

Insights on anxiety and its treatments

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Abstract

According to the WHO, 1 in every 8 people suffer from some mental disorder . It affects a person's thinking , emotional regulation and behavior traits. Anxiety is one of the most commonly prevalent psychiatric disorder. It is the intense feeling of worry, tension or stress that leads to complications like panic attacks. It has gained more importance after the corona pandemic due to its high incidence. As suggested by the WHO, around 264 million people suffer from anxiety, having a 15% hike since the year 2005. Anxiety negatively impacts a person's ability to carry out daily tasks with efficiency.

Key words : Psychiatric disorder, stress, emotional disorder, panic attacks.

Anxiety is defined by the American Psychological Association as –" An emotion characterized by feelings of tension , worried thoughts and physical changes like increased blood pressure". It is also widely responsible for the prevalence of other psychiatric disorders including depression, panic disorder, schizophrenia⁵⁵. It leads to impaired performance in day-to-day life. It can be caused due to multiple factors such as physical ;emotional or sexual abuse , victimization to crime, natural disasters, stress (financial, academic, relationship etc.), emotional trauma, adverse effect of medication.

It is usually characterized by excessive fear, avoiding probable threats and panic attacks. In case of real or perceived threats , adrenaline is released in the body leading to a 'fight-or-flight' response. It is a normal emotion but it often escalated to cause excessive fear and physical symptoms such as sweating, trembling, high blood pressure etc. Anxiety can be further classified into the following – generalized anxiety disorder, social anxiety, panic attacks, and specific phobias. Despite the presence of various treatment options, complete treatment of anxiety is still unachievable. Prescribing

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medications to patients is not preferred over psychological counselling by healthcare professionals³⁸. Since most of the anxiety disorders start during early childhood or adolescence, identification of people at risk and intervention at appropriate time is an essential part of treatment. Many impaired individuals suffering from chronic anxiety and having low income prefer to use government public mental health services⁵⁴. Despite its large prevalence, far less research has been done on anxiety treatment options as compared to other psychiatric disorders such as depression. Study proves that people suffering from anxiety disorders are more likely to self harm or attempt or commit suicides^{7,41}. This anxiety leads to anger or hatred towards self leading to self harm¹⁶.

Categories of anxiety :

The Diagnostic And Statistical Manual Of Mental Disorders (DSM-5), 5th edition classifies anxiety into different clinical types².

Social anxiety disorder (SAD) :

SAD is recognized by intense fear of being judged by others^{9,31}. Children suffering through both SAD and depression have difficulty in performing well at school, home and in public¹¹.

Generalized anxiety disorder (GAD) :

As described by the DSM-5, people suffering through GAD worry out of proportion for everyday occurrences such as bills, academics, work, health etc. GAD and depression are the largest psychiatric disorders

in Australia²⁵.

Specific phobia (SP) :

It is an irrational fear of something that possesses very minimal to no threat. Some people tend to outgrow their fears by adulthood. For e.g. Fear of the dark was outgrown with age¹⁰.

Panic disorder :

A panic attack refers to a situation when a person experiences 4 or more symptoms out of the 13 symptoms for panic attack as specified by DSM-5. Out of the 13 symptoms listed in DSM-5, the most important ones are – increased heart rate, difficulty to breathe, fear of dying, trembling, sweating profusely²³.

Agoraphobia :

People suffering through panic disorder tend to avoid places and situations that led to a previous panic attack. These people become restricted to their home space and this condition is called as agoraphobia (fear of open spaces)¹⁷.

Obsessive compulsive disorder (OCD) :

OCD sufferers have persistent unsettling thoughts and habits/rituals to control the anxiety that these thoughts produce⁵⁰. This ends up in the habits / rituals controlling the person rather than the person controlling them.

Post-traumatic stress disorder (PTSD) :

It develops after an incident of severe threat or actual physical, mental and emotional

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harm. Sufferers show symptoms of being startled easily, becoming emotionally numb, losing interest, being irritable, aggressive and violent⁴⁸.

Social phobia :

In this case , people have a constant and intense fear of being judged or watched by others²⁹. They tend to worry about a particular situation or a conversation weeks before it actually happens or in many cases, does not happen at all.

Separation anxiety :

This disorder affects toddlers and

infants after 3 years of age and is caused by the thought of being separated from the parent/ the primary caregiver. Separation anxiety causes a loss of sense of security³⁵.

Selective mutism :

In this type of anxiety, sufferers are unable to talk in certain situations but able to do so in other situations³³. They speak freely when comfortable and at other times, they feel extremely uncomfortable to talk and have frozen facial expressions and make little to no eye contact.

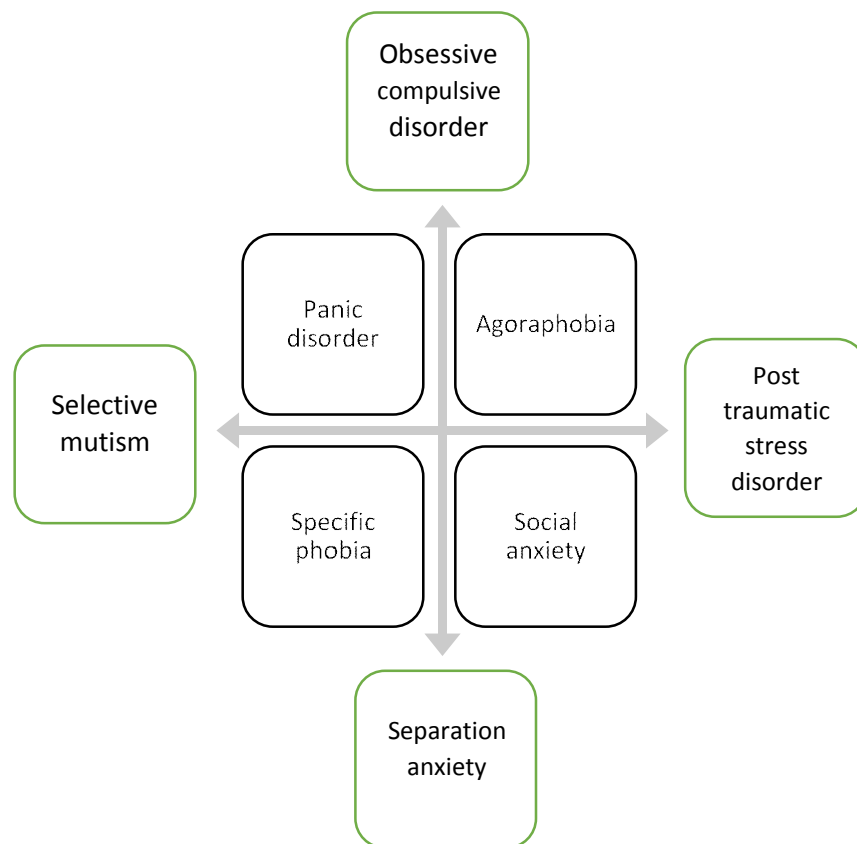


Figure 1. Different types of anxiety disorders

Etiology :

Table-1. Different etiological factors for anxiety disorders

Biological causes	Psychological causes	Social causes
Heredity	Low self esteem	Stress
Illness	Negative emotions	Lack of social skills
Medication	Personality traits	Adverse life experiences
Nutrition	Developmental crisis	Natural disasters
Neurotransmitter imbalance	Intra- and/or interpersonal crisis	Neglect
	Cognitive dissonance	Changing values
		Terrorism

The presence of co-morbidities such as diabetes, depression; having first degree relatives with GAD; environmental factors, child abuse, substance abuse etc. Is also responsible for the development of anxiety disorders. These anxiety disorder may also have genetic cause, although the actual genes have not been identified. A study suggested that women experience wider range of stress in contrast to men who react to limited range of stressful events²⁶. A feeling of loss of

control or helplessness contributes greatly to anxiety. Negative thoughts or emotions also have a similar impact on anxiety.

Pathophysiology :

Dysregulation of neurotransmitters, under activation of serotonergic system and over activation of nor-adrenergic system is mainly responsible for the pathogenesis of anxiety⁴².

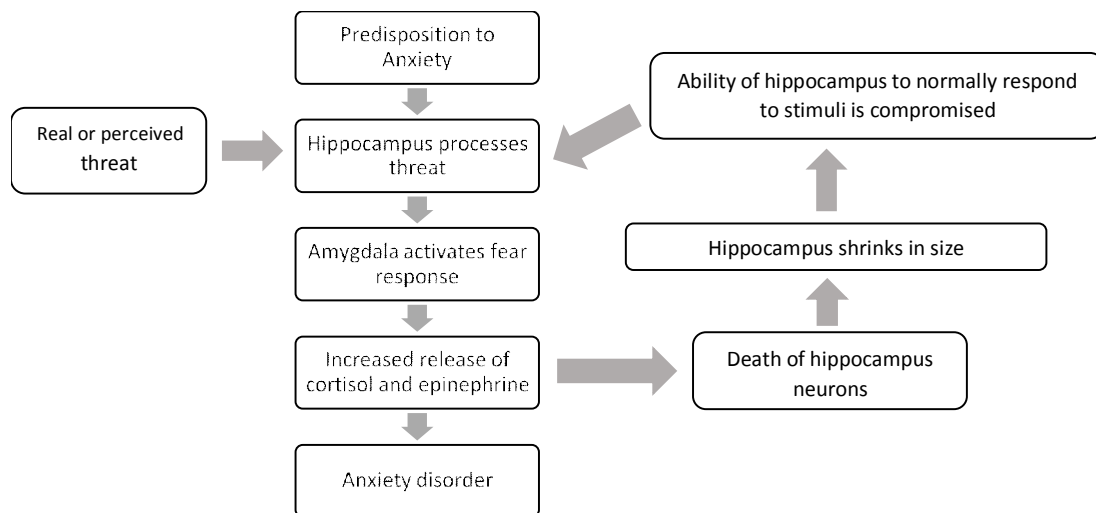


Figure 2. Pathogenesis of anxiety

Symptoms :

These symptoms can be broadly classified into 3 types -⁴⁴

Table-2. Different symptoms of anxiety

Physical	Psychological	Behaviorial
Dizziness	Irritability	OCD
Sweating	Impatience	Phobia
Nausea	Feeling 'on edge'	Avoiding stressful situations
Dry mouth	Excessive worry	Avoiding social situations
Headache	Fatigue	Lack of communication
Flushing	Vivid dreams	Unnecessary rituals / habits
Difficulty to breathe	Mind going blank	
Ache	Mind racing	
Pain	Indecisiveness	
Restlessness	Lack of concentration	
High heart rate	Decreased memory	

Diagnosis :

A medical professional may diagnose anxiety by two methods –

1. Psychological evaluation
2. Using checklist of DSM-5

Psychological evaluation :

The medical professional and the patient discuss regarding the patients thoughts, feelings and emotions. Symptoms and risk factors are identified. This type of evaluation is also useful to determine the existence of other psychological disorders.

Evaluation by referring the checklist of DSM-5⁵³:

The DSM-5 specifies certain criteria to conclude whether the patient suffers through

anxiety. The criteria are as follows –

- A. Excessive stress and anxiety manifested on a daily basis for a minimum of six months.
- B. The individual struggles to restrain anxiety.
- C. Three or more of the following six symptoms (with at least some symptoms present on more days than not for the preceding six months) are linked to anxiety and worry- Feeling tense, agitated, or on edge; Being easily worn out; Inability to focus or mental blankness; Irritability; Tense muscles & Sleep disturbances.
- D. The disturbance is not better explained by another mental illness
- E. Neither another medical condition nor the physiological consequences of a substance can be the cause of the disturbance.
- F. The focus of the worry and anxiety is not limited to characteristics of any other disorder.

Treatment : reuptake inhibitors) and SSRIs (selective serotonin reuptake inhibitors) have been licensed by the FDA for the management of PD, GAD, and SAD.

A. Medications : Many SNRIs (serotonin norepinephrine

Table-3. Various medications used to treat Anxiety

Class of drug	Name of drug	Description
Mixed antidepressants	Mirtazapine ⁵	Works by postsynaptic inhibition of 5-HT ₂ and 5-HT ₃ receptors, antagonism of the α -2 adrenergic receptor & antagonism of histamine-1 (H ₁) receptors.
	Bupropion ⁴⁰	Despite the widespread belief that it increases anxiety, studies prove that it may not be entirely true.
	Benzodiazepines ^{56,3}	Most widely prescribed medications used for anxiety.
Anticonvulsants	Pregabalin ³²	Inhibits the release of neurotransmitters by activation of the α -2 delta calcium channels.
	Gabapentin ¹	Works similarly as pregabalin .Widely used off label for fibromyalgia.
	Tigabine ⁴⁶	Authorized by the FDA to treat partial seizures and preclinical research indicates that it may have anxiolytic effects.
	Lamotrigine ³⁰	Studies demonstrate anxiolytic properties.
Antihistamines	Hydroxyzine	Only antihistamine approved by FDA for anxiety.
Alpha and Beta Adrenergic agents	Propranolol ⁴⁹	Used for high blood pressure, migraine, tremors, angina, arrhythmias and atrial fibrillations.
	Clonidine ⁸ & Guanfacine ⁵¹	α -2 adrenergic receptor agonists used for treating high blood pressure.
Antipsychotics	Trifluoperazine ²⁷	FDA approved first generation of antipsychotic used for anxiety.

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Serotonergic agents	Vilazodone ¹⁵	Listed as an SSRI ,it has been studied in GAD & SAD.
	Vortioxetine ⁵⁸	FDA approved drug for MDD, however it is unclear if it assists with anxiety.
	Gepirone ⁴³	Extended release formulation has anxiolytic effects.
	Tandospirone ³⁶	Useful for patients with anxious depression.
	Ondansetron ⁴⁷	was shown to reduce anxiety in an open-label PD trial in GAD.
Glutamate modulators	Ketamine ³⁹	The FDA has approved intranasal S-ketamine to treat MDD in adults in 2019.
	Riluzole ⁵²	its effectiveness in anxiety was confirmed by animal research.
	Cycloserine ¹²	D-cycloserine is an NMDA partial agonist. It is not known to be effective as monotherapy.
	Memantine ⁴⁵	An NMDA receptor antagonist that has been researched as a possible antidepressant.
Neuropeptides	Oxytocin ³⁴	Low oxytocin has been linked to high anxiety.
	Substance P ¹⁴	There has been a decline in pharmaceutical studies as a result of multiple trials' failure to show that Substance P is effective in reducing anxiety.
	Neuropeptide Y ²⁸	A small RCT on NPY given intranasally to patients with MDD suggested that it might be beneficial for depression.
	Cholecystokinin ⁵⁹	CCK-2 antagonists can reduce human anxiety while CCK agonists cause panic attacks, thus current state of CCK in research is complicated.
	Orexin ¹⁸	Study demonstrates usefulness in anxiety.
	Neurosteroids ²⁴	Studies prove that anxiety is associated with abnormal neurosteroid homeostasis.

B. Psychotherapy :

Psychotherapy entails working with a therapist to lessen the symptoms of anxiety. It can be an adjuvant along with medications⁴. For anxiety disorders, cognitive behavioral

therapy (CBT) is the most successful type of psychotherapy. Cognitive Behavioral Therapy (CBT), teaches specific skills to help manage symptoms and progressively resume the activities that have been avoided due to anxiety.

Formulations available for the treatment of anxiety :

Table-4. Different dosage forms used to treat anxiety along with marketed examples

Formulation	Advantages	Disadvantages	Marketed example	Active pharmaceutical ingredient
Tablet ⁵⁷	<ol style="list-style-type: none"> 1. Simple to administer 2. Better dose precision. 3. Sustained release formulation can be prepared 4. Unpleasant taste or odor can be masked. 5. Can be produced on a large scale. 6. Packaging and handling is simple. 7. High stability. 8. embossing allows easy identification. 	<ol style="list-style-type: none"> 1. not suitable for bedridden or unconscious patients. 2. difficulty in swallowing for pediatric and geriatric patients. 3. not suitable for drugs with low bioavailability. 4. coating might be necessary in some cases thus increasing cost. 5. When taken as tablets, some medications can irritate the stomach. 	Xanax, Alpracon 0.25 Rivotril Ativan Serax Valium tranxene	Alprazolam Clonazepam Lorazepam Oxazepam Diazepam Chlorazepate
Capsule ⁶	<ol style="list-style-type: none"> 1. Easy to mask unpleasant odor or taste of drugs. 2. Simple to swallow. 3. Quick and simple digestion 4. Easy to handle 5. Less expensive 	<ol style="list-style-type: none"> 1. Hygroscopic capsule shell may absorb water and become brittle. 2. Concentrated solutions should not be used unless diluted to avoid stomach irritation. 3. It requires specific conditions for storage. 	Fluxit-60 Paxil, brisdelle	Fluoxetine Paroxetine

(1987)

	<p>6. The gelatin shell can shield the medication from light</p> <p>7. The capsule shells are inert</p> <p>8. Greater bioavailability as compared to tablets.</p> <p>9. Simple to formulate.</p>	<p>4. The production rate is lower.</p> <p>5. Materials that react with gelatin cannot be dispensed.</p> <p>6. It is not possible to dispense high dose medications, low density, or low melting point components.</p>		
Emulsion ²⁰	<p>1. Unpalatable oils and oil solvable drugs can be administered.</p> <p>3. The water phase can be easily flavored.</p> <p>4. The oily sensation is easily removed.</p> <p>5. The rate of absorption is increased.</p> <p>6. It is possible to include two incompatible components, one in oil phase and the other in aqueous phase.</p>	<p>1. Preparation needs to be shaken prior to use.</p> <p>2. A measuring instrument is required for administration.</p> <p>3. Storage atmosphere influences stability.</p> <p>4. Bulky, tough to transport and susceptible to container breakage.</p> <p>5. Liable to microbial contamination.</p>	Diprivan, Diprikoda-10, Propifol	Propofol
Suspension ²²	<p>1. Easier to administer drugs with poor solubility.</p> <p>2. Can mask</p>	<p>1. Formulation expertise is needed.</p> <p>2. It is challenging to formulate pharmaceutical</p>	Flunil	Fluoxetine hydrochloride

(1988)

	<p>unpleasant taste of the drug.</p> <ol style="list-style-type: none">3. Easy administration for geriatric and pediatric patients.4. Higher drug bioavailability5. Can be designed to deliver drugs in a controlled manner.6. Certain medications' chemical stability increases.	<p>suspensions that are elegant.</p> <ol style="list-style-type: none">3. Dosage accuracy is a challenge.4. Bulky in nature.5. The formulation needs shaking preceding administration.6. Problems with syringeability and pourability.7. The formation of crystals (Ostwald ripening) and suspension breaking.		
Syrup ³⁷	<ol style="list-style-type: none">1. Syrups retard oxidation since sugar acts as an antioxidant2. Sucrose acts as self preservative.3. Palatable due to the sweetness of sugar.4. Can mask the bitter taste.5. Good patient compliance.	<ol style="list-style-type: none">1. Not used for emergency purposes.2. Delayed onset of action.3. Syrups cannot be used for diabetic patients.4. Crystallisation of the sugar within the screw cap.	Atarax	Hydrox-yazine
Transdermal patch ¹³	<ol style="list-style-type: none">1. Provides constant plasma concentration of drug.2. Avoids the pH fluctuations due to GI transit.3. Avoids first pass hepatic metabolism4. Self-administration is manageable.	<ol style="list-style-type: none">1. May cause irritation, erythema etc.2. Hydrophilic drugs cannot cross the stratum corneum without modifications.3. Suitable for potent drugs.4. Doses of 5mg or less can only be given on a daily basis.5. The skin barrier is	Bupreplast Emsam	Buprenor-phine Selegiline

(1989)

	<p>5. drug effects can be stopped at any time by merely removing the patch.</p> <p>6. Improved patient compliance and reduced side effects.</p> <p>7. Non-invasive</p> <p>8. Comparable characteristics with intravenous infusion.</p> <p>9. Suitable for patients who are nauseated or unconscious.</p>	<p>variable in nature and changes with age, gender, person, climate etc.</p> <p>6. The patch might be uneasy to wear.</p> <p>7. Cannot be used to bring about high plasma drug concentration.</p> <p>8. Not suitable for ionic drugs.</p> <p>9. The patch may fall off accidentally.</p>		
Orally disintegrating tablet ¹⁹	<p>1. Easy to administer</p> <p>2. Easy to handle</p> <p>3. Useful for unconscious or bedridden patients.</p> <p>4. Rapid onset of action.</p> <p>5. Quick absorption.</p> <p>6. No risk of choking or suffocation.</p>	<p>1. Insufficient mechanical strength</p> <p>2. Difficult to mask the unpleasant taste /texture of the drug</p> <p>3. Larger doses are difficult to formulate.</p>	Rest -0.5	Clonazepam
Nasal spray ²¹	<p>1. Rapid onset of action</p> <p>2. Non-invasive</p> <p>3. Avoids GI drug degradation</p> <p>4. Bypasses first pass metabolism</p> <p>5. Rapid drug absorption</p> <p>6. Easy administration</p> <p>7. Reduced systemic side effects.</p>	<p>1. Mucociliary clearance</p> <p>2. Interference due to allergy, nasal congestion.</p> <p>3. Suitable for potent drugs.</p> <p>4. May cause nasal irritation.</p> <p>5. Dosage depends on the manner of administration.</p>	Insed	Midazolam nasal spray

Anxiety disorder is very common worldwide and is one of the major reasons for disability. In chronic state, it can affect a person adversely and cause hindrances in day to day life. Early identification of risk factors and symptoms in an individual may assist in avoiding progression of the disorder. Self-management is possible and successful treatment can be done with the help of psychotherapy and medications. There is a need of further investigation and development of novel therapies to improve the efficacy of treatment for anxiety.

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