**Calcutta University**

**SEM-IV**
**CORE COURSE-8**

**UNIT- 2**
**CLINICAL PICTURES (DSM-V) AND AETIOLOGY OF DISORDERS-I**

**Anxiety Disorders**- a group of disorders, as identified by DSM, where clinically significant anxiety and fear play significant roles, and so it is important to understand these two emotions in detail.

**Anxiety** : most simply, anxiety can be defined as apprehension over an anticipated problem; a feeling of impending danger. Anxiety is a response to threat that is mostly unknown and vague.

**Fear:** is defined as a reaction to known, definite, immediate danger.

Though conceptually anxiety is 'future' oriented and fear is 'present' oriented, both anxiety and fear can involve arousal, or sympathetic nervous system activity, where anxiety often involves moderate arousal, and fear involves higher arousal. Anxiety and fear are not necessarily "bad"—in fact, both are adaptive. Fear is fundamental for "fight-or-flight" reactions—that is, fear triggers rapid changes in the sympathetic nervous system that prepare the body for escape or fighting. In the right circumstance, fear saves lives. On the other hand Anxiety is adaptive in helping us notice and plan for future threats—that is, to increase our preparedness, to help people avoid potentially dangerous situations, and to think through potential problems before they happen. However, too much of anxiety is maladaptive in nature and decrease performance.

Now a group of disorders which all have unrealistic, irrational fears or anxieties of disabling intensity as their principal and most obvious symptom manifestation are classified as the anxiety disorder. Anxiety disorders as a group are the most common type of psychiatric diagnosis. In any 12-month period, about 18 percent of the adult population suffers from at least one anxiety disorder (Kessler, Chiu, et al., 2005), and they create enormous personal, economic, and health care problems for those affected and for society more generally. Anxiety disorders have the earliest age of onset of all mental disorders (Kessler, Aguilar-Gaxiola, et al., 2009) and are associated with an increased prevalence of a number of medical conditions including asthma, chronic pain, hypertension, arthritis, cardiovascular disease, and irritable bowel syndrome (Roy-Byrne et al., 2008).

Among the disorders recognized under this group in current *DSM-5* are:

1. specific phobia

2. social anxiety disorder (social phobia)

3. panic disorder

4. agoraphobia

5. generalized anxiety disorder

Obsessive-compulsive disorder, however, is no longer classified as an anxiety disorder. Instead, it is now listed in a new *DSM-5* category called obsessive-compulsive and related disorders.

## CLINICAL PICTURE AND AETIOLOGY OF GENERALISED ANXIETY DISORDER (GAD)

Anxiety and worry are very common. All of us have worried or got anxious at some point of our lives. The term *worry* refers to the cognitive tendency to chew on a problem and to be unable to let go of it (Mennin, Heimberg, & Turk, 2004). Often, worry continues because a person cannot settle on a solution to the problem. Most of us worry from time to time, but the worries of people with GAD are excessive, uncontrollable, and long-lasting. On the other hand, anxiety is even an adaptive emotion, as it helps us plan and prepare for possible threat. But, for some people, anxiety and worry about many different aspects of life including minor events becomes chronic, excessive, and unreasonable. In these cases, **generalized anxiety disorder (GAD)** (formerly known as free-floating anxiety) may be diagnosed. People suffering from GAD live in a relatively constant, future-oriented mood state of anxious apprehension, chronic tension, worry, and diffuse uneasiness that they cannot control. They also show marked vigilance for possible signs of threat in the environment and frequently engage in subtle avoidance activities such as procrastination, checking, or calling a loved one frequently to see if he or she is safe (Barlow, 2002). Such anxious apprehension also occurs in other anxiety disorders (for example, the person with agoraphobia shows anticipatory anxiety about future panic attacks and about dying, and the person with social anxiety is anxious about possible negative social evaluation). But this apprehension is the essence of GAD, leading Barlow and others to refer to GAD as the "basic" anxiety disorder (Roemer et al., 2002).

### *DIAGNOSTIC CRITERIA (DSM-V)*

**A**. Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least 6 months, about a number of events or activities (such as work or school performance).

**B.** The individual finds it difficult to control the worry.

**C.** The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):

*Note: Only one item is required in children*.

1. Restlessness or feeling keyed up or on edge.

2. Being easily fatigued.

3. Difficulty concentrating or mind going blank.

4. Irritability.

5. Muscle tension.

6. Sleep disturbance (difficulty falling or staying asleep, or

restless, unsatisfying sleep).

**D.** The anxiety, worry, or physical symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

**E.** The disturbance is not attributable to the physiological effects of a Substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).

**F.** The disturbance is not better explained by another mental disorder (e.g., anxiety or worry about having panic attacks in panic disorder, negative evaluation in social anxiety disorder [social phobia], contamination or other obsessions in obsessive-compulsive disorder, separation from attachment figures in separation anxiety disorder, reminders of traumatic events in posttraumatic stress disorder, gaining weight in anorexia nervosa, physical complaints in somatic symptom disorder, perceived appearance flaws in body dysmorphic disorder, having a serious illness in illness anxiety disorder, or the content of delusional beliefs in schizophrenia or delusional disorder).

(*Source: Reprinted with permission from the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (Copyright 2013). American Psychiatric Association.*)

People with GAD do frequently show up in physicians' offices with medical complaints (such as muscle tension or gastrointestinal and/or cardiac symptoms) and are known to be over-users of health care resources.

MULTIPLE SOMATIC SYMPTOMS:

1. Palpitation
2. Increased rate of breathing ie. Hyperventilation leading to tingling and numbness of fingers, toes, lips and may lead to fainting.
3. Butterflies in stomach
4. Headache – band like headache- as if a band has been tied around the head
5. Mascular aching- all over body
6. Appetite- may increase or decrease
7. Nausea
8. Dry throat and mouth- difficulty in speaking
9. Increased thirst, leading to excess water intake
10. Due to increased kidney activity – frequent urge to pass urine and stool.
11. Due to less salivation, difficulty in swallowing

People with GAD have difficulty making decisions, and after they have managed to make a decision they worry endlessly, over possible errors and unforeseen circumstances that may lead to disaster. They have no appreciation of the logic by which most of us conclude that it is pointless to torment ourselves about possible outcomes over which we have no control. So, it is not surprising that those with GAD experience a similar amount of role impairment and lessened quality of life to those with major depression (Hoffman et al., 2008).

PREVALENCE

Generalized anxiety disorder is a relatively common condition; current estimates from the National Comorbidity Survey-Replication are that approximately 3 percent of the population suffers from it in any 1-year period and 5.7 percent at some point in their lives (Kessler, Chiu, et al., 2006). It also tends to be chronic. One 12-year follow-up study of people diagnosed with GAD found that 42 percent had not remitted 13 years later and of those who had remitted, nearly half had had a recurrence (Hoffman et al., 2008).

GENDER:

Gender wise, several studies suggest that women are at least twice as likely as men to be diagnosed with an anxiety disorder (de Graaf, Bijl, Ravelli, et al., 2002).

AGE OF ONSET

Age of onset is often difficult to determine because 60 to 80 percent of people with GAD remember having been anxious nearly all their lives, and many others report a slow and insidious onset (Roemer et al., 2004). GAD typically begins in adolescence, though many people who have GAD report having had a tendency to worry all their lives (Barlow, Blanchard, Vermilyea, et al., 1986). Once it develops, GAD is often chronic; in one study, about half of people with GAD reported ongoing symptoms 5 years after an initial interview (Yonkers, Dyck, Warshaw, & Keller, 2000). However, research has also documented that GAD often develops in older adults, for whom it is the most common anxiety disorder, (Stein, 2004).

CULTURE

People in every culture seem to experience problems with anxiety disorders. But the focus of these problems appears to vary by culture. Several culturally specific syndromes provide examples of how culture and environment may shape the focus of an anxiety disorder. For example, *Kayak-angst*, a disorder that is similar to panic disorder, occurs among the Inuit people of western Greenland; seal hunters who are alone at sea may experience intense fear, disorientation, and concerns about drowning. Other syndromes, such as *koro* - a sudden fear that one's genitals will recede into the body—reported in southern and eastern Asia. Cultures differ with regard to factors such as attitudes toward mental illness, stress levels, the nature of family relationships, and the prevalence of poverty—all of which are known to play a role in the occurrence or reporting of anxiety disorders.

**AETIOLOGY OF GAD**

GAD is the result of biological factors in combination with psychological and psychosocial factors acting on individuals.

**BIOLOGICAL FACTORS:**

**GENETIC FACTORS:**

Risk for GAD does seem to run in families and has a heritability estimate of approximately 30% (Gottschalk & Domschke, 2017).

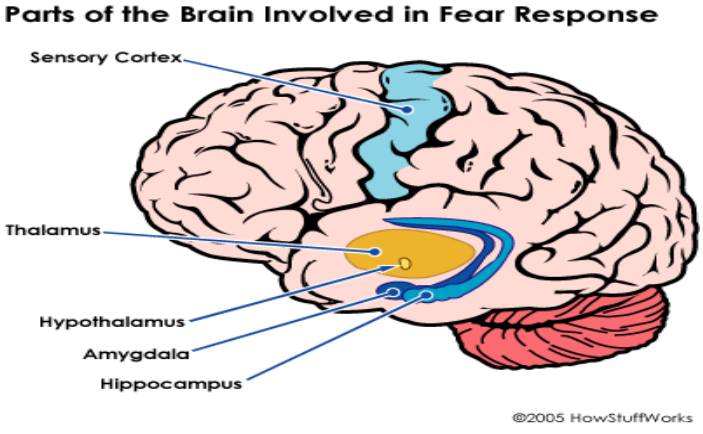
- **Family studies:** concordance rate for first degree relatives = 25%
- **Twin studies**: concordance rate for monozygotic twins = 50%

concordance rate for dizygotic twins = 15%

Overall findings suggest that genes play a significant although moderate role in the aetiology of GAD. Although, heritability has been found for a particular trait, called *anxiety sensitivity, which is the tendency to become* distressed in response to arousal related sensations arising from beliefs that these anxiety-related sensations have harmful consequences (Davies, et.al, 2015).

## NEUROANATOMICAL FACTORS:

**FEAR CIRCUIT**:- A set of brain structures called the **fear circuit** tend to be involved when people are feeling anxious or fearful (Malizia, 2003). Fear circuit is a set of brain structures i.e. connective pathway between amygdala and medial prefrontal cortex. One part of the fear circuit that seems particularly activated among people with anxiety disorders is the amygdala. The amygdala is a small, almond-shaped structure in the temporal lobe that appears to be involved in assigning emotional significance to stimuli as well as conditioning fear responses by sending signals to a range of different brain structures involved in the fear circuit. In animals, the amygdala has been shown to be critical for the conditioning of fear. Studies suggest that when shown pictures of angry faces (one signal of threat), people with several different anxiety disorders respond with greater activity in the amygdala than do people without anxiety disorders (Blair, Shaywitz, Smith, et al., 2008).
On the other hand, **Medial prefrontal cortex** is known to regulate the activity of amygdala. It is involved in extinguishing fears as well as using emotion regulation strategies to control emotions (Kim, Loucks, Palmer, et al., 2011). Since, this fear circuit is tend to be involved anxious or fearful feelings, elevated activity in the fear circuit, particularly the amygdala, may help explain many different anxiety disorders. Research found that people who meet diagnostic criteria for anxiety disorders display less activity in the medial prefrontal cortex, (Shin, Wright, Cannistraro, et al., 2005)



New evidence suggests that the pathway, or connectivity, linking these two regions may be deficient among those with anxiety disorders (Kim et al., 2011). These deficits in connectivity between the medial prefrontal cortex and the amygdala may interfere with the effective regulation and extinction of anxiety (Yehuda & LeDoux, 2007).

Many of the neurotransmitters involved in the fear circuit are also involved in anxiety disorders.

**NEUROCHEMICAL FACTORS:**

**A Functional Deficiency in GABA :** Gamma amino butyric acid (GABA) receptors are inhibitory and reduce anxiety. In the 1950s, the benzodiazepine category of medications was found to reduce anxiety. Later, in the 1970s it was found that these drugs probably exert their effects by stimulating the action of GABA. This neurotransmitter is now strongly implicated in generalized anxiety (Nutt et al., 2006). It appears that highly anxious people have a kind of functional deficiency in GABA, which ordinarily plays an important role in the way our brain inhibits anxiety in stressful situations. The benzodiazepine drugs appear to reduce anxiety by increasing GABA activity in certain parts of the brain implicated in anxiety, such as the limbic system, and by suppressing the stress hormone cortisol. Whether the functional deficiency in GABA in anxious people causes their anxiety or occurs as a consequence of it is not yet known, but it does appear that this functional deficiency promotes the maintenance of anxiety.

More recently, researchers have discovered that another neurotransmitter— **serotonin**—is also involved in modulating generalized anxiety (Goodman, 2004; Nutt et al., 2006). Serotonergic neurons are involved in the alteration of appetite mood sleep and cognitive function in anxiety. The role of and higher-than-normal levels of **norepinephrine** (Geracioti, Baker, Ekhator, et al., 2001) is also being speculated, though the exact functioning is still unknown. At present, it seems that GABA, serotonin, and perhaps norepinephrine all play a role in anxiety, but the ways in which they interact remain largely unknown (LeDoux, 2002).

**The Corticotropin-Releasing Hormone (CRH) System:** An anxiety-producing hormone called corticotropin releasing hormone (CRH) has also been strongly implicated as playing an important role in generalized anxiety. When activated by stress or perceived threat, CRH stimulates the release of ACTH (adrenocorticotropic hormone) from the pituitary gland, which in turn causes release of the stress hormone cortisol from the adrenal gland (Leonardo & Hen, 2006); cortisol helps the body deal with stress.The CRH hormone may play an important role in generalized anxiety through its effects on the bed nucleus of the ***stria terminalis,*** which is an extension of the amygdala;, which is now believed to be an important brain area mediating generalized anxiety

**PSYCHOLOGICAL FACTORS**

**The Psychoanalytic Viewpoint**:

Sigmund Freud (1856-1939) proposed three types of anxieties. ***Realistic anxiety***, which results from a real threat in the physical world to one's well-being, e.g- facing a mad dog! Then there is **Neurotic anxiety**, which results from the ego feeling overwhelmed by the id, which threatens to come to conscious, and ego feel the fear of external punishment for such expression. Last is ***Moral anxiety, b***ased on a feeling that one's internalized values are

about to be compromised, resulting in self-punishment (e.g., guilt). Moral anxiety is a function of the development of the superego. Whatever the anxiety, the ego seeks to reduce it. Operating at the unconscious level, it employs defense mechanisms to distort or deny reality.

To explain GAD, Freud developed the **signal theory** of anxiety, where anxiety serves as the signal to ego of a threat in the form of an unconscious wish arising from the id. According to this viewpoint, generalized or free-floating anxiety results from an unconscious conflict between ego and id impulses that is not adequately dealt with because the person's defense mechanisms have either broken down or have never developed. Freud believed that it was primarily sexual and aggressive impulses that had been either blocked from expression or punished upon expression that led to free-loating anxiety. Defense mechanisms may become overwhelmed when a person experiences frequent and extreme levels of anxiety, as might happen if id impulses are recurrently blocked from expression. As a result, receiving the signal, ego fails to mobilise defense mechanisms to deal with it and the person suffers from anxiety as a consequence.

**Behavioural Viewpoint**:

This view primarily focuses on conditioning. **Mowrer's two-factor model** of anxiety disorders, published in 1947, continues to influence thinking in this area. Mowrer's model suggests two steps in the development of an anxiety disorder (Mowrer, 1947):

**1.** Through *classical conditioning*, a person learns to fear a neutral stimulus (the CS) that is paired with an intrinsically aversive stimulus (the UCS).

**2.** Through *operant conditioning*, a person gains relief by avoiding the CS. This avoidant response is maintained because it is reinforcing (it reduces fear).

Operant conditioning thus may play a huge role in the disease process of GAD. Just as "avoiding" in Panic disorder serves as reinforcement to the fear, constant worrying might play the role of reinforcement to not facing the actual problem. It is found, that when people with GAD worry, their emotional and physiological responses to aversive imagery are actually suppressed. This suppression of aversive emotional physiological responding insulates the person from fully experiencing or processing the topic that she or he is worrying about and may serve to reinforce the process of worry, (Borkovec et al., 2004)

**COGNITIVE FACTORS**

**Sustained Negative Beliefs about the Future;** People with anxiety disorders often report believing that bad things are likely to happen. As pointed out by David Clark and colleagues (Clark, Salkovskis, Hackmann, et al., 1999), the key issue is not why people think so negatively initially but, rather, how these beliefs are sustained. It might result from their history of experiencing many important events as stressful and threatening. Moreover, people with GAD clearly have far less tolerance for uncertainty than nonanxious controls and than people with panic disorder (Koerner & Dugas, 2008).

**Perceived lack of Control :** Uncontrollable and unpredictable aversive events are much more stressful than controllable and predictable aversive events, so it is perhaps not surprising

that the former create more fear and anxiety. This has led researchers to hypothesize that people with GAD may have a history of experiencing many important events in their lives as unpredictable or uncontrollable.People who think that they lack control over their environment are at greater risk for a broad range of anxiety disorders. People with anxiety disorders report experiencing little sense of control over their surroundings (Mineka & Zinbarg, 1998).Childhood experiences, such as traumatic events punitive and restrictive parental training, or abuse, may generate this perceived lack of controllability. Similarly, anxiety disorders often develop after serious life events that threaten the sense of control over one's life. Indeed, more than 70 percent of people report a severe life event before the onset of an anxiety disorder (Finlay-Jones, 1989). Some evidence indicates that people with GAD may be more likely to have had a history of trauma in childhood than individuals with several other anxiety disorders (Borkovec et al., 2004). Moreover, people with GAD have far less tolerance for uncertainty than nonanxious controls and even people with panic disorder (Koerner & Dugas, 2008). This low tolerance for uncertainty in people with GAD suggests that they are especially disturbed by not being able to predict the future. Moreover, the greater the intolerance of uncertainty, the more severe the GAD (Dugas et al., 2007).

**Effect of stress:** Similarly, anxiety disorders often develop after serious life events that threaten the sense of safety in one's life. Indeed, more than 70 percent of people report a severe life event before the onset of an anxiety disorder

**Biased Attention to Threat:** Not only do people with GAD have frequent frightening thoughts, they also process threatening information in a biased way, perhaps because they have prominen danger schemas.People with anxiety disorders have been found to pay more attention to negative cues in their environment when both positive and negative cues are present. This tendency to interpret ambiguous information negatively has actually been shown to increase anxiety in several situations, including watching a stressful video, (Wilson et al., 2006).Researchers further proposed that this heightened attention to threatening stimuli happens automatically and very quickly—before people are even consciously aware of the stimuli (Öhman & Soares, 1994; Staugaard, 2010). It might be said that people with GAD has shallow processing of information. This attentional vigilance for threat cues can occur at a very early stage of information processing, even before the information has entered the person's conscious awareness. If a person is already anxious, having her or his attention automatically focused on threat cues in the environment would seem only to maintain the anxiety or even make it worse. Moreover, recent evidence also strongly supports the idea that such attentional biases play a causal role in anxiety as well (MacLeod & Mathews, 2012). In sum, anxiety disorders are associated with selective attention to signs of threat.

**The role of Worry:** The worry process is now considered the central feature of GAD. Research have found the people with GAD believe that worry serves some positive functions like- copping and preparations, avoidance of deeper emotional topics, superstitious avoidance of catastrophic events. Some evidence suggests that for a subset of people with GAD, these positive beliefs about worry play a key role in maintaining high levels of anxiety and worry, especially in the early phases of the development of GAD (Dugas et al., 2007). When people with GAD worry, their emotional and physiological responses to aversive imagery are actually suppressed. Since worry suppresses physiological responding, it also insulates the person from fully experiencing or processing the topic that she or he is worrying about. This suppression of aversive emotional physiological responding may serve to reinforce the process of worry (that is, to increase its probability, McLaughlin et al., 2007). So, anxiety continues since full processing of information is necessary for termination of anxiety to

occur. On the other hand worry can have some negative effect also like lowering mood and increasing sense of threat and danger.

Finally, there is now considerable evidence that attempts to control thoughts and worry may paradoxically lead to increased experience of intrusive thoughts and enhanced perception of being unable to control them (Abramowitz et al., 2001). Somewhat paradoxically, these intrusive thoughts can serve as further trigger topics for more worry, and a sense of uncontrollability over worry may develop in people caught in this cycle that occurs in GAD. As we have noted, perceptions of uncontrollability are also known to be associated with increased anxiety, so a vicious circle of anxiety, worry, and intrusive thoughts may develop (Mineka, 2004).

**Personality: behavioral inhibition and neuroticism:** Some infants show the trait of **behavioral inhibition**, a tendency to become agitated and cry when faced with novel toys, people, or other stimuli. This behavioral pattern, which has been described in infants as young as 4 months old, may be inherited and may set the stage for the later development of anxiety disorders. One study followed infants from 14 months through 7.5 years; 45 percent of those who showed elevated behavioral inhibition levels at 14 months showed symptoms of anxiety at age 7.5, compared to only 15 percent of those who had shown low behavioral inhibition levels (Kagan & Snidman, 1999). Behavioral inhibition appears to be a particularly strong predictor of social anxiety disorder: 30 percent of infants showing elevated behavioral inhibition developed social anxiety disorder by adolescence (Biederman, Rosenbaum, Hirshfeld et al., 1990).

On the other hand, Neuroticism is a personality trait defined by the tendency to react to events with greaterthan- average negative affect. Establishing a relation between neuroticism and anxiety disorder, a sample of 7,076 adults, neuroticism was found to predict the onset of both anxiety disorders and depression (de Graaf et al., 2002). People with high levels of neuroticism were more than twice as likely to develop an anxiety disorder as those with low levels. In another study of 606 adults followed over 2 years, neuroticism was a major correlate and predictor of anxiety and depression (Brown, 2007).

REFERENCE:

Abramowitz, J. S., Tolin, D. F., & Street, G. P. (2001). Paradoxical effects of thought suppression: A meta-analysis of controlled studies. *Clin. Psychol. Rev., 21*(5), 683–703.

Barlow, D. H. (Ed.). (2002). *Anxiety and its disorders: The nature and treatment of anxiety and panic* (2nd ed.). New York: Guilford Press.

Barlow, D. H., Blanchard, E. B., Vermilyea, J. A., Vermilyea, B. B., & DiNardo, P. A. (1986). Generalized anxiety and generalized anxiety disorder: Description and reconceptualization. *American Journal of Psychiatry, 143*, 40–44.

Biederman, J., Rosenbaum, J. F., Hirshfeld, D. R., & Faraone, S. V. (1990). Psychiatric correlates of behavioural inhibition in young children of parents with and without psychiatric disorders. *Archives of General Psychiatry, 47*, 21–26.

Blair, K. S., Shaywitz, J., Smith, B. W., Rhodes, R., Geraci, M., Jones, M., . . . Mondillo, K. (2008). Response to emotional expressions in generalized social phobia and generalized anxiety disorder: Evidence for separate disorders. *American Journal of Psychiatry, 165*, 1193–1202.

Borkovec, T. D., Alcaine, O. M., & Behar, E. (2004). Avoidance theory of worry and generalized anxiety disorder. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), *Generalized anxiety disorder: Advances in research and practice.* (pp. 77–108). New York: Guilford Press.

Clark, D. M., Salkovskis, P. M., Hackmann, A., Wells, A., Ludgate, J., & Gelder, M. (1999). Brief cognitive therapy for panic disorder: A randomized controlled trial. *J. Consult. Clin. Psychol., 67,* 583–89.

Davies, M. N., Verdi, S., Burri, A.,Trzaskowski, M., Lee, M., Hettema, J. M., Jansen, R., Boomsma, D. I., & Spector, T. D. (2015).

de Graaf, R., Bijl, R. V., Ravelli, A., Smit, F., & Vollenbergh, W. A. M. (2002). Predictors of first incidence of DSMIII- R psychiatric disorders in the general population: Findings from the Netherlands Mental Health Survey and Incidence Study. *Acta Psychiatrica Scandinavica, 106,* 303–313.

Dugas, M. J., Savard, P., Gaudet, A., Turcotte, J.,Laugesen, N., Robichaud, M., et al. (2007). Can the components of a cognitive model predict the severity of generalized anxiety disorder? *Behav.Ther., 38*(2), 169–78.

Finlay-Jones, R. (1989). Anxiety. In G. W. Brown & T. O. Harris (Eds.), *Life events and illness* (pp. 95–112). New York: Guilford.

Generalized anxiety disorder: A twin study of genetic architecture, genome-wide association and differential gene expression. *PlosOne, 10*(8), e0134865

Geracioti, T. D., Baker, D. G., Ekhator, N. N., West, S. A., Hill, K. K., Bruce, A. B., . . . Kasckow, J. W. (2001). CSF norepinephrine concentrations in posttraumatic stress disorder. *American Journal of Psychiatry, 158,* 1227–1230.

Goodman, W. K. (2004). Selecting pharmacotherapy for generalized anxiety disorder. *J. Clin.Psychiatry, 65*(113), 8–13.

Gottschalk, M. G., & Domschkle, K. (2017), Genetics of generalized anxiety disorder and related traits. *Dialogues in Clinical Neuroscience, 19,* 159–168.

Hoffman, D. L., Dukes, E. M., & Wittchen, H. U. (2008). Human and economic burden of generalized anxiety disorder. *Depression and Anxiety, 25,* 72–90.

Kagan, J., & Snidman, N. (1999). Early childhood predictors of adult anxiety disorders. *Biological Psychiatry, 46,* 1536–1541.

Kessler, R. C., Aguilar-Gaxiola, S., Alonso, J.,Chatterji, S., Lee, S., Ormel, J., et al. (2009). The global burden of mental disorders: An update from the WHO World Mental Health (WMH) Surveys. *Epidemiology and Psychiatric Services, 18*, 23–33.

Kessler, R. C., Chiu, W. T., Demler, O., & Walters, E. E. (2005). Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. *Arch.Gen. Psychiatry, 62*, 617–27.

Kessler, R. C., Chiu, W. T., Jin, R., Ruscio, A. M., Shear, K., & Walters, E. E. (2006). The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. *Archives of General Psychiatry, 63*, 415–424.

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behavioural Brain Research*. doi: 10.1016/j.bbr.2011.04.025

Kim, M. J., Loucks, R. A., Palmer, A. L., Brown, A. C., Solomon, K. M., Marchante, A. N., & Whalen, P. J. (2011). The structural and functional connectivity of the amygdala: From normal emotion to pathological anxiety. *Behavioural Brain Research*. doi: 10.1016/j. bbr.2011.04.025

Koerner, N., & Dugas, M. J. (2008). An investigation of appraisals in individuals vulnerable to excessive worry: The role of intolerance of uncertainty. *Cog. Ther. Res.*, *32*(5), 619–38. doi:10.1007/s10608-007-9125-2

MacLeod, C., & Mathews, A. (2012). Cognitive bias modification approaches to anxiety. *Annu. Rev. Clinical Psychology, 8*, 189–217.

Malizia, A. L. (2003). Brain imaging and anxiety disorders. In D. Nutt & J. Ballenger (Eds.), *Anxiety disorders* (pp. 201–228). Malden, MA: Blackwell.

McLaughlin, K. A., Borkovec, T. D., & Sibrava, N. J. (2007). The effects of worry and rumination on affect states and cognitive activity. *Behavior Therapy, 38*(1), 23–38.

Mennin, D. S., Heimberg, R. G., & Turk, C. L. (2004). Clinical presentation and diagnostic features. In R. G. Heimberg, C. L. Turk, & D. S. Mennin (Eds.), *Generalized anxiety disorder* (pp. 3–28). New York: Guilford.

Mineka, S. (2004). The positive and negative consequences of worry in the aetiology of generalized anxiety disorder: A learning theory perspective. In J. Yiend (Ed.), *Cognition, emotion and psychopathology: Theoretical, empirical and clinical directions* (pp. 29–48). New York: Cambridge University Press.

Mineka, S., & Zinbarg, R. (1998). Experimental approaches to the anxiety and mood disorders. In J. G. Adair, D. Belanger, & K. L. Dion (Eds.), *Advances in psychological science: Vol. 1. Social, personal, and cultural aspects*. (pp. 429–454), Psychology Press, East Sussex, UK

Mowrer, O. H. (1947). On the dual nature oflearning—A reinterpretation of "conditioning"and "problem-solving." *Harvard Educational Rev.,17,* 102–48.

Nutt, D., Argyropoulos, S., Hood, S., & Potokar, J.(2006). Generalized anxiety disorder: A comorbid disease. *European Neuropsychopharmacology, 16*(2),109–18.

Öhman, A., & Soares, J. J. F. (1994). "Unconscious anxiety": Phobic responses to masked stimuli. *Journal of Abnormal Psychology, 103,* 231–240.

Roemer, L., Orsillo, S. M., & Barlow, D. H. (2002).Generalized anxiety disorder. In D. H. Barlow (Ed.), *Anxiety and its disorders: The nature and treatment of anxiety and panic* (pp. 477–515). New York: Guilford.

Roy-Byrne, P. P., Davidson, K. W., Kessler, R. C., Asmundson, G. J., Goodwin, R. D., Kubzansky, L., . . . Stein, M. B. (2008). Anxiety disorders and comorbid medical illness. *General Hospital Psychiatry, 30*(3), 208–225. doi:10.1016/j.genhosppsych.2007.12.006

Shin, L. M., Wright, C. I., Cannistraro, P. A., Wedig, M. M., McMullin, K., Martis, B., . . . Rauch, S. L. (2005). A functional magnetic resonance imaging study of amygdale and medial prefrontal cortex responses to overtly presented fearful faces posttraumatic stress disorder. *Archives of General Psychiatry, 62,* 273–281.

Staugaard, S. R. (2010). Threatening faces and social anxiety: A literature review. *Clinical Psychology Review, 30*(6), 669–690. doi: 10.1016/j.cpr.2010.05.001

Stein, D. J., Ipser, J. C., & Balkom, A. J. (2004). Pharmacotherapy for social anxiety disorder. *Cochrane Database of Systematic Reviews*, CD001206. doi: 10.1002/14651858.CD001206.pub2

Wilson, E. J., MacLeod, C., Mathews, A., & Rutherford, E. M. (2006). The causal role of interpretive bias in anxiety reactivity. *J. Abn. Psych., 115*(1), 103–11.

Yehuda, R., & LeDoux, J. (2007). Response variation following trauma: A translational neuroscience approach to understanding PTSD. *Neuron, 56*(1), 19–32. doi: 10.1016/j.neuron.2007.09.006

Yonkers, K. A., Dyck, I. R., Warshaw, M., & Keller, M. B. (2000). Factors predicting the clinical course of generalised anxiety disorder. *British Journal of Psychiatry, 176*, 544–549.