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Review Article

Etiopathogenesis and novel molecular targets in anxiety and related disorders

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Abstract

Anxiety is a natural acknowledgment of stress but if it sustains for a prolonged duration, unreasonably and disproportionately, and hampers normal life severely, then it is referred to as anxiety disorder. Traditionally, a dual form of anxiety is recognized namely "trait anxiety" and "state anxiety". State anxiety is a pattern of anxiety that an individual experiences for a moment/situation/fraction of time and augmentation is directly affiliated with the presence of anxiogenic factors whereas trait anxiety is a constitutive character of a person. Anxiety disorder is a ubiquitously prevalent emotional, behavioral, and psychiatric disorder that is a significantly disabling and lasting disease with lifetime prevalence and has afflicted approximately 1/3rd of the population in the United States (US). The worldwide statistics for anxiety disorders are alarming and are reported to have plagued around 1/8th of the population throughout the sphere. They are predominant in the adult population with females being the predominant victim at a ratio of 2:1 in comparison to males.

Keywords: anxiety; behavior; therapy; risk factors; GABA; serotonin

1. Introduction

Anxiety is a natural acknowledgment of stress but if it sustains for a prolonged duration, unreasonably and disproportionately, and hampers normal life severely, then it is referred to as anxiety disorder (McNaughton, 2011). Traditionally, a dual form of anxiety is recognized namely "trait anxiety" and "state anxiety". State anxiety is a pattern of anxiety that an individual experiences for a moment/situation/fraction of time and augmentation are directly affiliated with the presence of anxiogenic factor whereas trait anxiety is a constitutive character of a person (Clement *et al*., 2002; Panthee and Kritpracha, 2011). Anxiety disorder is a ubiquitously prevalent emotional, behavioral, and psychiatric disorder that is a significantly disabling and lasting disease with lifetime prevalence and has afflicted approximately 1/3rd of the population in the United States (US). The worldwide statistics for anxiety disorders are alarming and is reported to have plagued around 1/8th of the population throughout the sphere (Kessler *et al*., 2005). They are predominant in the adult population with females are predominant victims at a ratio of 2:1 in comparison to males (Arikian and Gorman, 2001). Its overall lifetime prevalence is around 25% which implies that it

is more chronic than substance abuse disorders. Anxiety disorders precipitate mostly in childhood or adolescent age. They are affiliated with a considerable unfavorable blow to the communal, sentimental, and intellectual growth of children (Soodan and Arya, 2015). The exact prevalence is troublesome to ascertain since minute differences in diagnostic criteria, interview technique or study approach will cause a substantial variation in outcome. If a patient suffering from an anxiety disorder is not clinically managed it causes marked disruption in operations, a low standard of life, and an enormous financial burden (Hoffman *et al.*, 2008). Anxiety disorders are of paramount concern, given current lifestyle modification, professional competence, and worldwide issues, as outer factors play a crucial role in the evolution of anxiety disorders (Gross and Hen, 2004). Anxiety is the most consecutive co-morbid disease precipitated with other medical conditions like depression, eating disorders, and gastrointestinal diseases (Cosci *et al.*, 2015).

2. Symptoms of Anxiety Disorders

The symptoms vary according to the type of anxiety disorder and as per subject but can be broadly assorted into 3 components namely the physiological, cognitive, and behavioral (Shelton, 2004; Soodan and Arya, 2015). The constellation of symptoms that fall under these units are summarized in Fig 1.

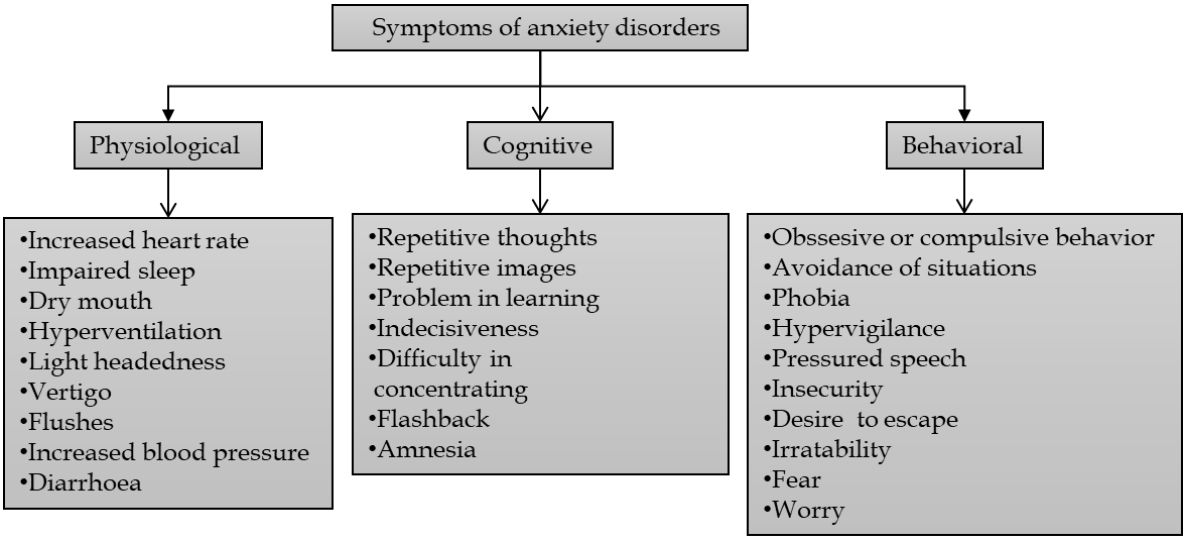

Fig. 1 Symptoms of anxiety disorders

3. Etiology of Anxiety Disorders

The research done so far on mental illness implies that these disorders are a consequence of multiple factors including transformation in the brain and environmental conditions (Gross and Hen, 2004; Martin *et al.*, 2009). Like other mental disorders, it is postulated that anxiety disorders precipitate due to metamorphosis in the operation of neuronal networks in the brain that are crucial for mediating fear and other sort of emotions. Studies reveal that prolonged stress causes modifications in nerve cells which impairs the transmission of signals in the neuronal circuit. Parallel to these studies have shown that structural metamorphosis was observed in some specific domains of the brain responsible for the modulation of emotion and fear in patients affected by anxiety disorders (Canteras *et al.*, 2010; Schmidt *et al.*, 2018). Other researchers insist that like cardiovascular disease and cancer, the chances of the evolution of anxiety disorders are also governed by a family history of anxiety disorders. Furthermore, numerous external factors such as trauma may act as triggers for subjects who are inheritably prone to the evolution of anxiety disorders (Gross and Hen, 2004; Thibaut, 2017). Thus, like other psychiatric disorders, anxiety disorders are too manifestations of multifactorial etiology (Fig 2). Diversified sort of

biological, psychological, genetic, and social factors make an individual prone to the development of anxiety which are listed below.

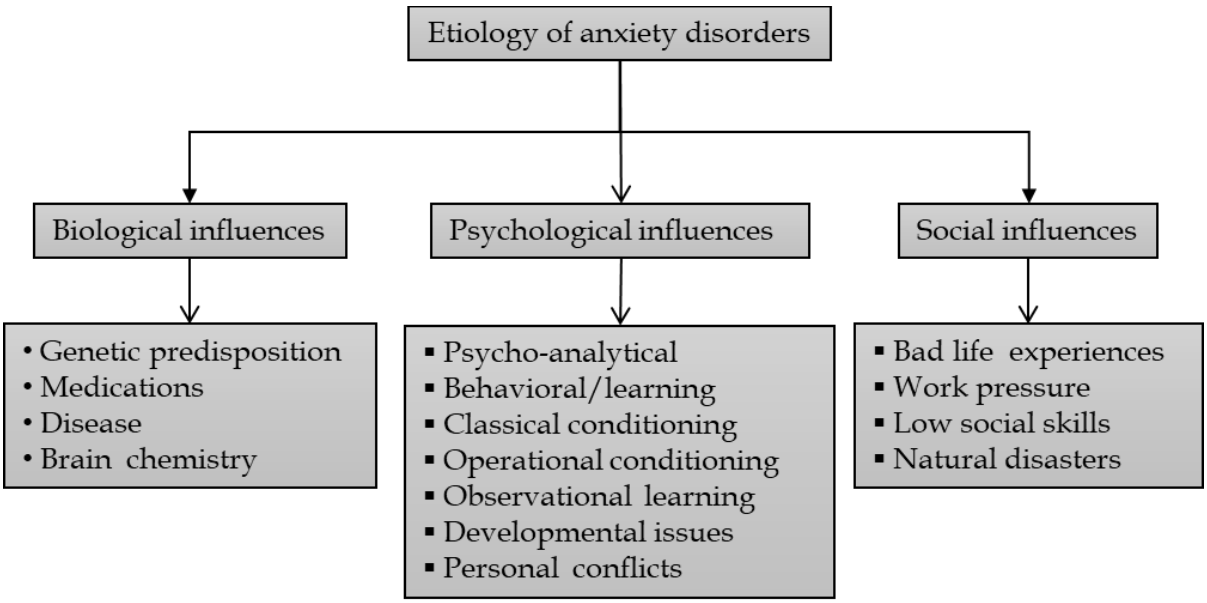

Fig. 2 Etiology of anxiety disorders

3.1. Biological Factors

i) Genetic factors: Individuals with a family history of anxiety disorders are more prone to get affiliated with anxiety disorder compared to individuals with a naïve family history with respect to anxiety disorder. Studies suggest 50% more chances of developing panic disorder in a subject who has a history of this disease in any member of his/her family tree (Morris-Rosendahl, 2002).

ii) Neurotransmitter imbalance: Functional and brain imaging studies show an imbalance in neurotransmitters mainly norepinephrine, serotonin, and gamma amino butyric acid are involved in the pathogenesis of anxiety disorders. Drugs that modulate these neurotransmitters are therapeutically used in the clinical management of anxiety disorders (Millan, 2003).

iii) Medical disorders: Numerous medical conditions such as cardiovascular disease, diabetes, and hyperthyroidism are afflicted with trigger anxiety symptoms (Gross and Hen, 2004).

3.2. Psychological Factor: Anxiety precipitates in situations where innate and exterior stress exceeds an individual's struggling capacity or there is depreciation in one's normal struggling capacity. Some psychological factors are outlined below (Soodan and Arya, 2015).

i) Psychodynamic: When innate mental functions and impulses contradict, triggering distress.

ii) Behavioral: Some past situations and experiences accumulate and precipitate anxiety.

iii) Spiritual: A feeling of disproportionate desolation and worthlessness triggering distress.

3.3. Social Factors: Traumatic events like the loss of someone, divorce, professional distress or major illness makes also an individual susceptible to the development of anxiety (Brook and Schmidt, 2008).

4. Diagnosis and Classification of Anxiety Disorders

Anxiety disorders are the most prevalent disorders confronted in clinical practice. Diagnosis of anxiety disorders is closely scrutinized and is continuously upgraded. The diagnosis of anxiety disorders is assorted majorly into dimensional and structural diagnoses both having their own constrain. Both forms of diagnosis are applied in clinical practice and the drug development process (Bystritsky *et al.*, 2013). Currently, the diagnostic approach is getting more attentive towards imaging and genetic tools. Patients suffering from anxiety present with a constellation of symptoms that vary from subject to subject. For ease in diagnosis and prescription of medication, anxiety disorders can be classified as described below. The Diagnosis and classification of anxiety disorders provided by DSM-V (2013) is currently applicable. Two disorders, firstly Obsessive-Compulsive disorder and the second, Post-traumatic stress disorder (PTSD) are excluded from being listed as anxiety disorders in DSM-V. However, anxiety is still a component of Obsessive-Compulsive disorder which is well recognized by DSM-V. Therefore, to be comprehensive and mindful of APA's suggestion, the various anxiety disorders as included in DSM-IV-Text Revision (TR) (1994) and DSM-V are described below (NIMH, 2011; Kupfer, 2015; Bandelow *et al.*, 2017; Ströhle *et al.*, 2018) (Fig 3).

4.1. Panic Disorders (PD): It is manifested in the form of acute terror attacks with physical signs like chest pain, sticky sweat, dyspnea, faintness, abdominal discomfort, hot flushes, and tingling sensation. The rate of prevalence of panic disorders is around 1-2% with a greater likelihood of precipitation in females (almost twice) than in males. Panic attacks commonly break out with MDD and social phobia. It has already distressed close to 2.4 million adults in the US alone.

4.2. Generalized Anxiety Disorders (GAD): An individual is categorized to be a victim of GAD if he/she has been experiencing in minimum 3 or more symptoms out of 6 described below for half a year and in case children a least one 1) feeling of tension or agitation 2) feeling of asthenia 3) problem in concentrating 4) bad temperament 5) muscular ache 6) disorientation of sleep pattern. It has disabled life of around 4 million individuals within the US with women affected at a rate twice compared to men.

4.3. Obsessive-Compulsive Disorder (OCD): OCD manifests in the form of intractable obsessions (repetitive ideas or incitation that are invasive or irrelevant and cause anxiety to affected individuals) and compulsions (ceaseless behaviors). Around 3 million US adult population is under the influence of OCD.

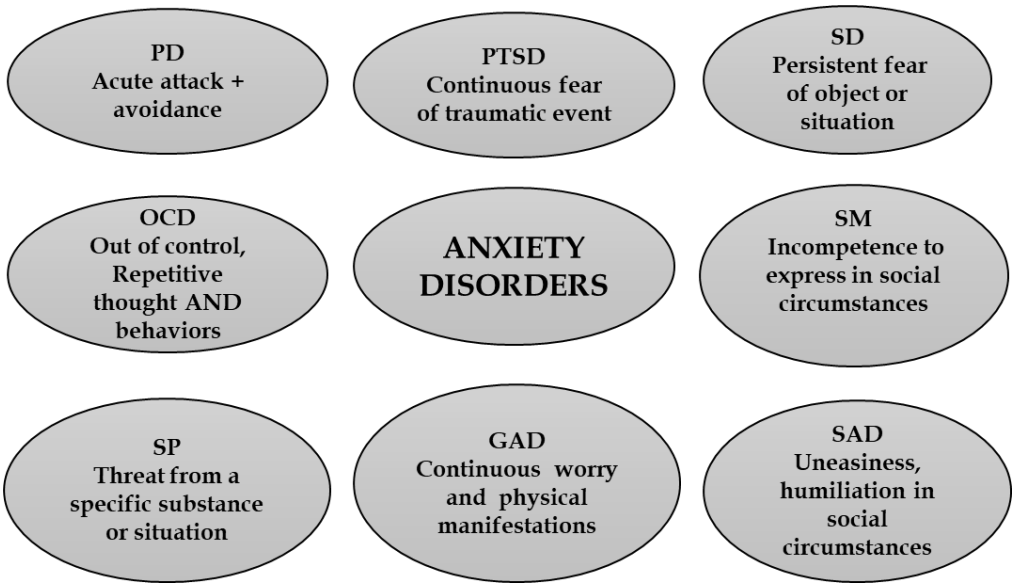

Fig. 3 Classification of anxiety disorders

4.4. Post-Traumatic Stress Disorders (PTSD): PTSD manifests in the form of relentless symptoms, dissociative symptoms, nightmares, nightmares feelings of uselessness, hostility and social withdrawal, and numbing of emotions that trigger downstream to traumatic incidents such as sexual abuse, natural calamity or war. An individual is diagnosed to be affected with PTSD if he/she is experiencing profound fear, helplessness or worry about an actual or virtual fear of loss of life or injury for at least a month. PTSD has already submerged approx. 3.6% adult population in the US alone and women are more affiliated with disease than men.

4.5. Specific Phobia (SP): SP is manifested as a disproportionate fear of a substance or situation, and exposure to that trigger's anxious reaction. It has plagued around 6 million adults in the US with two-fold women patients compared to men.

4.6. Social Anxiety Disorder (SAD): It manifests in the form of profound situational fear that might subject an individual to an awkward position**.** Both sexes are equally afflicted and 5 million adults in the US alone have been diagnosed with SAD**.**

4.7. Selective Mutism (SM): It is an uncommon anxiety disorder that generally precipitates during childhood to adolescence age tenure. The diagnosis of this disorder usually is made after the child has commenced schooling. It is recognized as persistent incapability to vocalize in the social ambiance in which the person is apprehended to vocalize otherwise the person is enough competent to speak out in other circumstances. People are categorized under the category of "Total mutism", if they fail to exhibit any form of oral expression like laughing, coughing, etc. irrespective of situation. The rate of occurrence of this disorder is estimated to be less than 1%.

4.8. Separation Disorder (SD): It is manifested in the form of redundant and exorbitant suffering related to homesickness or separation from near one(s). It is usually spotted in early childhood when manifestations become disproportionate according to age and hinder routine life operations. However, current statistics indicate its increasing precipitation in adulthood as well. It exhibits a prevalence rate of 4.8%.

5. The Neuroanatomy of Anxiety Disorders

The diverse brain regions implicated in anxiety disorders are discussed along with the corresponding anxiety disorders they mediate. The amygdala is the most consistently determined hyperactive region in anxiety patients. It mediates major responses in acknowledgment of emotional and social stimuli such as unpredictability processing and reward learning. Dysfunction in the amygdala leads to disproportionate fear perception and emotional disbalance which is core to many anxiety disorders (Adolphs, 2010). The fusiform gyrus seems to command the amygdala in transforming emotional responses in SAD patients. Also, stimulation of the fusiform gyrus was inversely related to the scoring of avoidance-associated behavioral computations (Pujol *et al*., 2009). Fear learning has been demonstrated to be affiliated with the anterior cingulate cortex (Sehlmeyer *et al*., 2009. Upon exposing the subjects to emotional distraction while performing a working memory test, stimulation in the PFC region was demonstrated. Insula is affiliated with deregulated processing of averse stimulus in individuals prone to anxiety (Schmidt *et al*., 2018). A tremendous stimulation of the insula was observed in individuals subjected to anxiogenic stimuli like images of spiders. The aberrant anticipatory formulation has been linked with hyperstimulation of the amygdala (Straube *et al*., 2007).

6. Pathophysiology of Anxiety Disorders

Despite its high prevalence and the disabling that it causes, the clear-cut pathogenic pathway leading to anxious states in humans remains an issue of concern. The involvement of multiplex of neurotransmitters, receptors, and complex neuronal networks along with the lack of technique to easily monitor the metamorphosis

of the brain in patients with anxiety disorder make it difficult to ascertain exact pathogenic pathways (Martin *et al*., 2009). Dysfunction of numerous neurochemicals namely serotonin, GABA, noradrenaline, dopamine, and certain other along receptors are afflicted with anxiety disorders. Though each neurochemical and receptor plays a distinctive role, all are at the same level in the modulation of anxiety as all seem to be connected directly or indirectly (Molchanov and Guimaraes, 2002; Klausberger and Somogyi, 2008). Some of the crucial mediators of anxiety are discussed below.

6.1. Gamma-Aminobutyric Acid: It has been computed that a minimum of 30% of central nervous system (CNS) neurons employ GABA as its elementary neurotransmitter (Kilb, 2012). GABA-mediated inhibition is crucial for sustaining equality amongst excitation and inhibition of neurons, for rigid supervision of transsynaptic signaling in the temporal and spatial region, temporal tuning of neuronal excitability, and also for surveillance of waving 'pacemaker' activity occurring in different regions of the brain (Klausberger and Somogyi, 2008). Two forms of GABA receptors are known namely, $GABA_A$ (ionotropic, fast-acting ligand-gated Cl^- channels) and $GABA_B$ (metabotropic, G-protein receptor with slow response). GABA receptors are ubiquitously present in the brain and spinal cord (Sieghart, 2006; Kilb, 2012). Benzodiazepines interact with postsynaptic GABA receptors to intensify GABAergic action by stimulating inward traffic of chloride anion and thereby causing stabilization of neuronal membrane (Sieghart, 2006; Bowery, 2010). GABA triggers the release of additional neurotransmitters like cholecystokinin and suppresses the activity of neurons pertaining to pathways of serotonin and noradrenaline thereby modulating anxiety levels (Nuss, 2015). It is well known that diverse pathologies escort the development of anxiety disorders, but the GABA circuits are a constitutive part of anxiety disorders. Abatement in GABA content and $GABA_A$-benzodiazepine receptor binding sites was observed in subjects afflicted with anxiety disorders in neuroimaging studies (Möhler, 2012). GABAergic neurotransmission specifically in the region of the amygdala is an assuring target for tweaking of anxiety-associated responses (Lydiard, 2003; Nuss, 2015). In animal studies, anxiolytic effects were observed following the infusion of GABA receptor agonists into the amygdala while augmentation of fear and anxiety levels was seen due to the infusion of GABA receptor antagonists in the amygdala (Möhler, 2012). Furthermore, the effects of benzodiazepines were arrested by the exclusive deactivation of glutamic acid decarboxylase residing in the amygdala. Similarly, negative emotional stimuli mediated activation of the amygdala was prevented by the administration of benzodiazepine in humans (Davids *et al*., 2006; Nuss, 2015).

6.2. Serotonin: The serotonin system is unparalleled because of its well-recognized contribution to the clinical management of anxiety disorders. The neuronal network of serotonin originates from raphé nuclei proliferating to an extensive complex framework that is implicated in anxiety disorders *i.e*. amygdala, cortex, hypothalamus, and hippocampus (Mann, 2013). Additionally, certain drugs that are clinically used in the abatement of anxiety symptoms are known to work *via* the modulation of serotonergic pathways further consolidating the contribution of serotonin (Davids *et al*., 2006). Aberrant monitoring in serotonin release and/or reuptake or impaired sensitivity to receptors may escort in the evolution of anxiety disorders. The 5-HT_{1A} receptor is recognized to have a crucial role in influencing anxiety symptoms. The specific form of polymorphism pertaining to the gene responsible for coding the 5-HT_{1A} receptor was found to be correlated with patients manifesting panic disorder and agoraphobia (Mann, 2013; Garcia-Garcia *et al*., 2014).

6.3. Tachykinins and Substance P: Tachykinins are well known for mediating anxiety symptoms in acknowledgment of stress. Studies on rodents have demonstrated abatement in anxiety symptoms following treatment with an antagonist of the neurokinin-1 receptor (Ebner *et al*., 2009).

6.4. Glutamate: Glutamate is the chief excitatory neurotransmitter that is afflicted with anxiety associated state. A surfeit of glutamate is released in acknowledgment of stress and adverse situations (Popoli *et al*., 2011). Anxiolytic effects have been shown upon the antagonism of the *N*-Methyl-D-aspartate (NMDA) receptor while its agonism triggered anxiety-like behavior in animal studies (Molchanov and Guimaraes, 2002).

6.5. Cholecystokinin (CCK): CCK is one of the richest neuropeptides found in the brain and is crucial in mediating numerous behaviors. Brain regions that are of paramount importance in the regulation of anxiety such as periaqueductal gray and basolateral amygdala are abundant in CCKB receptors. Precipitation of panic attacks was observed in control subjects and patients suffering from panic disorders following the administration of CCK-4 (Rotzinger *et al*., 2003).

6.6. Hypothalamus Pituitary Adrenal Axis: It's a crucial organization that liberates hormones in acknowledgment of stress. The hypothalamus liberates CRF which stimulates the pituitary to dispense ACTH in blood. The adrenal cortex is sensitive to ACTH and dispenses cortisol. Cortisol monitors its liberation by feedback structure. It attaches to receptors on the hypothalamus and pituitary and restrains the further liberation of CRF and ACTH (de Kloet, 2003). Chronic exposure to stressful triggers impairs the HPA axis feedback system and the subject enters a pathogenic state of mood disorder including anxiety (Risbrough and Stein, 2006; Lenze *et al*., 2011). The amygdala documents this emotional network creates emotional cognition and further consolidates anxious responses. Augmented anxiety state manifests in the form of paradoxical physiological repercussions, namely surfeit of cortisol values, hypertension and tachycardia, impaired healing operations, a decline in the immune network, and a boost in susceptibility to infection (Faravelli *et al*., 2012).

6.7. Glucagon-like Peptide-1: It's majorly concentrated in neurons of the brain stem which protrudes to the hippocampus, amygdala, and locus cerulus. Glucagon-like peptide-1 agonists augment stress-mediated anxiety while it was arrested by glucagon-like peptide-1 antagonists in animal studies (Kinzig *et al*., 2003).

6.8. Corticotropin-Releasing Factor: CRF is a CNS neuropeptide that specifically stimulates pituitary corticotrophin secretion and modulates the endocrine, autonomic, and immune response to stressful conditions. Patients suffering from anxiety disorders were found to have an elevated level of CRF (Risbrough and Stein, 2006).

6.9. Corticotropin-Releasing Hormone: CRH is crucial in mediating response to stress as evidenced by stress-triggered surfeit generation of CRH from the hypothalamus. Diminished anxiety level was observed in stressed rats in whom biosynthesis of CRH was arrested by giving antisense oligodeoxynucleotide complementary to the initiation-coding region of CRH messenger ribonucleic acid (mRNA) (Skutella *et al*., 1998).

6.10. Cortisol: It is well known to mediate a wide array of operations which includes organization of energy stores, augments arousal, increased attentiveness, cognitive genesis, arresting reproductive system growth, and restraining immune response. It is well-known to aid in encoding emotion-associated cognition and augment the repercussions of CRH on fear conditioning (Lenze *et al*., 2011).

7. Management of Anxiety Disorders

When anxiety symptoms become exorbitant, and disproportionate and intrude with the normal routine of life and its activities, then clinical management of anxiety disorders is of paramount importance. Although anxiety disorders are not as evident as Parkinson's disease, depression, and bipolar disorder, they are equally handicapping. Anxiety disorders can be clinically managed with psychopharmacological and pharmacological therapies in an effective manner. Each intervention targets a different zone of symptoms, therefore logical composite of interventions needs to be applied to obtain enhancement of results. Novel alternatives are

anticipated that are crucial for the management of treatment-resistant cases (Davids *et al.,* 2006; NIMH, 2009; Bystritsky *et al*., 2013).

7.1. Pharmacological Therapies for Management of Anxiety Disorders: In anxiety disorders, the deregulation of multiple neurotransmitters is implicated and each one of them serves as the potential for the management of disease but only a handful of categories are used in clinical practice (Davids *et al*., 2006; NIMH, 2009). The numerous pharmacological therapies available are assorted below in Table 1.

7.2. Psychotherapy for Anxiety Disorders: This is an elementary choice of therapy for managing anxiety disorders excluding scenarios where anxiety symptoms are so disabling that an instant abatement of symptoms is imperative to reestablish normal life and to prohibit immediate and long-term repercussions. It is widely accepted that pharmacological treatment is substandard in the absence of psychological therapy either due to the unavailability of a therapist or economic issues (Bystritsky *et al*., 2013). The numerous psychopharmacological approaches currently in practice are listed below:

7.2.1. Cognitive behavioral therapy: CBT has got enormous extent of backing as psychological therapy for the management of anxiety disorders. CBT stands as a front line of therapy with SSRIs. CBT therapists constitute clear targets with patients and employ an evidence-based approach by evoking subjects' feelings and physical sensations, eliminating unreasonable thoughts and behaviors that act as anxiogenic stimuli. CBT therapist treats the individual in a warm and non-subjective ambiance in order to make the patient feel and work better in the real world (Compton *et al*., 2004).

7.2.2. Exposure: It includes **a** progressive and organized technique of featuring anxiogenic stimulus *i.e*. thoughts, pictures, or subjects for a longer span of time in order to minimize the anxious feelings of the patient without rescuing from the stimulus (Bystritsky *et al*., 2013).

7.2.3. Mindfulness: It is recognized as an acceptance-based CBT technique. This is also recognized as the third wave of CBT. The first one is behavior, the second one is cognitive, and the third is acceptance. This technique has been adopted from Buddhist psychology and began under a US-based professor as a stress buster technique in his clinical for managing anxious patients (Churchill *et al*., 2010).

7.2.4. Acceptance and commitment therapy: It includes mindful focus, and the application of multiple exercises that are projected at the meta-cognitive stage to assist patients in apprehending their thoughts and ensuing anxious behaviors to be dichotomized pattern, and minimal recognized with, their feelings of own. Anxiogenic stimuli are to be viewed and acknowledged, not to be coped up or adjusted, as done in classical forms of CBT (Bystritsky *et al*., 2013).

7.2.5. Family therapy and parent training: The primacy locus is family members. It is based on an approach that it is difficult to improve members of the family if they lack understanding of the disagreement that arose during intercommunication. Each member is apprehended to share in combating the issue to be controlled (Soodan and Arya, 2015).

7.3. Experimental and Off-Label Nonpharmacological Therapeutic Strategies for Anxiety Disorders

7.3.1. Electroconvulsive therapy: It includes the administration of electrical stimulus to the scalp to trigger neuronal discharge, subsequently generating generalized seizure activity. Though, electroconvulsive therapy is capable of clinically combating treatment-resistant cases, however, information regarding its efficacy in treating anxiety is scarce (Beale *et al*., 1995).

7.3.2. Vagal nerve stimulation: Preliminary developed for management of epilepsy, it was applied in psychiatric subjects after which sustained amelioration of mood disorders was observed with this therapy. Vagal nerve stimulation is believed to activate brain areas

that are recognized in the processing of anxiety and fear (George *et al*., 2008).

7.3.3. Repetitive transcranial magnetic stimulation: It involves exciting or inhibiting cortical neurons by using focal magnetic stimulation of the scalp. It is less protruding than electroconvulsive therapy, without the need for anesthesia, and does not evoke generalized seizures (Pallanti and Bernardi, 2009).

7.3.4. Surgery: Numerous surgical procedures consisting of anterior cingulotomy, anterior capsulotomy, and subcaudal tractotomy are used for the management of treatment-resistant cases of anxiety disorders but follow-up studies have shown cognitive dysfunction including apathy and frontal lobe deregulation as side effects limiting its use (Greenberg *et al*., 2003).

7.3.5. Deep-brain stimulation: In this tiny electrode is inserted under careful stereotactic magnetic resonance imaging (MRI) directions. It is superior to surgery because it can be modified to provide tailored neurostimulation. Post implantation, various criteria of electrode stimulation *i.e*. intensity, and polarity, could be optimized (Velasques *et al*., 2014).

Table 1 Pharmacological therapies for anxiety disorders

Class	Drugs	Mechanism of action	Adverse effects	Advantages
Selective serotonin reuptake inhibitors	Paroxetine Fluoxetine Citalopram	Modulate the concentration of serotonin and desensitize serotonergic receptors	Nervousness Reduced libido	Manages co-morbid depression Low risk of mortality in overdose
Benzodiazepine	Clonazepam Diazepam Lorazepam Alprazolam	Augments the function of GABA	Sedation Rebound anxiety on withdrawal Risk of drug dependence	Quick onset
Anti-seizure medications	Gabapentin	Modulates GABA	Sedation	Fast onset
Tricyclic Anti-depressants	Imipramine	Augments serotonin and noradrenaline levels	Cardiotoxicity Anticholinergic side effects Risk in overdose	Manages co-morbid depression
Beta Blockers	Propanolol	Impairs the ability to generate adrenaline	Drowsiness Gastrointestinal upset	Quick onset Non-habit forming
Monoamine oxidase inhibitors	Isocarboxazid Phenelzine	Inhibits MAO enzyme and deaccelerates degradation of serotonin and noradrenaline	Risk of hypertensive crisis	Manages co-morbid depression
Azaspirones	Buspirone	Augments activity of serotonin	Insomnia Chest pain	Less sedating

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