

## **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”*

**Vladan Starcevic (2006).**

#### **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.

#### **Fear**

is a response to a real imminent threat (Crocq, 2015).

#### **Normal fear**

is adaptive. If an intruder comes into the house, most healthy persons will be fearful.

#### **Anxiety**

is the anticipation of future threat.

#### **Normal anxiety**

is 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. The healthy person who has lost her/his pay-packet will be anxious about paying outstanding bills.

#### **Pathological anxiety**

is diagnosed when there is excessive assessment of danger. The individual with pathological anxiety may be unable to make any response, or make an excessive protective response.

#### **Worry**

refers to the cognitive aspects of apprehensive expectation.

#### **Pathological worrying**

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

#### **Normal anxiety vs. pathological anxiety.**

Let’s not waste too much time on this distinction.

One view 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 about leaving the home).

## Stress

The word 'stress' is used in different ways. It can refer to external stimuli to which there is need to adapt – and in a stressful situation there may be a number of separate **stressors**. It is also used as a term to describe the state of being when subjected to stress ('I feel stressed'). Let's not 'worry' about whether there is a difference between "feeling stressed" and "feeling anxious".

### Yerkes-Dodson law (1908)

describes a relationship between arousal and performance. As arousal increases so performance increases/improves, to a certain point, beyond which, if arousal continues to increase, performance deteriorates. Sports coaches say that when the sports-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.

On the other side - when performance anxiety (stage-fright) is excessive, performance deteriorates (so, some performers use musical instrument players use beta blockers).

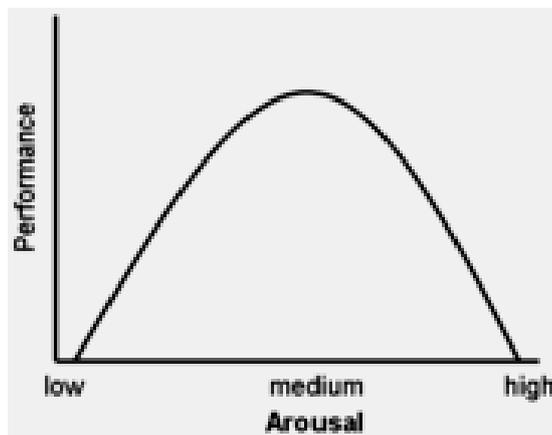


Illustration. The Yerkes-Dodson Law. As arousal increases, so does performance, to a certain point, beyond which increasing anxiety impairs performance.

## DSM-5 Anxiety Disorders

The way pathological anxiety has been classified has varied over time. (The disorders listed under OCD and stress-related disorders were once classified under pathological anxiety). The 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 refers not to events or activities which have occurred, but to (unwelcome) events and activities which might 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% (Kessler et al, 2012). The lifetime prevalence has been estimated as 5-7% (Kessler et al, 2005).

GAD is twice as common in females (Brandelow and Michaelis, 2015).

### **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).

### **Psychoanalytic model**

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.

### **Behavioural models**

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 model**

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

### **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 controls (Noyes et al, 1987). One study of twins concluded that GAD was moderately heritable (Mackintosh et al, 2006).

However, little progress has been made (Smoller, 2017).

### **Epigenetics**

All anxiety disorders may be influenced by experience. Given the high heritability and lack of a genetic explanation – there may be a role for epigenetic factors (Bartlet et al, 2017; Schiele & Domschke, 2018).

### **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 central nucleus of the amygdala may have increased volume (Etkin et al, 2009).

A DTI study (Tromp 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.

Alemanly et al (2013) reported volume reductions observed in the bilateral fusiform gyrus and the amygdala in monozygotic twins concordant for anxiety.

Yang et al (2018) reported reduced functional connectivity in right supramarginal gyrus (parietal lobe, Brodmann area 40) and the superior parietal gyrus/lobule (Brodmann area 5&7). They also they reported reduced connectivity between the supramarginal gyrus and a wide range of other structures.

Macpherson & Hikida (2019) reviewed generalized anxiety disorder and report PET studies have revealed decreased metabolic activity in the putamen and globus pallidus, reduced dopamine transporter levels in the striatum, and functional connectivity abnormalities in the basal ganglia similar to those of major depressive disorder.

### **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).

### **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.

### **Treatment**

**Psychological treatments** take many forms, commencing with psychodynamic psychotherapy more recently extending to cognitive behaviour therapy (CBT) and related approaches more recently.

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). ACT has been successful when internet-delivered (Kelson et al, 2019).

Some evidence suggest Mindfulness-based therapy is effective in the treatment of GAD (Navarro-Haro et al, 2019).

**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 chapter 17. In the first half of the 20<sup>th</sup> century, barbiturates were extensively used in the treatment of anxiety. However, these were found to be fatal in overdose – and benzodiazepines became the drugs of first choice. The benzodiazepines were then identified as ‘addictive’ and use is strongly discouraged. [In the opinion of the current author, this risk has been greatly exaggerated (Blanco et al, 2018).

The antidepressants (escitalopram, paroxetine, sertraline and venlafaxine) are now considered to be the first line pharmacological agents (Canadian et al, 2006).

Interestingly, anxiety disorders are the leading justification for the supply of **cannabis** for medicinal purposes in Canada (Turna et al, 2019) and possibly elsewhere.

## 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 19<sup>th</sup> century. Charles Darwin suffered panic disorder. 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. paraesthesia (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 – fear of leaving home and going out into public spaces).

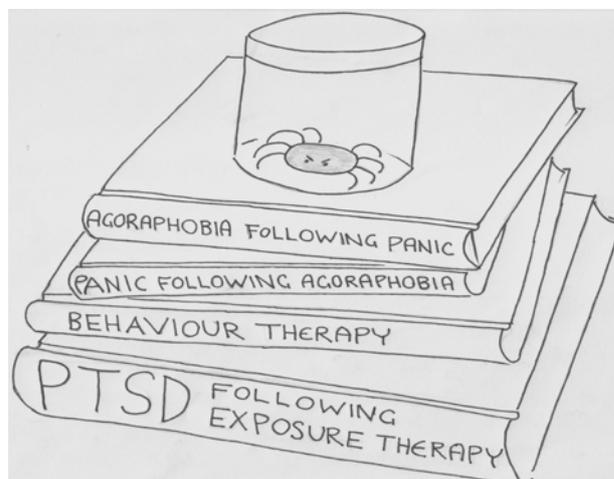
### DSM-5 diagnostic criteria Agoraphobia

- 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. Evidence suggests a 50% genetic and 50% environmental influence, with polygenetic inheritance and heterogeneity across families (Schumacher et al, 2011).

A meta-analysis suggests the Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) gene is a susceptibility factor for panic disorder (Chen et al, 2017).

### **Epigenetics**

See GAD

### **Cannabis**

Research (Zvolensky et al, 2006) suggests a lifetime history of cannabis use is significantly associated with an increased risk of panic attacks. 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.

This is a matter of concern – as mentioned under GAD - anxiety disorders are the leading justification for the supply of **cannabis** for medicinal purposes in Canada (Turna et al, 20119).

### **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**

The cessation of cannabis use is a sensible early treatment step.

**Psychological** 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.

**Pharmacological** treatment – see GAD.

**Psychological and pharmacological** therapies have roughly equal efficacy. The advantage of non-pharmacological therapies (particularly CBT) is that they appear to provide 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 (PHOBIA)**

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.

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 are the 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 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 and increases disability.

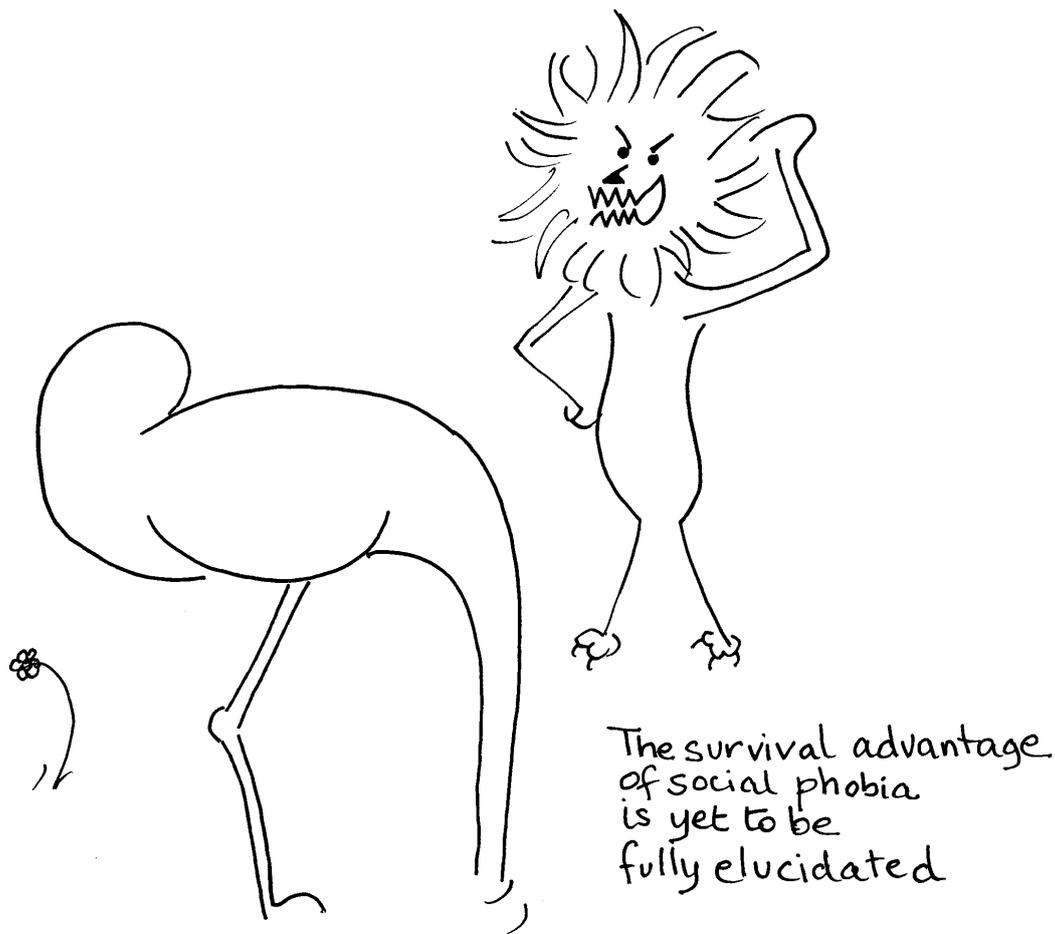
**Genetic factors** account for 1/3 of the variance in transmission. A major twin study found the concordance was greater for monozygotic (24.4%) than for dizygotic (15.3%) twins (Kendler et al, 1992). Environmental factors are also important.

**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.

Studies have suggested Social anxiety disorder is associated with more reactive (Kraus et al, 2018) and smaller (Foell et al, 2019) amygdala.

**Treatment** with antianxiety medication and CBT which involves a component of exposure may be beneficial.

**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. There is a risk of musicalizing the human condition.



[On seeing this cartoon, Prof Dan J Stein made contact and drew attention to his important paper on the topic (Stein & Bouwer, 1997).]

## **SPECIFIC PHOBIA**

The central 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 is avoided or endured with intense anxiety
- D. Fear is out of proportion to the actual danger
- E. See the DSM-5 for unnecessary details.

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.

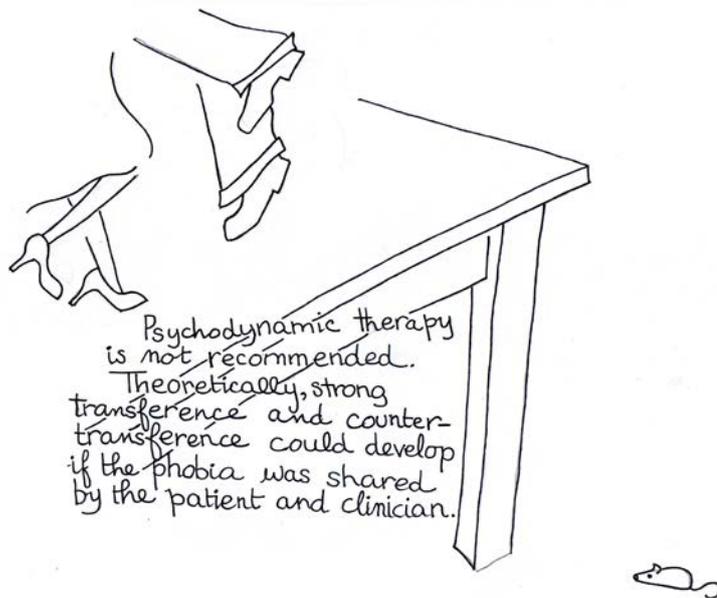
**Age of onset** appears to vary with the nature of the phobia. Animal phobia has the earliest age of onset +/- 7 years of age.

**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).

**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 (Sanchez-Navarro et al, 2018). This is most puzzling.

## **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](http://www.cnsforum.com).

## Hamilton Anxiety Rating Scale (HARS)

**Instructions:** This checklist is to assist the physician or psychiatrist in evaluating each patient as to his/her degree of anxiety and pathological condition. Please fill in the appropriate rating:

- 0 = None
- 1 = Mild
- 2 = Moderate
- 3 = Severe
- 4 = Severe, grossly disabling

Item	Symptoms	Rating
<b>Anxious mood</b>	Worries, anticipation of the worst, fearful anticipation, irritability	
<b>Tension</b>	Feelings of tension, fatigability, startle response, moved to tears easily, trembling, feelings of restlessness, inability to relax	
<b>Fears</b>	Of dark, of strangers, of being left alone, of animals, of traffic, of crowds	
<b>Insomnia</b>	Difficulty in falling asleep, broken sleep, unsatisfying sleep and fatigue on waking, dreams, nightmares, night terrors	
<b>Intellectual (cognitive)</b>	Difficulty in concentration, poor memory	
<b>Depressed mood</b>	Loss of interest, lack of pleasure in hobbies, depression, early waking, diurnal swing	
<b>Somatic (muscular)</b>	Pains and aches, twitchings, stiffness, myoclonic jerks, grinding of teeth, unsteady voice, increased muscular tone	
<b>Somatic (sensory)</b>	Tinnitus, blurring of vision, hot and cold flushes, feelings of weakness, pricking sensation	
<b>Cardiovascular symptoms</b>	Tachycardia, palpitations, pain in chest, throbbing of vessels, fainting feelings, missing beat	
<b>Respiratory symptoms</b>	Pressure or constriction in chest, choking feelings, sighing, dyspnoea	
<b>Gastrointestinal symptoms</b>	Difficulty in swallowing, wind, abdominal pain, burning sensations, abdominal fullness, nausea, vomiting, borborygmi, looseness of bowels, loss of weight, constipation	
<b>Genitourinary symptoms</b>	Frequency of micturition, urgency of micturition, amenorrhoea, menorrhagia, development of frigidity, premature ejaculation, loss of libido, impotence	
<b>Autonomic symptoms</b>	Dry mouth, flushing, pallor, tendency to sweat, giddiness, tension headache, raising of hair	
<b>Behaviour at interview</b>	Fidgeting, restlessness or pacing, tremor of hands, furrowed brow, strained face, sighing or rapid respiration, facial pallor, swallowing, belching, brisk tendon jerks, dilated pupils, exophthalmos	
<p><b>Total HARS Score</b> In general the higher the total score of a patient the more severe is his/her anxiety. Assignment of an anxiety level to a particular HARS score is difficult because of rating variations between physicians. Nevertheless the total scores are useful for monitoring the progress of patients through periodic reassessment with this scale.</p>		<b>Total</b>

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

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