) Genetic factors

Much evidence indicates that genetic factors play an important role, accounting for 30-72% of the vulnerability to develop PTSD. Many studies have attempted to link PTSD with genetic candidates, and not surprisingly genes associated with PTSD are also linked with other c common psychiatric disorders, including major depression, generalized anxiety disorder, panic disorder, and substance use. For example, numerous studies have pointed to the functional polymorphism in the promoter region of the serotonin transporter gene (SLC6A4) across many disorders. The short allele (5-HTTLP R S), which reduces serotonergic expression and uptake by nearly 50% has been linked with impaired extinction learning in both mice and humans **(10).**

Gene x environment association studies also show that a functional variant in FKBP5, a gene encoding a co-chaperone of the glucocorticoid receptor, increases risk for PTSD following trauma. Over 50 gene variants have been inked with PTSD, involved in the function of HPA axis; noradrenergic, dopaminergic and serotonergic systems; and neurotrophins **(11)**

However, this field is characterized by poor replication of findings, and accordingly there is convergent agreement that the most promising avenue for understanding the genetic basis of PTSD is via polygenic approaches.The largest genome-wide study to date was conducted by the Psychiatric Genomics Cons onsortium – Posttraumatic Stress Disorder Group, which recently reported an analysis of 20,730 people: no single nucleotide polymorphism was found to be significantly associated with PTSD, **(1)**

Early life stress is particularly relevant, with evidence that childhood trauma modifies the genetic risk for PTSD **(12).**

distinctive methylation in PTSD has been documented in a number of genes, including NR3C1, CRHR1 and FKBP5However, the evidence has relied to date on peripheral blood assessments, that may not reflect central mechanisms occurring in neural circuits **(11)**.

4) Cognitive behavioral models

Although deficits in numerous aspects of cognition and memory are seen in PTSD, declarative memory is particularly impaired when the index trauma is accompanied by comorbid traumatic brain injury (TBI)**.** TBI is often but not invariably present in individuals with PTSD. One hypothesis is that brain injury-related processes (inflammation, cell death) exacerbate the molecular adaptations that occur in response to non-injury-related stress. Deficits in declarative memory also frequently accompany an increased vulnerability

to PTSD in individuals who have experienced a natural disaster or motor vehicle accident. The brain region most associated with PTSD-related declarative memory deficits is the hippocampus, which is involved in memory formation, storage and consolidation **(13)**.

Notably, some of the oldest data on hippocampal structure indicate smaller hippocampal volumes in individuals with PTSD than in control participants. These findings have now been replicated in a much larger meta-analytic study In other studies, smaller hippocampal volume at 1-month post-trauma and decreased inhibition-related hippocampal activity both predicted PTSD severity at later time points (**14).**

5) Molecular mechanism and predictive factors

The mechanisms leading to posttraumatic stress disorder have not yet been fully elucidated. Recent literature suggests that both the neuroendocrine and immune systems are involved in the formulation and development of PTSD. After traumatic exposures, the stress response pathways of the hypothalamic–pituitary–adrenal (HPA) axis and sympathetic nervous system are activated and lead to the abnormal release of glucocorticoids (GC) and catecholamines. GCs have downstream effects on immunosuppression, metabolism enhancement, and negative feedback inhibition of the HPA axis by binding to the GC receptor (GR), thus connecting the neuroendocrine modulation with immune disturbance and inflammatory response. A recent meta-analysis of 20 studies found increased plasma levels of proinflammatory cytokines tumor necrosis factor-alpha (TNF-a), interleukin-1beta (IL-1b), and interleukin-6 (IL-6) in individuals with PTSD compared to healthy controls**.** In addition, some other studies speculate that there is a prospective association of C-reactive protein (CRP) and mitogen with the development of PTSD **(15).**

Mangement

A)Psychological intervention

1) Cognitive behavioral therapy

CBT seeks to change the way a person feels and acts by changing the patterns of thinking or behavior, or both, responsible for negative emotions. Results from a 2018 systematic review found high strength of evidence that supports CBT-exposure therapy efficacious for a reduction in PTSD and depression symptoms, as well as the loss of PTSD diagnosis**.** A 2021 Cochrane review assessed the provision of CBT in an Internet-based format found similar beneficial effects for Internet-based therapy as in face-to-face. However, the quality of the evidence was low due to the small number of trials reviewed. Exposure Exposure therapy is a type of cognitive behavioral therapy that involves assisting trauma survivors to re-experience distressing trauma-related memories and reminders in order to facilitate habituation and successful emotional processing of the trauma memory. Recent research on contextually based third-generation behavior therapies suggests that they may produce results comparable to some of the better validated therapies**.** Many of these therapy methods have a significant element of exposure and have demonstrated success in treating the primary problems of PTSD and co-occurring depressive symptoms**. (16)**

2) Eye movement desensitization and reprocessing (EMDR)

However, exposure by way of being asked to think about the experience rather than talk about it has been highlighted as one of the more important distinguishing elements of EMDR**.)** .There was some evidence that EMDR might prevent depression**.(17)**

3) Interpersonal psychotherapy

Other approaches, in particular involving social supports,may also be important. An open trial of interpersonal psychotherapy it was reported that high rates of remission from PTSD symptoms without using exposure**. (18).**

Pharmacological therapy

While many medications do not have enough evidence to support their use, four (sertraline, fluoxetine, paroxetine, and venlafaxine) have been shown to have a small to modest benefit over placebo with many medications, residual PTSD symptoms following treatment is the rule rather than the exception **(19)**

1)Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) may have some benefit for PTSD symptoms. Tricyclic antidepressants are equally effective but are less well tolerated. **(20)**

Evidence provides support for a small or modest improvement with sertraline, fluoxetine, paroxetine, and venlafaxine**.** Thus, these four medications are considered to be first-line medications for PTSD**. (21)**

2)Benzodiazepine

are not recommended for the treatment of PTSD due to a lack of evidence of benefit and risk of worsening PTSD symptoms.Some authors believe that the use of benzodiazepines is contraindicated for acute stress, as this group of drugs can cause dissociation Nevertheless, some use benzodiazepines with caution for short-term anxiety and insomnia.**(22)** .

3) Prazosin

Prazosin, an alpha-1 adrenergic antagonist, has been used in veterans with PTSD to reduce nightmares. Studies show variability in the symptom improvement, appropriate dosages, and efficacy in this population **(23)**

4) Glucocorticoids

Glucocorticoids may be useful for short-term therapy to protect against neurodegeneration caused by the extended stress response that characterizes PTSD, but long-term use may actually promote neurodegeneration**. (24)**

5) Cannabinoids

Cannabis is not rot recommended as a treatment for PTSD because scientific evidence does not currently exist demonstrating treatment efficacy for cannabinoids However, use of cannabis or derived products is widespread among U.S. veterans with PTSD**.** An increasing number of states permit and have legalized the use of medical cannabis for the treatment of PTSD **(25).**

(B) Major depressive disorder

Major depressive disorder (MDD) is considered a serious public health issue that adversely impacts an individual's quality of life and contributes significantly to the global burden of disease. Globally, more than 264 million people of all ages suffer from depression. Depression has been a leading cause of disability worldwide and is a major contributor to overall global burden of disease. MDD has been ranked as the third cause of the burden of disease worldwide in 2008 by WHO, which has projected that this disease will rank first by 2030 **(26)**

EPIDEMIOLOGY:

Incidence and prevalence:

The 12-month prevalence of major depressive disorder varies considerably across countries but is approximately 6% **(26).** It has a lifetime prevalence of about 5 to 17 percent, with the average being 12 percent **(27)**.

AGE:

The mean age of onset for MDD is about 40 years, with 50 % of all patients having an onset between the ages of 20 and 50 years. Major depressive disorder can begin in childhood or in old age **(28)•**

Gender:

Across the lifespan, MDD is almost twice as common in women than in men **(27)**. Prevalence is approximately 21% and 13%, respectively **(29).**

❖ **AETIOLOGY:**

Despite decades of basic science, clinical neuroscience, and psychiatric research, the pathophysiology of MDD is not well understood. Studies found that MDD has a multifactorial aetiology, with no single established mechanism that can explain all aspects of the disease **(30).** These factors include the following:

➢ **Biological factors:**

• **Monoamine neurotransmission:**

MDD was earlier considered to be mainly due to abnormalities in neurotransmitters, especially serotonin, norepinephrine, and dopamine. This has been evidenced by the use of different antidepressants such as selective serotonin receptor inhibitors, serotonin-norepinephrine receptor inhibitors, dopamine-norepinephrine receptor inhibitors in the treatment of depression. However, recent theories indicate that it is associated primarily with more complex neuroregulatory systems and neural circuits, causing secondary disturbances of neurotransmitter systems **(27)**.

Endocrine factors:

Alterations in endocrine function may play an important role in mechanisms underlying the pathophysiology of MDD. Studies found changes in hypothalamic pituitary axis(HPA) activity hormone (CRH)and cortisol and inadequate HPA axis suppression particularly increased corticotrophin releasing after pharmacological and psychological challenge. Studies found that the severity of depressive symptoms is proportionate to cortisol level **(31).**

Immune-inflammatory factors:

Several studies documented the role of inflammation in depression**.** Evidences support that are increased levels of pro-inflammatory cytokines such in MDD patients and increased risk of developing autoimmune diseases (rheumatoid arthritis, multiple sclerosis) in depressed patients **(32).**

Neurogenesis

Neurogenesis plays an important role in depression pathophysiology**.** Studies found reduction of Hippocampal Neurogenesis in depression**,** which is stimulated by TCAs, SSRIs, SNRIs and ECT **(33).**

➢**Genetic factors**

MDD is heritable, according to adoption and twin studies. It has previously been difficult to identify the genes that are responsible in a reliable manner. However, recent genome-wide association studies (GWAS) have begun to successfully discover several genes, risk variants, and replicated findings that could help to better understand the pathophysiology of MDD **(34)**.

➢**Environmental Stress Factors:**

Environmental stressors such childhood abuse, interpersonal conflict, and trauma have all been linked to the development of MDD. Depression can be precipitated by environmental and psychosocial factors. such"diathesis-stress model" is common in psychiatry **(35).**

NEUROPATHOLOGY

Brain imaging detected significant gray matter reductions in depression. Patients with depression exhibit smaller volumes of the basal ganglia, thalamus, hippocampus, frontal lobe, orbitofrontal cortex and gyrus rectus, as well as a smaller hippocampal volume is detectable in patients during a depressive episode compared to patients in remission **(36).**

❖**DIAGNOSIS:**

According to DSM5:

Diagnostic Criteria for Major Depressive Episode

Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.

1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, hopeless) or observation made by others (e.g., appears tearful).
2. Markedly diminished interest or pleasure in all, or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation

3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day

5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning

C. The episode is not attributable to the physiological effects of a substance or to an-other medical condition

TREATMENT

➢Pharmacological treatment:

there are numerous evidence-based treatments available for depression. Starting with the MAO inhibitors and the tricyclic antidepressants which are still among the most efficacious drugs available. These medications have been replaced by newer drugs with more pharmacologically selective actions and, as a result, fewer side-effects. SSRIs (sertraline, paroxetine, citalopram, escitalopram, fluvoxamine), SNRIs (including duloxetine and venlafaxine), and, finally, a number of other compounds (bupropion, nefazodone, trazodonemirtazapine, vortioxetine, reboxetine, agomelatine) were introduced were were introduced, giving a wide range of options for treatment **(37).**

Psychotherapy

Evidence-based psychotherapies, most notably CBT and interpersonal psychotherapy, are clearly effective in the treatment of MDD and there is some evidence of the efficacy of more psychodynamically based psychotherapies.Treatment of MDD also include electroconvulsive theray for severe, treatment-resistant MDD and psychotic depression**,** Repetitive transcranial magnetic stimulation (rTMS) for treatment-resistant depression **&**Vagal nerve stimulation approved by FDA for treatment for refractory depression **(38).**

(C) Generalized anxiety disorder

Generalized anxiety disorder (GAD) is a common and disabling psychiatric disorder that can cause substantial dysfunction affecting daily physical, psychological, and social functioning. GAD is characterized by persistent, excessive and unrealistic worry about everyday things difficult to control accompanied by nonspecific physical and psychological symptoms (restlessness, fatigue, difficulty concentrating, irritability, muscle tension, or sleep disturbances) **(39).**

❖EPIDEMIOLOGY:

Incidence and prevalence:

lifetime prevalence of GAD is ranging from 5.1% to 11.9%. The 12-month prevalence has been estimated to be about 1·7% in patients under age 65 years, and about 3·4% in patients older than age 65 years **(40).**

Age and gender:

This disorder peaks in middle age, with a notable decline across later years of life, although it is the most common anxiety disorder in the elderly population.
Women are twice as likely to be diagnosed with GAD compared to men **(39).**

PATHOPHYSIOLOGY AND RISK FACTORS

32 of a "threat circuit" in the brain, consisting of the reciprocal connections between the dorsomedial prefrontal cortex, insula, and amygdala. Threatening stimuli have been shown to activate this circuit in healthy individuals**,** and increased activation of this circuit is positively correlated to state and trait levels of anxiety in individuals with anxiety disorders. Fonzo and colleagues reported that those with generalized anxiety disorder show a pattern of greater amygdala activation when processing fearful facial expressions compared to happy facial expressions, which was correlated to levels of anxious traits **(41).**

Several factors have been shown to regulate activity in this circuit. The threat circuit has been shown to be inhibited by serotonin. Selective serotonin reuptake inhibitors (SSRIs), first-line treatments for a variety of anxiety disorders, have been demonstrated to reduce neurobiologicalneurobiological activity in the dorsomedial prefrontalcortex–amygdala circuit to aversive stimuli**.** The dorsolateral prefrontal cortex is thought to play a key role in emotional regulation through exerting top-down cognitive control on limbic structures, especially via attentional processes. Psychotherapies for anxiety, such as cognitive-behavioral therapy, are felt to exert their effects biologically through enhanced cortical modulation of amygdala activity **(42).**

➢Genetic Factors

Genetic heritability estimates for anxiety disorders have been estimated as 30% to 50% suggesting that genetics play prominent role in the genesis of anxiety disorders **(43).**

➢Environmental Factors:

Adversities in childhood, such as abuse and neglect, have been related to an increased risk of developing anxiety disorders. Studies found that extreme types of adversity have been linked to changes in the neurocircuitry involved in fear and emotional processing **(44).**

❖DIAGNOSIS:

DSM-5 Diagnostic Criteria for Generalized Anxiety Disorder
A. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).
B. The individual finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months); Note: Only one item is required in children.
1. Restlessness or feeling keyed up or on edge.
2. Being easily fatigued.
3. Difficulty concentrating or mind going blank.
4. Irritability.
5. Muscle tension.
6. Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).

D. The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
F. The disturbance is not better explained by another mental disorder (e.g., anxiety or worry eg).

❖TREATMENT

Cognitive behavioural therapy and pharmacological treatment are the two basic therapies for generalised anxiety disorder. A combination of the two may be most beneficial to patients. **(45)**

Pharmacological treatment:
Generalized anxiety disorder is treated with a variety of medications.
Serotonergic/Norepinephrinergic Antidepressants:
The Food and Drug Administration (FDA) has approved several selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) for treatment of GAD **(46).**

Selective serotonin and SNRIs are both first-line treatments for GAD **(46).**

Buspirone:

Buspirone is a 5-HT1A partial agonist, categorised among the azapirones, is FDA-approved for anxiety treatment and is widely used in conjunction with SSRIs or SNRIs, primarily for GAD. **(47).**

Benzodiazepines:

Benzodiazepines have been a longstanding treatment for anxiety, and they are still one of the most often prescribed psychiatric drugs in the world. Benzodiazepines are no longer considered first-line monotherapy for anxiety disorders but can be used in the short-term on either a standing or as-needed basis for GAD in conjunction with SSRIs and SNRIs **(48).**

Pregabalin:
Tricyclic antidepressants (TCA): TCA are now less frequently prescribed TCA are due to concerns about side effects, and risk of mortality with overdose **(47).**
Agomelatine: Agomelatine is an antidepressant which acts as an agonist for melatonin receptor and 5-HT2C receptor antagonist. Several studies documented that it is effective in GAD **(49).**

Hydroxyzine: It is the most extensively researched antihistamine for anxiety and the only antihistamine licenced by the FDA for this use. studies about GAD reported that hydroxyzine was superior to placebo and comparable to benzodiazepines and buspirone **(50).**

Psychotherapy
Although various psychotherapeutic approaches delivered on an individual or group basis can be used to treat GAD (with or without adjunctive medications), those in the family of cognitive behavioral therapy (CBT) have the largest body of evidence **(50).**

Conflicts of Interest: The authors declare no conflict of interest.

References

1. **Duncan LE et al.** Largest GWAS of PTSD (N=20 070) yields genetic overlap with schizophrenia and sex differences in heritability. Mol. Psychiatry 23, 666–673 (2018).
2. **Christiansen DM.** Sex and gender differences in trauma victims presenting for treatment. In: Legato MJ, editor. Principles of Gender-Specific Medicine. 3 ed. London: Academic Press (Elsevier); 2017. p. 497–511.
3. **Kessler RC, Aguilar-Gaxiola S, Alonso J, Benjet C, Bromet EJ, Cardoso G, Degenhardt L, de Girolamo G, Dinolova RV, Ferry F, Florescu S, Gureje O, Haro JM, Huang Y, Karam EG, Kawakami N, Lee S, Lepine JP, Levinson D, Navarro-Mateu F, Pennell BE, Piazza M, Posada-Villa J, Scott KM, Stein DJ, Ten Have M, Torres Y, Viana MC, Petukhova MV, Sampson NA, Zaslavsky AM, Koenen KC (27 October 2017).** "Trauma and PTSD in the WHO World Mental Health Surveys". European Journal of Psychotraumatology. 8 (sup5): 1353383.
4. **Yehuda R, Halligan SL, Golier JA, Grossman R, Bierer LM (April 2004).** "Effects of trauma exposure on the cortisol response to dexamethasone administration in PTSD and major depressive disorder". Psychoneuroendocrinology. 29 (3): 389–404.
5. **Zohar J, Juven-Wetzler A, Myers V, Fostick L (January 2008).** "Post-traumatic stress disorder: facts and fiction". Current Opinion in Psychiatry. 21 (1): 74–7.
6. **Olszewski TM, Varrasse JF (June 2005).** "The neurobiology of PTSD: implications for nurses". Journal of Psychosocial Nursing and Mental Health Services. 43 (6): 40–7.
7. **Hughes KC, Shin LM (February 2011).** "Functional neuroimaging studies of post-traumatic stress disorder". Expert Review of Neurotherapeutics. 11 (2): 275–85.
8. **Etkin A, Wager TD (October 2007).** "Functional neuroimaging of anxiety: a meta-analysis o femotional processing in PTSD, social anxiety disorder, and specific phobia". The American Journal of Psychiatry. 164 (10): 1476–88.
9. **Skelton K, Ressler KJ, Norrholm SD, Jovanovic T, Bradley-Davino B (February 2012).** "PTSD and gene variants: new pathways and new thinking". Neuropharmacology. 62 (2): 628–37.
10. **Hartley CA, McKenna MC, Salman R et al.** Serotonin transporter polyadenylation polymorphism modulates the retention of fear extinction memory. Proc Natl Acad Sci USA 2012;109:5493-8.
11. **Sheerin CM, Lind MJ, Bountress KE et al.** The genetics and epigenetics of PTSD: overview, recent advances, and future directions. Curr Opin Psychol 2017;14:5-11.
12. **Binder EB, Bradley RG, Liu W et al.** Association of FKBP5 polymorphisms and childhood abuse with risk of posttraumatic stress disorder symptoms in adults. JAMA 2008;299:1291-305.
13. **Parsons RG & Ressler** KJ Implications of memory modulation for post-traumatic stress and fear disorders. Nat. Neurosci. 16, 146–153 (2013)..
14. **Ben-Zion Z et al.** Neuroanatomical risk factors for posttraumatic stress disorder in recent trauma survivors. Biol. Psychiatry Cogn. Neurosci. Neuroimaging 5, 311–319 (2020)..
15. **Eraly SA, Nievergelt CM, Maihofer AX, Barkauskas DA, Biswas N, Agorastos A, et al.** Assessment of plasma C-reactive protein as a biomarker of posttraumatic stress disorder risk. JAMA Psychiatry. 2014;71(4):423.
16. **Mulick PS, Landes S, Kanter JW (2005).** "Contextual Behavior Therapies in the Treatment of PTSD: A Review" (PDF). International Journal of Behavioral Consultation and Ther apy. 1 (3): 223–228.
17. **Jonas DE, Cusack K, Forneris CA (April 2013).** Psychological and pharmacological treatments for adults with posttraumatic stress disorder (PTSD). Comparative Effectiveness Reviews No. Rockville, MD: Agency for Healthcare Research and Quality.
18. **Bleiberg KL, Markowitz JC (January 2005).** "A pilot study of interpersonal psychotherapy for posttraumatic stress disorder". The American Journal of Psychiatry. 162 (1): 181–3.
19. **Krystal JH, Neumeister A (October 2009). "**Noradrenergic and serotonergic mechanisms in the neurobiology of posttraumatic stress disorder and resilience". Brain Research. 1293: 13–23.
20. **Puetz TW, Youngstedt SD, Herring MP (28 May 2015).** Hashimoto K (ed.). "Effects of Pharmacotherapy on Combat-Related PTSD, Anxiety, and Depression: A Systematic Review and Meta-Regression Analysis". PLOS ONE.10(5):e0126529. Bibcode:2015PLoSO..1026529P.
21. **Jeffreys M, Capehart B, Friedman MJ (2012). "**Pharmacotherapy for posttraumatic stress disorder: review with clinical applications". Journal of Rehabilitation Research and Development. 49 (5): 703–715.
22. **Kapfhammer HP (June 2014).** "Patient-reported outcomes in post-traumatic stress disorder. Part II: focus on pharmacological treatment". Dialogues in Clinical Neuroscience (in English, Spanish, and French). 16 (2): 227–237.

23. **Waltman SM, Shearer D, Moore BA (11 October 2018).** "Management of Post-Traumatic Nightmares: a Review of Pharmacologic and Nonpharmacologic Treatments Since 2013". Current Psychiatry Reports. Springer Science and Business Media LLC. 20 (12): 108.
24. **Griffin GD, Charron D, Al-Daccak R (November 2014).** "Post-traumatic stress disorder: revisiting adrenergics, glucocorticoids, immune system effects and homeostasis". Clinical & Translational Immunology. 3 (11): e27.
25. **Gregg K (13 July 2016).** "Raimondo signs law allowing marijuana for treatment of PTSD". The Providence Journal. Archived from the original on 16 August 2016. Retrieved 18 August 2016.
26. **Malhi, G. S., & Mann, J. J. (2018).** Course and prognosis. Lancet, 392, 2299-312.
27. **Bains, N., & Abdijadid, S. (2021).** Major depressive disorder. StatPearls [Internet].
28. **Kaplan, H. I., & Sadock, B. J., (2015):** Comprehensive Textbook of Psychiatry.
29. **Dwyer, J. B., Aftab, A., Radhakrishnan, R., Widge, A., Rodriguez, C. I., Carpenter, L. L**., ... & APA Council of Research Task Task Force on Novel Biomarkers and Treatments. (2020).
30. **Dudek, A., Dion-Albert, L., Kaufmann, N., Tuck, E., Lebel, M., & Menard, C. (2019).** Neurobiology of resilience in depression: immune and vascular insights from human and animal studies Eur J Neurosci.
31. **Nandam, L. S., Brazel, M., Zhou, M., & Jhaveri, D. J. (2020).** Cortisol and major depressive disorder—translating findings from humans to animal models and back. Frontiers in psychiatry, 10, 97.
32. **Andersson, N. W., Gustafsson, L. N., Okkels, N., Taha, F., Cole, S. W., Munk-Jørgensen, P.,& Goodwin, R. D. (2015).** Depression and the risk of autoimmune disease: a nationally representative, prospective longitudinal study. Psychological Medicine, 45(16), 3559-3569.
33. **Segi-Nishida, E. (2017).** The effect of serotonin-targeting antidepressants on neurogenesis and neuronal maturation of the hippocampus mediated via 5-HT1A and 5-HT4 receptors. Frontiers in cellular neuroscience, 11, 142.
34. **Wray, N. R., Ripke, S., Mattheisen, M., Trzaskowski, M., Byrne, E. M., Abdellaoui, A., ... & Viktorin, A. (2018).** Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. Nature genetics, 50(5), 668-681.
35. **Uher, R., & Zwicker, A. (2017).** Etiology in psychiatry: embracing the reality of poly-gene- environmental causation of mental illness. World Psychiatry,16(2),121-129.
36. **Kempton, M. J., Salvador, Z., Munafò, M. R., Geddes, J. R., Simmons, A., Frangou, S.,&Williams, S. C. (2011).** Structural neuroimaging studies in major depressive disorder: meta-analysis and comparison with bipolar disorder. Archives of general psychiatry,68(7),675-690.
37. **Nemeroff, C. B. (2020).** The state of our understanding of the pathophysiology and optimal treatment of depression: Glass half full or half empty?. American Journal of Psychiatry,177(8),671-685.
38. **Conway, C. R., Kumar, A., Xiong, W., Bunker, M., Aaronson, S. T., & Rush, A. J. (2018)**.,Chronic vagus nerve stimulation significantly improves quality of life in treatmentresistant major depression. The Journal of clinical psychiatry, 79(5), 0-.
39. **American Psychiatric Association. (2013).** Diagnostic and statistical manual of mental disorders (DSM-5). American Psychiatric Publishing.
40. **Slee, A., Nazareth, I., Bondaronek, P., Liu, Y., Cheng, Z., & Freemantle, N. (2019**).Pharmacological treatments for generalised anxiety disorder: a systematic review and network meta-analysis. The Lancet, 393(10173), 768-777.
41. **fonzo, G. A., Ramsawh, H. J., Flagan, T. M., Sullivan, S. G., Letamendi, A., Simmons, A. N.,... & Stein, M. B. (2015).** Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. The British Journal of Psychiatry, 206(3), 206-215.
42. **Doerig, N., Krieger, T., Altenstein, D., Schlumpf, Y., Spinelli, S., Späti, J., ... & GrosseHoltforth, M. (2016).** Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression. The British Journal ofPsychiatry,208(2),175-181.
43. **Meier, S. M., & Deckert, J. (2019).** Genetics of anxiety disorders. Current psychiatry reports,21(3),1-8.
44. **Juruena, M. F., Eror, F., Cleare, A. J., & Young, A. H. (2020).** The role of early life stress in HPA axis and anxiety. Anxiety Disorders, 141-153.
45. **Latas, M., Trajković, G., Bonevski, D., Naumovska, A., Vučinić Latas, D., Bukumirić, Z., & Starčević, V. (2018).** Psychiatrists' treatment preferences for generalized anxiety disorder. Human Psychopharmacology: Clinical and Experimental, 33(1), e2643.
46. **sartori, S. B., & Singewald, N. (2019).** Novel pharmacological targets in drug development for the treatment of anxiety and anxiety-related disorders. Pharmacology & thera peutics, 204, 107402.
47. **Bandelow, B., Michaelis, S., & Wedekind, D. (2017).** Treatment of anxiety disorders. Dialogues in clinical neuroscience, 19(2), 93.
48. **National Institute for Health and Care Excellence (NICE)** Genearalised Anxiety Disorder and Panic Disordr in Adults: Management. Available online at: https://www.nice.org.uk/guidance/cg113 (accessed November 13, 2020).
49. **Stein, D. J., Khoo, J. P., Ahokas, A., Jarema, M., Van Ameringen, M., Vavrusova, L., ... & de Bodinat, C. (2018).** 12-week double blind randomized multicenter study of efficacy and safety of agomelatine (25–50 mg/day) versus escitalopram (10–

20 mg/day) in outpatients with severe generalized anxiety disorder. European Neuropsychopharmacology, 28(8), 970-979.

50. Guaiana, G., Barbui, C., & Cipriani, A. (2010). Hydroxyzine for generalised anxiety disorder. Cochrane Database of Systematic Reviews, (12).