CHAPTER 19.

FEAR AND ANXIETY

Introduction

“It remains unclear whether anxiety states are to be better conceptualized as several putatively distinct diagnostic entities or as one broadly conceived syndrome within which there are no clear boundaries between various manifestations of anxiety”


“Worry is a down payment on a problem you may never have”

Joyce Meyer

Arousal.
Applies to the total organism, it refers to a state of readiness for activity, and involves increased sensory excitability, muscular tone and sympathetic and endocrine activity.

Anxiety
Most non-medical dictionaries define anxiety in this manner: “a feeling of worry, nervousness, or unease about something with an uncertain outcome”

Non-medical synonyms for anxiety include “worry”.

This is consistent with medical definitions:
“Anxiety is a general term for several disorders that cause nervousness, fear, apprehension, and worrying.”

Thus, at the current time, the terms “worry” and “anxiety” are interchangeable.

In earlier textbooks anxiety disorders were conceptualized as requiring two sets of symptoms - cognitive (worry) and somatic (tremor, sweating, palpitations, etc.). This continues to be the case with the current International Classification of Disorders (ICD 10). However, in the DSM5, somatic symptoms in the form of those mentioned above, need not be present.

Normal anxiety
Normal anxiety has been applied to states of arousal/anxiety which occur in everyday life, in response to stimuli. It has an adaptive role and is a signal to take action. In normal anxiety the assessment of the danger is appropriate and the action taken is effective. The healthy person who has lost her/his pay-packet will be anxious about paying outstanding bills.

Experiencing occasional anxiety is a normal part of life (Mayo Clinic, 2015).

Fear is generally regarded to be an extreme form of normal anxiety. If an intruder comes into the house, most healthy persons will be fearful.
Pathological anxiety
Pathological anxiety is diagnosed when there is excessive assessment of danger. The individual may be unable to make any response, or make an excessive protective response. The person with pathological anxiety may be so disabled that he/she is unable to conduct his/her usual duties, such as prepare a meal, or overestimate a danger and make maladaptive adjustments (the person who is unduly anxious about lifts will have to take the stairs).

“Pathological worrying is incessant and fruitless overthinking that inhibits problem solving and decision making” (Starcevic, 2015).

Normal anxiety vs. pathological anxiety.
One perspective is that normal anxiety is a normal response to an abnormal situation (anxiety at being threatened by a mugger) and pathological anxiety is an abnormal response to a normal situation (anxiety at needing to leave the home). However, this is too sensible to be widely embraced.

At the current time, the distinction between “normal” and “pathological” worry/anxiety is arbitrary and depends on frequency and degree of arousal.

Stress
Stress refers to external stimuli to which there is need to adapt. In a stressful situation there may be a number of separate stressors. Stress is also used as a term to describe the state of being when subjected to stress (under stress; feeling stressed). It is unclear whether there is a difference between “feeling stressed” and “feeling anxious”.

Yerkes-Dodson law (1908) has face validity in everyday life. This “law” describes a relationship between arousal and performance. As arousal increases so performance increases/improves, to a certain point, beyond which, as arousal continues to increase, performance deteriorates. Sports coaches say that when the spots-person does not feel some pre-games “nerves/tension” they do not perform at their best. Some even advise that when pre-game tension is no longer experienced, it is time to retire.

When performance anxiety (stage-fright) is excessive, and causes instrumentalists performs poorly, some take beta-blockers to reduce hand trembling.

Illustration. The Yerkes-Dodson Law. As arousal increases, so does performance, to a certain point, beyond which increasing anxiety impairs performance.
DSM-5 Anxiety Disorders

DSM-5 lists the following anxiety disorders. Not all will be considered here.
- Separation anxiety
- Selective mutism (in children)
- Specific phobia
- Social anxiety disorder
- Panic disorder
- Agoraphobia
- Generalized anxiety disorder

GENERALIZED ANXIETY DISORDER (GAD)

The diagnostic criteria of GAD are listed below. The first criterion is “Excessive anxiety…about a number of events or activities”. This wording is not clear, but refers not to events or activities which have occurred, but to (unwelcome) events and activities which may occur in the future. GAD symptoms have also been described as “unspecified or free-floating”, and often, the patient cannot identify what “is making” them anxious.

GAD is common and can be disabling. It has high rates of comorbidity, commonly occurring along with depression and other forms of anxiety. It is also associated with alcohol abuse, suicidality and high use of health care resources (Brown et al, 2001). Symptoms of GAD may lead to various primary care complaints including fatigue, sleep disturbance and chronic pain. GAD is a chronic condition which waxes and wains, and relapse is common.

DSM-5 Criteria for GAD

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 activities).
B. The person finds it difficult to control the worry.
C. The anxiety and worry are associated with three (or more) of the following
   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.

Epidemiology

The 12 month prevalence of GAD in a community sample was 3.8% (Blazer et al, 1991). The lifetime prevalence has been estimated as 5-7% (Kessler et al, 2005).

GAD is twice as common in females.
Comorbidity
Over 2/3 (68%) of individuals with GAD have an additional diagnosis – most commonly, other anxiety disorders and depression. One study found personality disorder in 49% of people with GAD (Sanderson et al, 1994).

Theoretical aetiological models
Models of GAD have been advanced by various schools of thought. No single model is appropriate in every case, and perhaps all models have something to contribute to every case.

Biological models postulate people are predisposed to develop anxiety disorders by genetic inheritance. More recently, it has become clear that epigenetic factors/mechanisms impact on gene expression.

Behavioural models are based on the learning theory. These are often criticized as simplistic (Starcevic, 2005). Nevertheless, the therapy based on these models (behaviour therapy) has much to offer.

Cognitive models of anxiety disorders emphasize the role of specific beliefs and modes of thinking in influencing the experience of emotion.

The psychodynamic models depend on concepts that are now often considered untenable (Starcevic, 2005). They propose anxiety occurs as a result of intrapsychic conflicts between sexual or aggressive urges and defences against these urges.

Genetic factors
Genetic factors appear to play a modest role in the aetiology of GAD. It is five times more common in the first-degree relatives of index cases than among the first-degree relatives of controls (Noyes et al, 1987). One study of twins concluded that GAD was moderately heritable (Mackintosh et al, 2006). There is a shared heritability for GAD and mood disorders (Kendler et al, 1992a), and recent the genetic risk for “internalizing psychiatric disorder” (mood and anxiety disorders) was estimated as 50% (Kendler et al, 2011).

Genetic variation of the corticotropin-releasing hormone receptor 1 (CRHR1) gene appears to increase the risk of anxiety disorders (Rogers, 2013).

Epigenetics
Epigenetics is of great interest throughout psychiatry – a process by which gene expression can be altered without alteration of the DNA sequence. All anxiety disorders may be influenced by experience, and evidence suggest that some anxiety disorders may be underpinned by epigenetic marks/mechanisms (McGhee and Bell, 2014; Hommers et al, 2015).
Neurobiological mechanisms

The neurobiology of anxiety and anxiety disorders is yet to be fully explained. The next few paragraphs come from Nuss (2015).

The amygdala, in the median temporal lobe, is activated by threatening stimuli. Patients with anxiety disorders activate the amygdala in response to given stimuli more than non-anxious controls.

It is composed of a number of nuclei, including the basolateral amygdala complex (BAL) and the central nucleus of the amygdala (CeA). See the Illustration. The BAL receives negative emotional signals from the thalamus, and the sensory association cortex. It (BAL) activates the CeA, which in turn activates the bed nucleus of the stria terminalis (BNST).

Neurons from both the CeA and the BNST project to the brainstem, hypothalamus and basal forebrain. Activation of the brainstem and hypothalamus structures produces the somatic manifestations of anxiety (tachycardia etc). Activation of basal forebrain nuclei (ventral tegmental area and locus ceruleus) may produce the dysphoria of anxiety.

Further, the medial prefrontal cortex (mPFC) and anterior cingulate cortex (ACC) both send input to and receive input from the BAL. The mPFC can modulate the activity of the BLA (and the anxious experience). The mPFC may enable conscious and unconscious control of anxiety.

[Neurosteroids (neuroactive steroids) have recently been described, and may have a role in anxiety (Nuss, 2015). Pregnenolone, which is secreted by the adrenals is an example; others are believed to be produced by nervous system cells.]
The above illustration is provided for any trainee psychiatrist who may be slumming. It is not for medical students. The subgenual cortex refers to the cortex inferior to the anterior bend (L. genu = knee) of the corpus callosum. Palomero-Gallagher et al (2015), using cytoarchitectural methods have identified region s32 as being associated with fear processing (and s24 as being associated with sadness).

**Neuroimaging**
In GAD, amygdala connection variations have been observed, including increased connectivity to the parietal lobe, and decreased connection with the insula and cingulate. Further, the CeA may have increased volume (Etkin et al, 2009).

A recent DTI study (Trop do, et al, 2012) found bilateral decreased functional connectivity between the anterior cingulate cortex and the amygdala – specifically, in GAD; the integrity of the uncinate fasciculus was reduced. This was not observed in other white matter tracts.

Gray matter in anxiety has also been studied. Alemany et al (2013) report volume reductions observed in the bilateral fusiform gyrus and the amygdala in mz twins concordant for anxiety.

**Psychosocial mechanisms**
Stressful life events may trigger GAD. The greater the number of negative life events experienced, the greater the likelihood of GAD (Blazer et al, 1987).

Early life experiences are important. A healthy parent-child relationship leads to the child developing a sense of control over the environment and a repertoire of adaptive responses. In the absence of such a relationship and development, the child may be vulnerable to anxiety (Chorpita & Barlow, 1998).

Such findings are supported by epigenetic research.
Prognosis
GAD is a chronic disorder. In a large study (Yonkers et al, 1996), the mean age of onset was 21 years and the average duration was 20 years. Although 80% received treatment, only 15% remitted after one year, and 27% had remitted after 3 years.

Remission rates are even lower in the presence of comorbid psychiatric disorders.

Treatment
Self-help books and activities may have a place (Hirai & Clum, 2006).

Psychological treatments take many forms, from a behavioural approach at one end of the spectrum, to psychodynamic psychotherapy at the other. Most therapists would claim to use some form of cognitive behaviour therapy (CBT). The original feature of cognitive therapy was the challenging of illogical and self-defeating thinking. However, the term CBT has absorbed a number of earlier stand alone treatments such as relaxation therapy, hypnosis, patient education, and even systematic desensitization (once the cornerstone of behaviour therapy), and it has emerged into an eclectic, and effective, active treatment.

Acceptance and Commitment Therapy (ACT) is an emerging form of talking therapy (based unsurprisingly on acceptance and commitment, and employing mindfulness and behaviour change) which is proving effective (A-Tjak et al, 2015).

Pharmacological treatments are helpful in the majority of cases. Alcohol is the most widely used substance in the management of anxiety - however, long-term use worsens anxiety and precipitates depression, in addition to serious physical consequences, and is discouraged. Antianxiety drugs are described in a separate chapter. Until recent years the term antianxiety drugs was synonymous with benzodiazepines. However, for various reasons (some substantiated and others not) various antidepressants (escitalopram, fluoxetine, paroxetine, sertraline and venlafaxine) are now regarded to be the first line pharmacological agents (Canadian et al, 2006).

PANIC DISORDER
The term panic comes from the Greek god, Pan. He was the god of music, sensuality and sexuality. He was also the god of nightmares, and took pleasure in frightening (panicking) people in the woods. Panic symptoms were first described by Hippocrates circa 400 BC, and panic is known in all cultures. Modern accounts were recorded in the 19th century. Charles Darwin suffered panic disorder (Noyes & Barloon, 1997), but it was not until the 1960’s that the high prevalence and disability which may accompany the disorder began to be fully recognized.
Illustration. Pan, a Greek god who enjoyed frightening (panicking) people and animals. He was (perhaps is) part man and part goat (ears, legs and horns).

**DSM-5 Diagnostic criteria for Panic disorder**

A. Recurrent unexpected panic attacks – abrupt surge of intense fear which reaches a peak in 4 minutes, and includes 4 or more of the following:

1. palpitations
2. sweating
3. trembling or shaking
4. shortness of breath or sensation of smothering
5. feeling of choking
6. chest pain or discomfort
7. nausea or abdominal distress
8. feeling dizzy, unsteady, light-headed, or faint
9. derealization (feelings of unreality) or depersonalization (being detached from oneself)
10. fear of losing control or going crazy
11. fear of dying
12. paresthesia (numbness or tingling sensations)
13. chills or hot flushes

B. At least one of the attacks has been followed by 1 month of one or both:

1. Persistent concern about additional attacks
2. Maladaptive change in behaviour related to attacks (designed to avoid attacks, such as avoiding unfamiliar situations)
AGORAPHOBIA

Agoraphobia is anxiety about, or avoidance of, places from which escape might be difficult (or embarrassing), or places where help may not be available. (It derives from the Greek, “agora”, meaning market place - the place where agricultural products are sold).

DSM-5 diagnostic criteria Agoraphobia

A. Marked fear/anxiety about two or more of the following situations:
   1. Using public transport
   2. Being in open spaces
   3. Being in enclosed spaces
   4. Standing in line or being in a crowd
   5. Being outside of the home alone

B. Avoids these situations because of thoughts that help might not be available.

PANIC DISORDER AND AGORAPHOBIA

Panic disorder and agoraphobia are now considered separate disorders. However, they frequently co-exist. Evidence suggests there can be a two-way causal relationship (Bienvenu et al, 2006).

The conceptualization has treatment implications. Where panic attack is considered primary, treatment often involves education and relaxation exercises. Where the phobic component is considered primary, treatment often involves some form of exposure therapy. However, both approaches can be applied simultaneously.
Prevalence
Panic attacks are common. A recent study found the lifetime prevalence of panic disorder to be 4.7% (Kessler et al, 2005). Females are twice as commonly affected. There are two onset peaks, one in early adult life (14-24 yrs) and one in middle age (45-54 yrs). Onset after 65 years is rare.

Genetics
There is a genetic predisposition to panic attacks and agoraphobia. For panic disorder the concordance rates in monozygotic is 2-3 times higher than in dizygotic twins. In a population based twin study the estimated heritability component of panic disorder was 30-40% (Kendler et al, 2001). Other evidence suggests a 50% genetic and 50% environmental influence, polygenetic inheritance and heterogeneity across families (Schumacher et al, 2011).

A recent study (Konishi et al, 2014) indicates that a brain derived neurotrophic factor (BDNF) gene polymorphism may increase trait anxiety in panic disorder.

Epigenetics
Patients with panic disorder exhibit significantly lower glutamate decarboxylase promoter methylation than healthy controls (Domschke et al, 2013).

Cannabis
Research (Zvolensky et al, 2006) suggests a lifetime history of cannabis use is significantly associated with an increased risk of panic attacks. Those with a lifetime history of both panic attacks and cannabis use have a significantly lower age of onset of panic (19 years) than those with a lifetime history of panic attack and no cannabis abuse (28 years). The causal direction is unknown. It may be that those who are predisposed to develop panic treat themselves with cannabis; on the other hand, it may be that cannabis abuse triggers panic attacks.

Neurotransmitters
Evidence supports an etiological role for the noradrenalin pathways and the locus ceruleus (LC) in panic disorder. Most effective antianxiety drugs decrease LC firing.

A role for serotonin pathways in panic disorder is suggested by the observation that SSRIs have beneficial effects, and a role for gamma-aminobutyric acid (GABA) pathways is suggested by the beneficial effects of the benzodiazepines.

Prognosis
The disorder tends to a chronic relapsing course. Recovery rates vary from 25-75% in 1-2 year follow-up studies. In pharmacological trials, 50-70% of patients have an excellent acute response. In behavioural therapy programs, some trials have indicated improvement in 75% of patients at up to 9 years follow-up. While not symptom free, after some form of treatment, the majority make a functional recovery.

Treatment
Self-help books and activities have a place (Hirai & Clum, 2006).

The cessation of cannabis use is a sensible early treatment step.
Non-pharmacological treatments include exposure therapy, psychodynamic psychotherapy and cognitive-behaviour therapy (CBT). Exposure therapy includes gradual exposure (systematic desensitization) and rapid exposure (flooding). In large studies of exposure therapy, about 75% of patients have become symptom free, and this status has remained for years. Unfortunately, this therapy is anxiety-provoking and 25% of patients may drop out. Psychodynamic psychotherapy remains popular, but little research has been conducted on efficacy in panic disorder and agoraphobia. CBT is based on the theory that patients with panic disorder misinterpret their symptoms, and therapy focuses on challenging these misinterpretations. As with GAD above, ACT is an emerging treatment.

The pharmacological treatment of anxiety disorders is covered in a separate chapter. The benzodiazepines are effective, but have been relegated to second line status. The SSRIs and the selective noradrenalin and serotonin reuptake inhibitor, venlafaxine, are effective, lack the potential for addiction and are generally considered the medications of first choice.

Evidence suggests that pharmacological and non-pharmacological therapies have roughly equal efficacy. The advantage of non-pharmacological therapies (particularly CBT) is that they appear to have a lower rate of relapse. The advantage of pharmacological therapy is a more rapid onset of relief. Some patients find either pharmacological or non-pharmacological treatment unacceptable, but the other acceptable. Each form has clinician and patient supporters. Combined pharmacological and non-pharmacological treatment was considered to improve response, but this is not supported by evidence.

SOCIAL ANXIETY DISORDER

There are many phobias (morbid fear or dread). From the clinical perspective a phobia is characterized by a fear which is persistent and intense, there is a compelling desire to flee or avoid the phobic place/object, and the fear is irrational. Agoraphobia (anxiety triggered by the thought of, or being in particular environments) has been described above.

Social phobia is the experience of intense fear of being negatively evaluated by others or of being publicly embarrassed because of impulsive acts.

DSM criteria of Social anxiety disorder

A. A marked of persistent fear of one or more social situations in which the individual is exposed to the possible scrutiny by others – conversation, observed eating, giving a speech.
B. The individual fears that he or she will act in a way or show anxiety symptoms that will be humiliating or embarrassing.
C. The social situation almost always provokes fear or anxiety.
D. These situations are avoided or endured with intense anxiety.
E. The anxiety is out of proportion to the actual threat.
F. The person recognizes that the fear is excessive or unreasonable.
G. Etc.
Social phobia has the highest **prevalence** of the phobias (and is the third most common psychiatric disorder, following depression and alcohol abuse). The lifetime prevalence is 8-12% (Shields, 2004). Social phobia is more common in **females** (as with other anxiety disorders). **Age of onset** is early, with two peaks, at 0-5 years and 11-15 years.

Resulting **disability** may be very high. People with social phobia may remain single and discontinue their education prematurely more often than people without this disorder (Schneier et al, 1994).

Psychological and physiological evidence indicates that **eye contact** with another person is aversive and arousing for adolescents with social anxiety disorder (Myllyneva, et al, 2015).

**Comorbidity** with other psychiatric disorders is very high (Liebowitz et al, 2005), and increases disability.

**Genetic factors** account for 1/3 of the variance in transmission. A major twin study found the concordance was greater for monozygotic (24.4%) than for dizygotic (15.3%) twins (Kendler et al, 1992b). Environmental factors are also important.

**Neuroimaging**: a meta-analysis of functional imaging (Etkin & Wagner 2007) in social anxiety disorder, specific phobia and PTSD found that in all three disorders, hyperactivity was identified in the amygdala and insula.

A study (Liao et al, 2011) found, in social anxiety disorder, decreased grey matter volumes. However Frick et al (2013) found significantly increased thickness of the left inferior temporal cortex in social anxiety disorder relative to controls, and a negative association was found between social anxiety symptom severity and thickness of the right rostral anterior cingulate cortex.

The **course** is chronic and unlikely to remit without treatment.

**Treatment** with antianxiety medication and CBT which involves a component of exposure may be beneficial. Pharmacological treatment gives more rapid relief, CBT treated patients are at less risk of relapse.

**Demarcation** between shyness and social phobia may be difficult/impossible. Non-generalized social phobia, is a term applied when symptoms are limited to specific situations such as public speaking. Interestingly, most individuals believe they are more nervous than others (Stein et al, 1994). There is a risk of medicalizing the human condition. Diagnosis should be limited to situations where individuals experience “significant distress and functional impairment”.
SPECIFIC PHOBIA

The specific phobias feature marked and persistent fears which are excessive to any risks. Commonly feared objects include animals, insects, heights, injections/blood, and dental procedures, etc.

DSM-5 criteria of specific phobia
A. Marked fear or anxiety about a specific object or situation (flying, spiders, injections)
B. The phobic object or situation almost always provokes immediate fear.
C. Phobic object avoided or endured with intense anxiety
D. Fear is out of proportion to the actual danger
E. Etc.

Many individuals with simple phobias are able to live a relatively normal life, making minor adjustments to avoid the feared object.

Sub-classification
1. animal type
2. natural environment type
3. situational type
4. blood/injection type (see next entry)
5. other type

Comorbidity with other psychiatric disorders is very high (>80%; Mannuzza et al, 1990). Specific phobias tend to co-occur with other specific phobias.

Lifetime prevalence is >10% (Kessler et al, 2005). Most common are the situational/environmental phobias, followed by animals and injection/blood phobias.
Age of onset appears to vary with the nature of the phobia. Animal phobia has the earliest age of onset +/- 7 years of age.

Genetic contributions are detectable, but also vary with the nature of the phobia.

Experiential/learning factors are also important.

Neuroimaging: Functional neuroimaging, using symptom provocation paradigms, has shown abnormal activations in brain areas involved in emotional perception and early amplification - mainly the amygdala, anterior cingulate cortex, thalamus, and insula (Del Casale et al, 2012). Different neural substrates may differentiate SPs from other anxiety disorders and separate SP subtypes from one another.

Treatment. Specific phobias are the most treatable of the anxiety disorders. CBT with an exposure component is recommended. The latter may be imaginal or in vivo. The latter may be difficult to arrange, in which case imaginal exposure is an effective alternative. Relaxation during exposure is an important component. Benzodiazepines have been used to reduce anxiety to enable patient co-operation with exposure.

BLOOD/INJECTION PHOBIA

Blood/injection phobia appears to be a special case. In all other phobias, exposure is associated with increased sympathetic activity - with elevated BP and pulse. In blood/injection phobia, following brief sympathetic activity, parasympathetic activity predominates, leading to vasovagal syncope. This is most puzzling.

Accordingly, rather than maximal relaxation during exposure, patients are instructed to tense different muscle groups, thereby counteracting parasympathetic overactivity (Ost et al, 1991).
HAMILTON RATING SCALE FOR ANXIETY (HAM-A)

The HAM-A (Hamilton, 1959) is the most widely utilized assessment scale for anxiety symptoms. It is intended for use with people who have already been diagnosed with anxiety (that is, it is not a diagnostic tool, but a means of quantifying the experience of the patient). It is heavily focused on somatic symptoms and places reliance on the subjective report of the patient. The strengths of the HAM-A are that it is brief and widely accepted. The weaknesses are the focus on somatic symptoms and reliance on patient report. A printable version is freely available at www.cnsforum.com.

Illustration. The Hamilton Rating Scale for Anxiety (HAM-A).
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