

**Review article**

**Anxiety Disorders: Recent Global Approach to Neuro-pathogenesis, Drug Treatment, Cognitive Behavioral Therapy, and Their Implications**

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**Abstract**

Anxiety is a group of mental disorders characterized by the sudden feeling of intense fear, panic, shortness of breath, chest pain, restlessness, GIT problems, insomnia, fatigue, muscle tension, sweating, loss of memory, blurred vision, and impaired learning. It occurs typically in response to a stressful situation that may become pathological when it is no longer controlled or occurs in the absence of real threat. This review aimed to appraise the literature on the prevalence, classification, neuro-pathogenesis, diagnoses, and treatment of anxiety disorders (AD). The search was made using PubMed, Embase, MEDLINE, and PsycINFO databases. Anxiety disorders are the most common mental disorders affecting humans, especially among developing nations. In general, the lifetime prevalence of AD is about 14%, with an annual prevalence of 31%. Unfortunately, AD, in general, is underdiagnosed and undertreated globally.

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Anxiety disorders are classified based on the Diagnostic and Statistical Manual for Mental Health Disorder V (DSM-V). Examples of AD include generalized anxiety disorder, panic attack, agoraphobia, specific phobia, social anxiety disorder, separation anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, selective mutism, medication anxiety disorder, and medical condition anxiety disorder. Generally, anxiety is caused by biological, genetic, autonomic, biochemical, and environmental changes. Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the CNS. It is known for the induction of sleep, relaxation, and prevention of excitation; therefore, depletion of GABA in the occipital cortex is implicated in anxiety pathogenesis. Besides, hormones such as serotonin, dopamine, noradrenaline, and glutamate are involved in anxiety etiology. Treatments of anxiety disorders involve the use of drugs and cognitive behavioral therapy (CBT). Classes of drugs used in the management of anxiety include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, a tricyclic antidepressant, benzodiazepines, antihistamines, monoamine oxidase inhibitors, atypical antipsychotics, azapirones, and reversible inhibitors of monoamine oxidase.

**Keywords:** Anxiety, Disorders, Fear, Neuro-pathogenesis, Diagnosis, Pharmacotherapy.

## 1. Introduction

Anxiety is an abnormal response to a dangerous or stressful condition like the response to external stimuli. Anxiety is considered part of our daily lives; it can be adapted over time or applying some helpful coping strategies. Anxiety becomes pathological when it can no longer be controlled or occurs without real threat<sup>1-5</sup>. Anxiety affects both men and women, adults and children, and is cut across all races. Differences exist between fear and anxiety; fear is a normal reaction to danger, with no significant brain changes; it goes away when the threat is removed.

In contrast, anxiety occurs due to imaginary danger. It is a pathological response to danger; it causes brain changes and may remain even after the threat is removed<sup>1-5</sup>. Cognitive symptoms of anxiety refer to memory and thought due to a horrible experience, natural disaster, accident, or death. Physical symptoms of anxiety include the autonomic nervous system like headache, sweating, dry mouth, palpitation, chest pain, fast breathing, and heart throbbing. Others include a rise in blood pressure, muscle strain, and extremities' prickling<sup>1-2,4,6</sup>. Motor symptoms are restlessness, irritability, toe-tapping, twitching, and exaggerated startle response. Delayed symptoms emanate when anxiety is prolonged. They include severe stomach upset, muscle weakness, a sharp rise in blood pressure, stroke, heart attack, and even death<sup>1-2,4,6-7</sup>.

In general, the lifetime prevalence of AD is about 14%, with an annual prevalence of about 31%<sup>2,3,8</sup>.

The AD is less prevalent in Africa (3.5–8.1%) than in European countries (7.0–15.5%)<sup>9</sup>. Furthermore, the prevalence of AD is higher in females (23%) than males (14%), which poses a challenge to the family quality of life<sup>1,3,7,10</sup>. Anxiety disorders are the 6<sup>th</sup> most significant cause of disability globally. Unfortunately, four out five of patients with mental disorders in the developing nations are not covered by mental health programs, and about 50% of patients from advanced countries could not afford treatment<sup>11,12</sup>. Moreover, the report indicated that only 20% visit the doctor or seek medical assistance<sup>3,13</sup>. Notably, the numbers of mental health specialists are grossly inadequate, with 1 psychiatrist per 200,000 people or more globally<sup>11</sup>. Besides, AD caused severe insomnia, which causes daylight sleepiness and affects work performance<sup>14-16</sup>. It also causes loss of pleasure and family care, significant disability, and cognitive impairment<sup>17-19</sup>. Moreover, AD increases patients' utilization of primary healthcare facilities worldwide<sup>3,20,21</sup>. Untreated anxiety may precipitate comorbid diseases such as asthma, depression, increased heart attack risk, and substance abuse<sup>3,22</sup>. Reports showed that AD was responsible for 70% of attempted suicide worldwide<sup>23,24</sup>. In the USA, the annual cost of anxiety disorders was estimated at \$47.8 billion in 2001<sup>25-26</sup>. Afterward, the cost estimates later dropped to \$33.7 in 2013<sup>27</sup>. In Europe, the annual cost of anxiety disorders was estimated at £74.4 billion by 2010<sup>9</sup>.<sup>28</sup> These include the cost of morbidity, mortality, hospital stay, loss at the workplace, patients' social welfare, and drug treatment costs<sup>25-27</sup>. This review

aimed to appraise the literature on the prevalence, classification, neuro-pathogenesis, diagnoses, and treatment of anxiety disorders.

## 2. Materials and Methods

The search was made using PubMed, Embase, MEDLINE, and PsycINFO databases. Several articles written in the English language were retrieved and appraised. Papers including guidelines that discussed the prevalence, classification, neuro-pathogenesis, diagnoses, and treatment of AD were reviewed. Also, publications that reported the use of orthodox in the treatment of AD were included. However, articles that used in-vitro and in-vivo animal studies were excluded.

## 3. Findings

### 3.1. Prevalence of Anxiety Disorder

It is depicted in Table 1.

**Table 1:** Prevalence of Anxiety Disorder.

S/N	Disorder	Age of Onset	Prevalence		Reference
			One Year	Lifetime	
1	General Prevalence in Adult	30 years	31%	18%	Katzman et al., 2014 <sup>4</sup>
			18%, USA	14.3%	Kogan et al., 2016 <sup>29</sup>
				16%, UK	Shiri et al., 2012 <sup>30</sup>
				12%, Canada	Bandelow et al., 2017 <sup>31</sup>
				21%, New Zealand	Baldwin et al., 2014 <sup>32</sup>
	In Men	9%		Shiri et al., 2012 <sup>30</sup>	
	In Women	16%		Shiri et al., 2012 <sup>30</sup>	
	In Children	24.9%,	9-32%	Cresswell et al., 2014 <sup>33</sup>	
2	Generalized Anxiety Disorder	30 years	4%	29-31%	Kehoe et al., 2017; Maina et al., 2016 <sup>34,35</sup>
3	Panic Attack	24years	6.4-11.2%	4.7- 6.1%	Bandelow et al., 2017 <sup>31</sup>
4	Agoraphobia	20 Years	1.7	2.7%	Bandelow et al., 2017 <sup>31</sup>
5	Specific Phobia	7 Years	10-13%	6-8%	Bandelow et al., 2017 <sup>31</sup>
6	Social Anxiety Disorder	13 Years	8	13-16%	Bandelow and Michaelis, 2015 <sup>3</sup>
7	Separation Anxiety Disorder	7 Years			Kessler et al., 2005 <sup>36</sup>
8	Obsessive-Compulsive Disorder	20 years	1.2%	2.3-3%	Kessler et al., 2005 <sup>36</sup>
9	Posttraumatic Stress Disorder	24-50years	1-3%	6-15% in the USA	Shiri et al., 2012 <sup>30</sup>
10	Medication Anxiety Disorder			30%	Hollingworth et al., 2010 <sup>37</sup>

### 3.2. Types of Anxiety

Diagnostic and Statistical Manual for Mental Health Disorder V (DSM-V) Classification is the latest anxiety classification with some modifications [Figure 1] <sup>2,5,38</sup>.

#### 3.2.1. Generalized Anxiety Disorder (GAD)

Generalized anxiety disorder can be described as excessive fear about a different life aspect such as work, family, relationship, or health without a specific cause or real threat. The symptoms last for at least six months with signs such as insomnia, restlessness, muscle tension, excessive worry, and fatigue <sup>1,2,31,34,39-49</sup>. The co-morbidities associated with GAD include pain syndromes, hypertension, gastric irritations, and cardiovascular diseases. Comorbid depression often worsens the patient's condition, causes cognitive impairment and economic consequences. Generally, GAD prevalence is 2-3 times more in women than men <sup>1,2,40,41</sup>.

#### 3.2.2. Panic Attack (PA)

A panic attack is a sudden feeling of intense fear in the absence of triggers, in a crowd, open place, or home alone accompanied by more than four (4) of the following somatic symptoms such as palpitation, shaking, nausea, headache, sweating, and shortness of breath, dizziness, fear of dying, and rapid heart rate which are transient <sup>1-2,31,34,39</sup>. The panic attack may reach a peak within 10 minutes and may last for only 30-45 minutes. It has a rapid onset and shorter duration, causes depression, suicidal ideation, six months' delay of remission <sup>1-2,31,34,39</sup>.

#### 3.2.3. Agoraphobia (AG)

This is described as a fear of being in a place or situation where escape may be intricate, or help might not be available (fear of embarrassment). A situation like joining the long queue, market places, fear of farting, crowd or waiting in



**Figure 1:** Various Types of Anxiety.

bus or train station<sup>2, 4-5, 31, 34</sup>. Agoraphobia may last for more than six months, or longer the fear and avoidance cause clinically considerable cognitive impairment or grief<sup>2, 4-5</sup>.

### 3.2.4. Specific Phobia (SP)

Specific phobia is an unreasonable fear of particular objects or situations such as animals (e.g., spiders, rats, dogs, lion), natural environment (heights, storms, water), situational (boarding plane), and blood<sup>2, 5, 31, 35, 39</sup>. Specific phobia symptoms include dizziness, tachycardia, and shortness of breath and may last for up to 6 months<sup>2, 35, 39</sup>.

### 3.2.5. Social Anxiety Disorder (SAD)

Social anxiety disorder refers to worrying about people's judgment or laughing at one's appearance, dress, or fear of speaking in public or facing interviewers<sup>1, 2, 5, 31, 35, 39, 42</sup>. Social anxiety disorder involves fear of scrutiny or avoiding a dreadful situation. The disease is more prevalent among women than men<sup>1, 2, 39</sup>. Frequent co-morbidity associated with SAD includes avoidant personality disorder, body dysmorphic disorder, attention deficit hyperactivity disorder (ADHD), and schizophrenia<sup>2, 4, 39, 42</sup>.

### 3.2.6. Separation Anxiety Disorder (SD)

Separation anxiety disorder is an intense fear of separating a child from his parents or anybody from his loved ones<sup>2, 5, 31, 43</sup>. Symptoms include nightmares, excessive shyness, and somatic complaints such as restlessness, fatigue, muscle tension, irritability, and insomnia. They may last for up to 4 weeks in children and six months in adults<sup>2, 5, 35</sup>.

### 3.2.7. Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder involves constant obsession, recurrent and persistent thoughts, behavior, and feeling dirty or unwanted events that cause anxiety. A compulsion, repetitive behavior also accompanies it to alleviate the obsession, such as hissing, repeated checking, or washing hands<sup>1, 5, 31, 38, 39</sup>. The OCD is usually accompanied by cognitive and functional impairments, resulting in social distancing and loss at the workplace. Diseases regularly coinciding with OCD include mood disorders, psychotic disorders, and bipolar disorders<sup>1-2, 38, 39</sup>.

### 3.2.8. Posttraumatic Stress Disorder (PTSD)

It is an anxiety disorder characterized by flashbacks of horrible thoughts following terrifying experiences like war, accident, or rape attack<sup>1, 5, 16</sup>. Symptoms include nightmares, irritability, hallucination, flashback, loss of interest, hypervigilance, and illusion<sup>1, 2, 5, 30, 38, 42</sup>. Furthermore, other symptoms of PTSD include chronic pain, sexual dysfunction, insomnia, cognitive impairment, and a high risk of suicide attempts<sup>1, 2, 4, 38, 42</sup>.

### 3.2.9. Selective Mutism (SM)

This refers to the inability of children to speak in public or social gatherings, especially at school. This reduces their confidence and significantly affects their performance in classes<sup>2, 5, 17, 31</sup>.

### 3.2.10. Medication Anxiety Disorder (MAD)

This is caused by the adverse effects of a drug or due to withdrawal syndrome. Symptoms include panic, worry, phobia, and obsession<sup>17, 30</sup>. Drugs that induce anxiety include corticosteroids, estrogens, antihistamines, anticholinergics, anticonvulsants, antibiotics, caffeine, nicotine, thyroid hormone<sup>34, 35</sup>.

### 3.2.11. Medical Condition Anxiety Disorder (MCD)

Disease conditions such as ulcers, asthma, diabetes, hypertension, hyperthyroidism, cancer, and heart disease may cause anxiety as comorbidity. Also, anxiety may remain even after the underline cause has been successfully treated<sup>17, 30, 34, 35</sup>.

## 3.3. Neuro-Pathogenesis of Anxiety

**3.3.1. Biological Changes:** Amygdala in the brain comprises neurons that secrete neurotransmitters, and it is responsible for controlling fear and stress. The amygdala usually expands during anxiety. Besides hippocampus is the central storage and control center

of memory, which shrinks in an anxious condition<sup>1,44</sup>. Anxiety disorder occurs in response to stress, which activates the hypothalamus-pituitary-adrenal axis (HPA) and adrenergic neurons, thus triggering cortisol and noradrenaline release. Besides, corticotrophin-releasing factor (CRF) triggers adrenocorticotrophic hormone discharge (ACTH) from the pituitary gland, which also activates HPA, and causes behavioral and physiological changes in the body. Consequently, these hormones activate the amygdala, hippocampus, and limbic system connected to the brain's prefrontal cortex and cause anxiety<sup>1,7,44</sup>. Propranolol, a non-selective  $\beta_2$ -antagonist, reduces physical symptoms of anxiety by decreasing heart rate, tremors, and voice shaking during a public speech. Besides, Prazosin  $\alpha_1$ -antagonist reduces nightmares in PTSD. Furthermore, Venlafaxine (SNRI) enhances noradrenaline transmission and reduces agony and neuropathic pain in anxious patients<sup>1,7,43,45</sup>. Glutamate is an excitatory neurotransmitter that activates N-Methyl-D-aspartate (NMDA) receptors, affecting learning and memory and cause anxiety. NMDA antagonists such as Memantine and Riluzole were used to treat OCD<sup>7,43,45,46</sup>. Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter, and it is known for induction of sleep, relaxation, and prevention of excitation. Therefore, depletion of GABA in the occipital cortex is implicated in the pathophysiology of anxiety<sup>1,7,30,38,43,44</sup>. Hormones such as serotonin originate from the raphe nucleus; they modulate both adrenergic and dopaminergic pathways and regulate anxiety. A decrease in serotonergic activity causes stress via an unknown mechanism. Consequently, SSRI produces an anxiolytic effect<sup>1,43,45</sup>. Dopamine involvement in anxiety is complicated; its signals originate from the midbrain and substantia nigra and spread to the limbic, cortex, and infundibulum. An increase in dopaminergic signals, as well as blockage of  $D_2$ -dopaminergic receptors, decreases anxiety. As such, Bupropion, a dopaminergic agonist, reduces anxiety in some patients (by increasing dopaminergic signals) but worsens in others (activating  $D_2$ -receptors)<sup>1,7,5,47</sup>.

### 3.3.2. Neuro-Anatomical Changes

An increase in the gray matter (GM) volumes of the right amygdala and dorsomedial prefrontal cortex (PFC) was observed in GAD patients, indicating thought impairment, which was more in females than male patients. In contrast, there was a higher increase in gray matter (GM) volume of the right putamen and posterior cingulate cortex in GAD

patients and expressed more in males than in females<sup>1,44</sup>. In anxiety disorder, while GM volume increases, a decrease in white matter (WM) volumes were observed in the dorsolateral prefrontal cortex, anterior limb of the internal capsule (ALIC), and midbrain, indicating cognitive impairment. Furthermore, there was increased cortical thickness of the right inferior frontal gyrus, left inferior and middle temporal cortex, and the right lateral occipital cortex in an adolescent with GAD<sup>44</sup>.

### 3.3.3. Genetic Factors

Anxiety disorder can be hereditary because it can be transferred from parents to their offspring. Children may inherit poor cognition from parents, which could lead to difficulty in comprehension and, eventually, anxiety<sup>1,5,38,45,48</sup>. The meta-analysis revealed that studies involving twins reported that 32% of GAD is linked to heritability, but a higher estimate (49%) was recently reported<sup>44,49</sup>. A single-nucleotide polymorphism in the serotonin receptor 1A (5-HTR1A) and serotonin neurotransmitter transporter is linked to a panic attack<sup>43,44,49</sup>. Studies indicated that variation in genes for monoamine oxidase A (MAOA) has also been implicated in GAD's pathophysiology. Additionally, a rise in serum level of brain-derived neurotrophic factor (BDNF) and polymorphism of Met allele of the functional BDNF (Val66Met) is linked to an increased possibility of developing GAD<sup>43-44</sup>. In elderly patients who are amyloid- $\beta$  ( $A\beta$ )-positive, the presence of the *APOE*  $\epsilon 4$  allele amplified the intensity of anxiety disorders<sup>49</sup>. During SSRIs medication, potential markers predicting treatment prognosis include genes such as serotonin 2A receptor gene (HTR2A), serotonin transporter (5-HTT), dopamine receptor D3 (DRD3), and corticotropin-releasing hormone receptor 1 (CRHR1). However, genetic polymorphisms in dopamine receptor D2 (DRD2) or dopamine active transporter 1 (DAT1) genes could not predict the therapeutic response during treatment with SNRIs venlafaxine<sup>1,44</sup>.

### 3.3.4. Biochemical and Hematological Changes

Several studies linked the association between oxidative stress and anxiety disorder. Oxidative stress occurs due to high lipid hydroperoxide levels, a significant by-product of lipid metabolism<sup>7,44</sup>. There was a substantial increase in very-low-density lipoprotein (VLDL) and cholesterol in GAD patients but decreased in high-density lipoprotein (HDL) level. Besides, decreases in the level of lipid

peroxidation marker malondialdehyde and increased antioxidant glutathione concentration were seen in anxiety disorder <sup>7</sup>. Metabolic magnetic resonance imaging (MRI) in GAD patients revealed a higher *N*-acetyl aspartate/creatine (NAA/Cr) ratio in the right dorsolateral PFC in the untreated patient. Nevertheless, a lesser NAA/Cr ratio was identified in bilateral hippocampal of GAD patients treated with paroxetine. Furthermore, a high level of white blood cells (WBC) and decreased concentration of red blood cells (RBC) and mean corpuscular hemoglobin (MCH) was reported among anxious patients <sup>1, 7, 44</sup>.

**3.3.5. Environmental Factors**

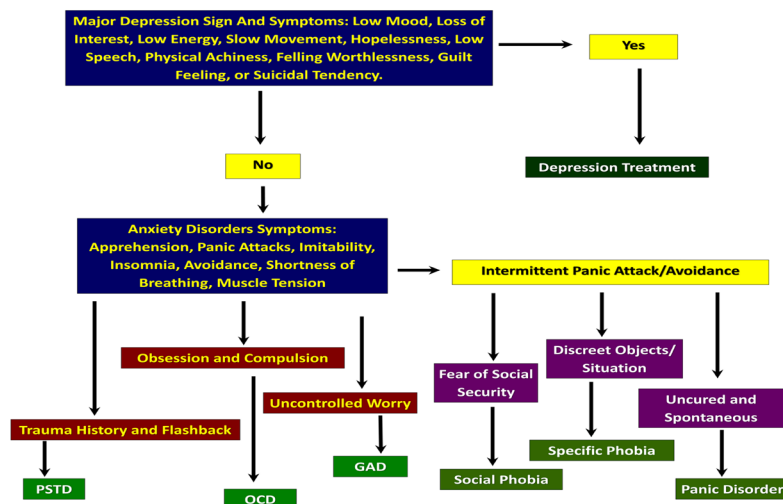
The hostility of the environment, especially during childhood, may result in anxiety. This includes maltreatment during childhood, the crowd’s presence, and stress and peer groups <sup>1, 38, 43, 45</sup>. Previous incidences of child physical and sexual abuses also contribute to anxiety development <sup>1, 50</sup>. The type of food and nutrients taken may play a key role; animals fed with a high-fat diet develop anxiety disorder <sup>7</sup>. The microbiota in the gut-brain axis (GBA) was identified as one of the causes of anxiety. Disruption of the enteric microbiota leads to the displacement of these organisms across the length of the intestinal tract and the production of toxic metabolites. Accordingly, the process triggers the release of pro-inflammatory cytokines, activation of the vagal nerve, and the HPA-axis, which precipitates anxiety <sup>7, 49</sup>.

**3.4. Diagnoses of Anxiety**

**3.4.1. Diagnosis of Various Types of Anxiety Disorders**

Diagnostic and Statistical Manual for Anxiety

Disorder V (DSM-V) is a new diagnostic criterion that classified all forms of anxiety into a group of anxiety disorders. Still, OCD and PTSD are classified into OCD and PTSD-related disorders. Besides, during this classification, selective mutism and medical condition anxiety disorder were included in the leading group <sup>2, 4, 5, 31</sup>. The GAD is diagnosed based on three indices, six-month prolonged symptoms, excessive worry, and three out of the following somatic symptoms: restlessness, fatigue, muscle tension, irritability, and insomnia. The extent of fear should also result in clinically significant cognitive impairment <sup>2, 4, 5, 39</sup>. A panic attack can be diagnosed based on the occurrence of many unpredictable, persistent panic attacks. This is accompanied by a constant worry about the subsequent episodes and or considerable behavioral modification for more than one month <sup>4, 5</sup>. The patient is considered to have agoraphobia when fear of presence in public places persists for more than six months. The avoidance of such a situation resulted in clinically considerable cognitive impairment or grief <sup>2, 4, 5</sup>. To diagnose specific phobia with the level of precision, one must distinguish it from panic disorder. This can be achieved by focusing on fear and avoidance of the feared conditions. The fear of height or boarding a plane is the specific phobia, while fear of crashing or dying while in-plane is the panic attack. Furthermore, specific phobia should be accompanied by persistent avoidance, marked distress, or cognitive impairment, and it should last for more than six months <sup>2, 5, 39, 51</sup>. Social anxiety disorder can also be established once the fear or avoidance is out of proportion to the actual threat posed by a social situation. The fear should cause significant distress or functional impairment and persists for more than six months <sup>2, 5, 39, 42</sup>. To identify



**Figure 2:** Algorithm Used for Assessment of Anxiety Disorder <sup>6, 32, 52</sup>.

OCD, both obsession and compulsion must coexist at the same time and should last for one hour daily. The disorder should have caused significant cognitive impairment<sup>2, 5, 39</sup>. The PTSD is diagnosed based on the history of trauma such as an accident or sexual abuse for more than six months before the signs of anxiety. The flashback or thought disturbance should last for more than three months, and it should cause significant distress and cognitive malfunction<sup>2, 5, 42</sup>.

### 3.4.2. Algorithm Used for Assessment of Anxiety Disorders

## 3.5. Treatment of Anxiety

### 3.5.1. Pharmacological Treatment

Selection of a particular class of drug or combination suitable for the treatment of anxiety is primarily based on the nature of the patient’s courage to participate in the treatment and behavioral modification, the intensity of patient’s anxiety, physicians’ expertise, and that of the behavioral therapist. Others include the nature of the patient response to the treatment and comorbid disease conditions [Figure 3]<sup>4, 53</sup>.

#### 3.5.1.1. Drug Treatment

##### First-Line Drugs

#### (i). Selective Serotonin Reuptake Inhibitors (SSRIs)

**Drugs:** Paroxetine, Fluoxetine, Fluvoxamine, Sertraline, Citalopram, Escitalopram<sup>1, 54, 55</sup>.

**Mechanism of Action:** These drugs inhibit the reuptake of serotonin (5HT) by presynaptic neurons, hence increase the serotonin quantity in the synapse<sup>1, 54-55</sup>.

**Indications:** Panic disorder, agoraphobia, OCD, SAD, and GAD<sup>1, 54, 55</sup>.

**Efficacy:** This class of drugs may be helpful within 2-4 weeks, but in some instances extended to 6-8 weeks before their action is seen<sup>1, 38, 45, 54, 55</sup>. In a situation where SSRIs are not sufficient, the patient should switch to clomipramine; augmentation can be done with low-dose antipsychotics (aripiprazole, risperidone) low dose anticonvulsants (pregabalin, lamotrigine)<sup>54-56</sup>.

**Adverse Effects:** Nausea, headache, gastrointestinal complaints, insomnia, restlessness, dizziness, fatigue, suicidal ideation, and serotonin syndrome. Long-term usage may cause weight gain and sexual dysfunction. Lowering the dose may reduce side effects and improve compliance<sup>54-56</sup>. **Contraindication:** Should not be used in children because of the high risk of suicide tendency, bipolar disorder, hemophilia,

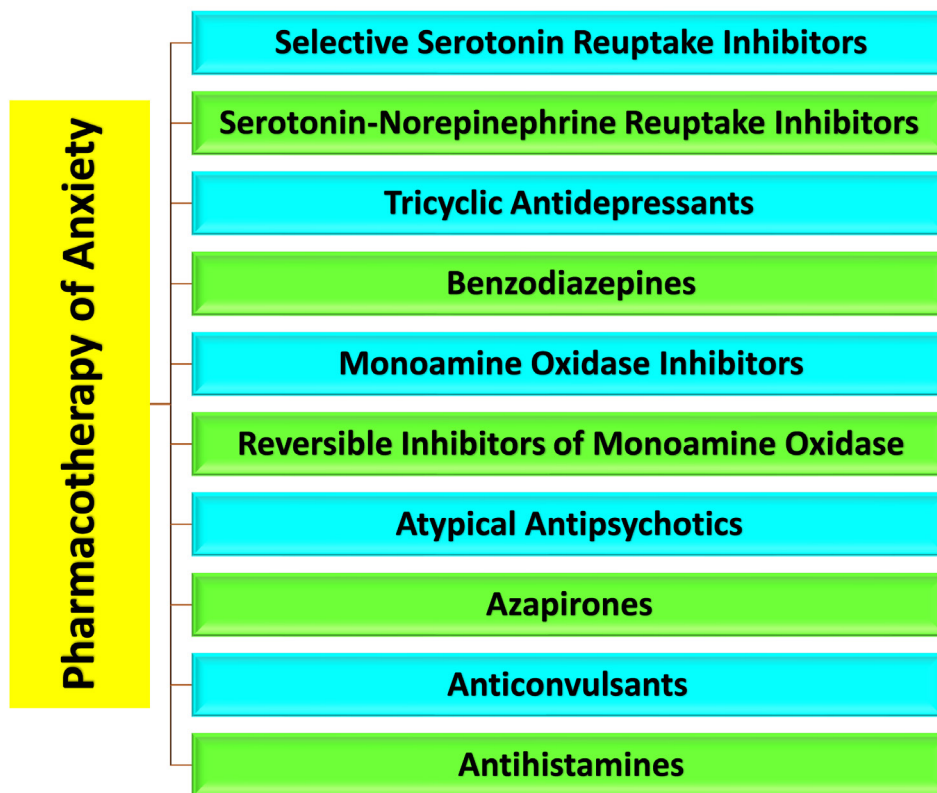


Figure 3: Several Drugs for The Treatment of Anxiety.

diabetes, epilepsy, and glaucoma<sup>54-56</sup>. During pregnancy and breastfeeding, the benefit must outweigh the risk. Also, SSRIs are not recommended in the first trimester, and paroxetine should not be taken at all. However, paroxetine or sertraline may be useful during breastfeeding. Also, SSRIs cannot be taken simultaneously with SNRIs or MAOIs to prevent serotonin syndrome<sup>54-56</sup>.

#### (ii). Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs)

**Drugs:** Venlafaxine, Duloxetine, Milnacipran<sup>1, 57, 58</sup>. **Mechanism of Action:** They act by inhibiting the reuptake of serotonin and norepinephrine by the presynaptic neuron, increasing their concentration at the synapse<sup>57, 58</sup>. **Efficacy:** Anxiolytic effect of this class of drugs may be seen within 2-4 weeks in panic disorder<sup>57-59</sup>. **Adverse Effects:** Gastrointestinal problems, dry mouth, tremor, insomnia, sexual dysfunction, upper hyponatremia, low bone mineral density, weight gain, drowsiness, and fatigue<sup>57-59</sup>. **Contraindication:** Not used in patients with high blood pressure, liver disease, or drinking alcohol. Before use in pregnancy and breastfeeding, the benefit must outweigh the risk. Also, SNRIs are not to be taken simultaneously with SSRIs or MAOIs to prevent serotonin syndrome<sup>57-59</sup>.

#### Second-Line Drugs

#### (iii). Tricyclic Antidepressants (TCAs)

**Drugs:** Clomipramine, Imipramine, Amitriptyline<sup>30, 31, 45, 60, 61</sup>. **Mechanism of Action:** They act by inhibiting both transporters for serotonin and norepinephrine, thereby preventing their reuptake and consequently increased their concentration at the synapse, and increase neurotransmission<sup>60, 61</sup>. **Efficacy:** Tricyclic antidepressants are effective in panic disorder and agoraphobia. Clomipramine is a drug of choice where SSRIs or SNRIs failed during the treatment of OCD<sup>45, 54, 60, 61</sup>. **Adverse Effects:** Blurred vision, urinary retention, restlessness, dizziness, sweating, weakness, hypotension, tachycardia, hallucinations, dry mouth, constipation, and weight gain<sup>60, 61</sup>. **Contraindication:** Glaucoma, enlarged prostate, heart problems, diabetes, liver disease, epilepsy. In pregnancy and breastfeeding, the risk-benefit ratio should be assessed. However, drugs like imipramine or amitriptyline can be administered with minimal toxicity than other antidepressants<sup>60, 61</sup>.

#### (iv). Benzodiazepines (BDZ)

**Drugs:** Diazepam, Bromazepam, Lorazepam, Clonazepam, Alprazolam<sup>1, 4, 38, 62</sup>. **Mechanism of Action:** They act by binding to and activating GABA<sub>A</sub>-receptor leading to the binding of GABA to its receptor, the opening of the chloride ion channel, chloride ion entry causing cellular inhibition<sup>4, 62</sup>. **Efficacy:** They have a much shorter onset than all other classes of anti-anxiety hence their effect can be seen within 1-2 minutes of administration<sup>4, 31, 38</sup>. **Adverse Effects:** Weakness, fatigue, dizziness, sedation, slurred speech, memory impairment, ataxia, dependence, and tolerance<sup>62-63</sup>. **Contraindication:** Benzodiazepines should not be taken together with alcohol and other psychoactive substances and should not be used for long-duration<sup>62-63</sup>. During breastfeeding, the drugs may be discontinued when high doses are involved. Also, the benefit of using BDZ must outweigh the risk. Pregnant women should be given the lowest dose for a short time, and diazepam or chlordiazepoxide are safer than triazolam and temazepam<sup>62-63</sup>.

#### Third-Line Drugs

#### (v). Monoamine Oxidase Inhibitors (MAOIs)

**Drugs:** Phenelzine, Tranylcypromine<sup>4, 38</sup>. **Efficacy:** Effective in treating panic disorder, social anxiety disorders<sup>4, 38</sup>. **Adverse Effects:** Dry mouth, nausea, diarrhea, constipation, headache, drowsiness, insomnia, dizziness, low blood pressure, weight gain, and muscle cramps<sup>4, 38</sup>. **Contraindication:** Risk-benefit should be assessed during pregnancy. Other side effects include renal disease, seizure disorder, cardiovascular disease, hyperthyroidism, hypertension, diabetes<sup>4, 38</sup>.

#### (vi). Reversible Inhibitors of Monoamine Oxidase (RIMA)

**Drugs:** Moclobemide<sup>31, 64</sup>. **Efficacy:** Moclobemide is helpful in treating social anxiety disorder<sup>31, 64</sup>. **Adverse Effects:** Dizziness, nervousness, insomnia, nausea, sweating, loss of appetite, dry mouth, blurred vision, stomach pain, chest pain, severe headache, stiff neck, confusion, fever, skin rash<sup>31, 64</sup>. **Contraindications:** Liver disease, thyroid disease, high blood pressure, allergies, alcohol drinking, pregnancy, breastfeeding<sup>31, 64</sup>.

#### (vii). Atypical Antipsychotics (Second-generation antipsychotic)

**Drugs:** Quetiapine, Olanzapine, Risperidone, Aripiprazole<sup>38, 65</sup>. **Efficacy:** Quetiapine is helpful in



treating GAD at the dose of 50 to 300mg/day, panic disorder, and OCD, while risperidone is given at a dose of 0.5-2mg/day<sup>38,65</sup>. **Adverse Effects:** Sedation, orthostatic hypotension, tardive dyskinesia, arrhythmias, extrapyramidal adverse effects. Others include weight gain, diabetes, and other metabolic adverse effects, including alterations in glucose and lipid levels<sup>65-66</sup>. **Contraindications:** Pregnancy and breastfeeding, stroke, dementia.<sup>65-66</sup>

#### (viii). Azapirones

**Drugs:** Buspirone<sup>4, 67</sup>. **Mechanism of Action:** The buspirone work activates the 5-HT<sub>1A</sub>-serotonergic receptor or blocks the D<sub>2</sub>-dopaminergic receptor<sup>1, 4</sup>. **Efficacy:** It is a 5HT<sub>1A</sub> agonist effective in treating GAD<sup>31, 45</sup>. **Indication:** It is also employed in the treatment of PTSD and PD. However, it is not effective in treating OCD (Sheehan et al., 1990; Antony and Swinson, 1996)<sup>[67-68]</sup>. **Adverse Effects:** Tremors, muscle stiffness, tardive dyskinesia, shortness of breath, chest pain, rash, itching, severe dizziness, trouble breathing<sup>38, 67, 68</sup>. **Contraindication:** Pregnancy, breastfeeding, bipolar disorder, parkinsonism, liver, and kidney problems<sup>38, 67, 68</sup>.

#### (ix). Anticonvulsants

**Drugs:** Pregabalin, Gabapentin, Topiramate, Lamotrigine, Divalproex, Levetiracetam<sup>4, 69</sup>. **Efficacy:** OCD, panic disorder, Patients taking these drugs may be relieved of anxiety symptoms within 24hours<sup>4, 69</sup>. **Adverse Effects:** Include dizziness, sedation, hallucination, somnolence<sup>4, 69</sup>.

#### (x). Antihistamines

**Drugs:** Diphenhydramine, Dimenhydrinate, Hydroxyzine<sup>38, 45, 70</sup>. **Efficacy:** Treatment of GAD<sup>38, 70</sup>. **Adverse Effects:** Sedation, confusion, blurred vision, delirium, and other anticholinergic adverse effects<sup>38, 70</sup>. **Contraindication:** Hyperthyroidism, glaucoma, peptic ulcer, enlarged prostate, and idiopathic constipation. The risk-benefit ratio should be weighed during pregnancy. However, diphenhydramine or chlorpheniramine can be used with minimal risk to the fetus<sup>38, 70</sup>.

### 3.5.1.2. Specific Treatment

#### (i). Generalized Anxiety Disorder

First-line drugs include are SSRIs, SNRIs, or anticonvulsants (e.g., Pregabalin). Second-line treatments include BDZ, TCAD, buspirone, hydroxyzine, or quetiapine. Third-line drugs include paroxetine, citalopram, or divalproex<sup>4, 38</sup>. Drugs such as propranolol, tiagabine, memantine, and

pexacerfont should not use in the treatment of GAD as various studies revealed the absence of efficacy. Notably, 60-80% of patients treated for a short period experienced relapse, and about 30% of GAD patients do not respond to treatment with BDZ<sup>4, 38</sup>. Ideally, GAD patients should be treated with SSRIs or SNRIs for 6-12 months, effectively preventing relapse. CBT should accompany drug treatment, and several reports have established its effectiveness. Peer-to-peer cognitive self-therapy is another helpful CBT<sup>30, 38, 39</sup>.

#### (ii). Panic Disorder and Agoraphobia

Treatment can be initiated using cognitive behavioral therapy alone or combined with pharmacotherapy. First-line drugs are short-acting BDZ, SSRIs, Azapirone, or venlafaxine. Long-term therapies involve the use of SSRIs, SNRIs, or TCAD. If used alone, drug treatment should be followed by CBT and exercise<sup>1, 38, 39</sup>. Unfortunately, 30-90% of patients with panic disorder may experience relapse, as such treatment may be prolonged to 8-12 months to prevent relapse<sup>1, 30</sup>.

#### (iii). Social Anxiety Disorder

First-line drugs are SSRIs, SNRIs (venlafaxine), or anticonvulsant (pregabalin). Once there is no response, a second-line such as irreversible MAOI (phenelzine), benzodiazepines (clonazepam), or anticonvulsants (Gabapentin) should be used. Third-line agents include antidepressants such as fluoxetine, olanzapine, and selegiline. Drug treatment should be accompanied by CBT<sup>4, 38, 39</sup>.

#### (iv). Specific Phobia

Exposure to the causative object or situation may be used as treatment. In severe cases, SSRIs are used in the treatment of specific phobia. Other drug treatments employed include d-cycloserine, a partial NMDA receptor agonist, which alleviates fear in patients undergoing exposure behavioral therapy<sup>38, 51</sup>. Besides, BDZ is used as an adjunct to exposure therapy; however, other studies showed that the addition of BDZ has no additional benefit<sup>39, 71</sup>

#### (v). Obsessive-Compulsive Disorders

First-line drugs are SSRIs or TCADs. The second-line drugs include clomipramine, citalopram, or venlafaxine. Third-line agents include duloxetine, phenelzine, tranylcypromine, and tramadol<sup>1, 38</sup>. Drug treatment should be accompanied by non-pharmacological treatment (CBT). The CBT session is two hours daily, twice a week or five days over

three weeks. Treatment may be prolonged for up to about 10 to 12 weeks to ensure maximum efficacy and prevent relapse<sup>1, 38, 39</sup>.

#### (vi). Posttraumatic Stress Disorders

Treatment is done using CBT, but SSRIs and venlafaxine are used as first-line treatment in more severe cases. Treatment of PTSD should extend to a period of 12-24 months. Second-line drugs include phenelzine, fluvoxamine, or mirtazapine. Third line agents are imipramine, amitriptyline, risperidone, or quetiapine<sup>4, 38</sup>. Notably, once there is a presence of early signs of PTSD, regular CBT could serve as a preventive treatment. Psychological management of PTSD includes educating the patient on his disease conditions and treatment modalities. Others include dialect behavioral therapy, online treatment session, regular exercise, and healthy meals. Long-term treatment is usually recommended especially following the fatal accident, for 6 to 18 months<sup>5, 38</sup>.

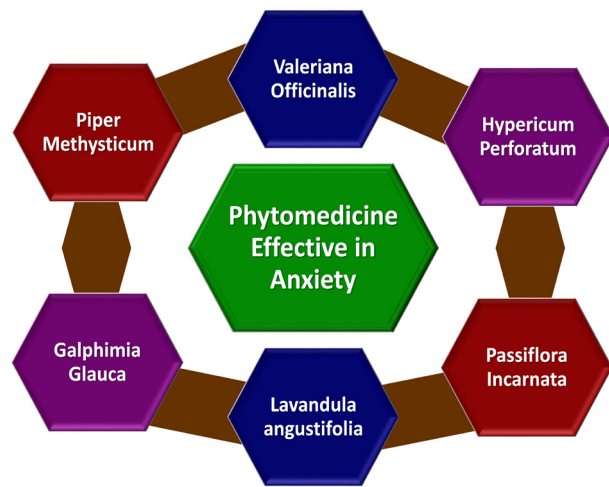
#### 3.5.1.3. Special Conditions

##### (i). Pregnancy

During pregnancy, the risk-benefit should be assessed first, and the drug should only be administered when the benefit outweighed the risk. During pregnancy, typical AD includes OCD and GAD, which may decrease women's conception, premature birth, or prompted delivery via cesarean section<sup>72</sup>. Anxiety may precipitate vitamin deficiency, anemia, and the possibility of drug addiction. Drugs such as SSRIs and BDZ are helpful and have not yet shown significant adverse effects during pregnancy; however, limited data is generally available<sup>38, 73</sup>. Paroxetine and Alprazolam and TCAs should be avoided in pregnancy because of the high risk of cardiac adverse effects<sup>74</sup>. Furthermore, atypical antipsychotic agents are not a drug of choice during pregnancy because of the report of low birth weight and increased risk of metabolic syndrome<sup>75</sup>.

##### (ii). Breast Feeding

The risk-benefit should be assessed first when prescribing drugs to breastfeeding women with AD. During the short-term treatment with BDZ, sedation, lethargy, and poor sucking in an infant should be monitored. In general, BDZ has no serious risk during breastfeeding; nevertheless, the drugs may be discontinued when high doses are involved<sup>76</sup>. Paroxetine and Sertraline do not affect babies; SSRIs and TCAs are excreted via breast milk but do not affect infants<sup>38, 77</sup>.



**Figure 4:** Herbal Therapeutic Options for Treatment of Anxiety.

##### (iii). Children and Adolescents

In general, the lifetime and annual prevalence of anxiety in children and adolescents is 24.9% and 31.9%, respectively<sup>78, 79</sup>. The prevalence of GAD for children and adolescent are (2.2% and 1.1%), PD (2.3% and 1.9%), SP (19.3% and 15.8%), social anxiety disorder (9.1% and 8.2%), separation anxiety disorder (7.6% and 1.6%), OCD (0.25% and 1%), and PTSD (5.0% and 3.9%) respectively<sup>4, 36, 79</sup>. Common signs of AD in children include nightmares, crying, stomach upset, headaches, throwing tantrums, and freezing. The diagnosis of AD in children includes anxiety symptoms lasting for at least four weeks, and the onset occurs before 18 years. The disturbance should also cause clinically significant distress or functional impairment<sup>4, 5, 79</sup>. First-line treatment includes SSRIs such as fluvoxamine, fluoxetine, or citalopram, which are effective, but the risk of suicidal ideation should be monitored in children<sup>4, 38, 80</sup>.

##### (iv). Treatment of Elderly Cohort

Management of anxiety in gerontology should be closely monitored to increase anticholinergic adverse effects. Drugs such as TCAs may cause orthostatic hypotension and ECG changes. Simultaneously, BDZ may lead to paradoxical adverse effects, including depression, aggressiveness, and phobia<sup>38, 81</sup>.

##### (v). Comorbid Diseases

Patients suffering from chronic diseases such as hypertension, diabetes, myocardial infarction, hyperthyroidism, or brain injury may also have anxiety as a comorbid disease. Consequently, Venlafaxine increases blood pressure, escitalopram causes QTC prolongation and platelet aggregation,

these agents should be avoided, and TCAs should not be used in cardiac diseases<sup>38,81</sup>.

#### 3.5.1.4. Medicinal Plants Used in the Treatment of Anxiety [Figure 4]

**(i). Valeriana Officinalis (Valerian Extract):** This plant was used earlier but could not successfully treat anxiety; adverse effects include headache and GIT upsets<sup>31,82</sup>.

**(ii). Lavandula angustifolia (Lavender Oil):** This oil has been tried and effectively treated GAD with comparable activity to lorazepam<sup>31,82</sup>.

**(iii). Hypericum Perforatum (St John's Warts):** The extract of this plant was used earlier in treating anxiety but was ineffective; adverse effects include weight gain, impotence, and suicide<sup>31,82</sup>.

**(iv). Passiflora Incarnata (Passionflower):** It uses in the treatment of anxiety with comparable efficacy to BDZ; adverse effects include dizziness, sedation, and increase blood pressure<sup>[82,83]</sup>.

**(v). Galphimia Glauca (Extract):** This extract is another phytomedicine useful in treating GAD, which is found to be as effective as lorazepam in a randomized controlled clinical trial<sup>84</sup>.

**(vi). Piper Methysticum (KAVA):** This plant was earlier used to treat anxiety but later withdrawn due to hepatotoxicity sedation<sup>31,82</sup>.

#### 3.5.2. Non-Pharmacological Treatment

**3.5.2.1. Electroconvulsive Therapy:** This involves the insertion of a small electrode under stereotactic MRI monitoring. The introduction of brief electrical impulses will cause neuronal discharge and treat panic, agoraphobia, and mood disorders<sup>45,85</sup>.

**3.5.2.2. Vagal Nerve Stimulation:** This involves stimulation of fear control centers such as the amygdala, hippocampus, insula, frontal cortex via afferent vagal nerves to cause the release of inhibitory neurotransmitter in the treatment of panic disorder agoraphobia<sup>45,85</sup>.

**3.5.2.3. Surgery:** This applies to resistant GAD and social phobia. They include anterior capsulotomy, sub caudate tractotomy, limbic leucotomy, and anterior cingulotomy<sup>45</sup>

**3.5.2.4. Cognitive Behavioral Therapy (CBT):** In general, CBT is a very significant component of anxiety treatment; it is more important than drug treatment in panic disorder<sup>2,6,39</sup>. The CBT component employed in panic disorder management includes exposure to the situation causing panic, modification

of negative thoughts, psycho-education, and coping skills<sup>2,6,39</sup>.

#### (1). Duration of CBT Treatment

CBT is done for up to 12 to 16 weeks, once every week for few hours; however, a one-hour session daily was more effective<sup>2,5,86</sup>.

#### (2). Modes of CBT

**(i). Interpersonal Therapy (IPT):** This involves recording and documenting individual fears and worries and treats them accordingly<sup>5</sup>.

**(ii). Dialectical Behavioral Therapy (DBT):** This is a kind of group therapy with contributions from the patient, relative, and psychotherapist to solve disturbing thoughts, limit talking, and tolerate distress (APA, 2013)<sup>[5]</sup>.

**(iii). Coping Cat (CC):** This involves teaching the patient coping skills, solving problems, modifying negative thoughts, exposure to the feared stimuli, and psycho-education by psychotherapists<sup>39,87</sup>.

**(iv). e-Therapist (ET):** Treatment of anxiety is offered through the internet, or video conferencing via several platforms such as Brave for Teenagers-Online, Brave for Children-online, Cool Teens, Camp-A-Lot, and Think to Feel Do<sup>2,39,88</sup>.

**(v). Biblio-Therapy:** This is a method of children and adolescents' anxiety management by their parent under clinician guide and instructions with a frequent reminder via phone call or giving them self-help books to read<sup>33,89</sup>.

**(vi). Face-To-Face CBT:** In this regard, patients suffering from anxiety meet with the psychotherapist or any trained medical staff to address their problems individually<sup>31,33,89</sup>.

#### Discussion

Anxiety disorder has significantly contributed to increased social problems such as rape, violence against women, divorce, and suicide, especially among the elderly. Anxiety disorders comprise a wide range of complex groups of mental disorders that require expert diagnosis, monitoring, and individualization of the treatment. The disease is caused by various biological changes, neuro-anatomical changes, genetic factors, biochemical and hematological changes, and environmental factors. Diagnostic and Statistical Manual for Anxiety Disorder V (DSM-V) is a new diagnostic criterion that classified all forms of anxiety into a group of anxiety disorders. Still, OCD and PTSD are classified into OCD PTSD-related

disorders. First-line drugs used for AD treatment include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, and tricyclic antidepressants benzodiazepines; and third-line drugs include monoamine oxidase inhibitors, reversible inhibitors of monoamine oxidase, atypical antipsychotics, azapirones, anticonvulsants, and antihistamines. Non-pharmacological treatments include electroconvulsive therapy, vagal nerve stimulation, surgery, and cognitive behavioral therapy. Anxiety disorder treatment requires a long duration and a combination of drugs and behavioral therapy combined with the most effective treatment. It is imperative to continue with behavioral therapy after discontinuation of drugs to prevent relapse. The behavioral therapy may last longer for two to three years. Anxiolytic drugs tend to cause CNS adverse effects, including dependence and possible tolerance, searching for safer alternative drug treatment.

### Conclusion

Anxiety is the most important among mental disorders affecting men and women, children, and adults and is cut across all races and social classes. The disorder is complex hence poorly understood and misdiagnosed. The misconception and stigmatization

attached to mental disorders by the larger society compelled the patients to avoid visiting a psychiatric clinic, affecting treatment prognosis. It is a chronic disease that requires regular medication and patient monitoring because of numerous adverse effects of the medicines, including drug addiction and increased risk of suicide. Besides, it requires behavioral therapy, lifestyle modification, and improved welfare. Anxiety disorder is a mental disorder with various neuronal involvements. Henceforth, understanding AD's neuro-pathogenesis, the standard guideline for pharmacotherapy and cognitive behavioral therapy, is critical among physicians and psychotherapists.

### Recommendations

Awareness seminars among medical professionals and public enlightenment on anxiety disorder will bring patients closer to clinicians and improve diagnosis and treatment prognosis. Policymakers should increase mental health program coverage, especially among developing countries. Anxiety disorder medication should be made free and easily accessible like HIV/AIDS, TB medications, etc. Teaching mental health programs among university medical students should be improved and step down to colleges of education.

### Article Highlights

- Anxiety is a feeling of apprehension or even fear and can have associated symptoms like palpitations, sweating, and stress
- Various types of anxiety disorders are Generalized Anxiety Disorder, Panic attacks, Obsessive-Compulsive Disorder, Post-Traumatic Stress Disorder, Social Anxiety Disorder, Selective Mutism, Agoraphobia, Specific Phobia etc.
- Biological changes in the brain, neuro-anatomical changes, genetic factors, biochemical and hematological changes and environmental factors are responsible for pathogenesis of anxiety
- Commonly used drugs are Selective Serotonin Reuptake Inhibitors, Serotonin-Norepinephrine Reuptake Inhibitors, Tricyclic Antidepressants, Benzodiazepines, Atypical Antipsychotics, Azapirones and Anticonvulsants
- Apart from pharmacotherapy, few phytomedicines and non-pharmacological therapies are also effective in the management of anxiety disorders.

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