

Anxiety disorders

— the disease and non-drug treatment

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About a fifth of the European population will suffer from an anxiety disorder at some time during their life.

The first part of this month's special feature sets out the aetiology, epidemiology and diagnosis of these conditions and outlines their psychological management



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Anxiety is a normal, adaptive and protective physiological response to, for example, unpleasant or threatening situations. Hence moderate anxiety can be beneficial since it can improve performance or ensure that appropriate action is taken (the so-called “fight-flight” response). However, when excessive, pervasive and accompanied by other symptoms, anxiety can become pathological, causing significant morbidity, personal distress and impairment of daily functioning.

Anxiety-like states were described as early as the 17th century in Robert Burton's text ‘The anatomy of melancholy’. It was not until the latter part of the 20th century, however, that the separate anxiety disorders were formally recognised and diagnostic classification systems were developed. Hence the umbrella term “anxiety disorders” refers to a variety of disorders, including generalised anxiety disorder (GAD), obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), panic disorder and phobic disorders including social phobia (or social anxiety disorder), agoraphobia and specific (or simple) phobias. Anxiety disorders

are commonly under-recognised and under-treated, with only about 24 per cent of patients receiving therapy.¹

— Epidemiology

Anxiety disorders are prevalent in the community and more so in primary care and hospital settings. While they are present across different age ranges, they are comparatively less common in the elderly population.¹ The prevalence of anxiety disorders among those with chronic physical illnesses is much higher than among the general population.² Overall, all anxiety disorders are twice as common in females than in males.³

Different studies have shown varying prevalence rates of anxiety disorders, partly because of the different research methodologies used. Epidemiological (ie, population-wide) studies on adult populations have shown lifetime prevalence rates of about 21 per cent for the presence of any anxiety disorder. Phobic disorders, especially specific phobias, are particularly common among the anxiety disorders. Panel 1 (p114) shows the one year and lifetime prevalence rates of anxiety disorders, based on some reviews and large scale studies across Europe and the US.³⁻⁶

Separated, divorced and widowed people and single parents are more likely to suffer

from anxiety disorders than married or cohabiting couples.^{1,4} Most anxiety disorders have an onset between adolescence and the late 20s, with the frequency of occurrence showing a slight increase until the early 40s.⁴ In PTSD, symptoms usually start within the first month and, less frequently, up to six months after exposure to a life-threatening event, although uncommonly this can be even more delayed. Anxiety disorders tend to take a chronic and fluctuating course, with about 60 to 80 per cent of patients showing some degree of response to treatment.⁷ As well as causing distress, anxiety disorders are linked to increased mortality as a result of suicide, accidental death and alcohol and drug dependence or misuse, particularly when they co-exist with affective disorders.⁴

— Aetiology

Genetic factors Evidence for genetic inheritance originates from twin and family studies. These have shown, for example, that there is an increased risk of anxiety disorders like GAD, OCD, PTSD, panic disorder and phobias in the families of “proband” (ie, the person who serves as the starting point of a genetic study).^{4,5,8} In studies of OCD, concordance rates of 80 to 87 per cent in monozygotic and 47 to 50 per cent in dizygotic twins have been seen⁸ — the higher

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Panel 1: Prevalence rates for anxiety disorders

Anxiety disorder	One year prevalence rate	Lifetime prevalence rate
Any anxiety disorder	12 to 17 per cent	21 per cent
Generalised anxiety disorder	2 to 4 per cent	4 to 7 per cent
Obsessive-compulsive disorder	1 to 2 per cent	1 to 3 per cent
Post-traumatic stress disorder	1 per cent	8 per cent
Panic disorder	1 to 2 per cent	4 per cent
Phobic disorders		
Social phobia only	2 to 8 per cent	3 to 13 per cent
Agoraphobia only	1 to 6 per cent	4 to 9 per cent
Specific phobia	6 to 9 per cent	11 to 13 per cent

Prevalence rates are rounded off to the nearest integer

concordance rate among the monozygotic twins implying a large degree of genetic heritability. In addition, genetic factors are known to contribute to the development of PTSD symptoms.⁹ Twin studies have also demonstrated that panic disorder is moderately heritable.⁵ Probable genetic factors have also been suggested for phobic disorders.

The lack of 100 per cent concordance among monozygotic twins suggests the contribution of other elements to the aetiology of anxiety disorders, such as psychological and social factors.

— Psychosocial factors

There is evidence to suggest that abnormalities in cognitive patterns of thinking and behavioural responses contribute to the development of anxiety disorders. Learning theories emphasise different models, such as classical conditioning, operant conditioning and observational learning that can play a part in inducing and maintaining phobias, fear and anxiety.

Mowrer's "two stage model" was a pioneering and influential concept in explaining phobias.⁵ The first stage, a classical conditioning process, involves a neutral stimulus (for example, a dog) becoming a threatening stimulus triggering fear after being associated with an aversive stimulus (such as being bitten). The second stage, an operant conditioning process, proposes that the fear is then maintained by negative reinforcement — avoiding the threatening stimulus (the dog) prevents the unpleasant anxiety symptoms and thereby strengthens the desire to avoid the threatening stimulus. Similar conditioning responses and fear can operate in maintaining the anticipatory anxiety in panic attacks, avoidance behaviours with agoraphobia and other specific phobias and in the avoidance of triggers related to traumatic events in PTSD. Compulsive behaviours, which reduce anxiety in OCD, are reinforced by the conditioning process.

Catastrophic misinterpretation of relatively benign situations and negative emotions and thoughts that perpetuate anxiety symptoms are key features of anxiety disorders. In panic disorder, catastrophic misinterpretation or irrational fear that something serious is going to occur, caused by autonomic arousal symptoms, results in a vicious cycle of increased anxiety, followed by a further heightened perception of threat. In GAD, individuals are more likely to perceive neutral situations as threatening and have excessive fear of facing stressful situations. Further, personality traits like perfectionism, perceived uncontrollability of situations and shyness have been implicated in phobia, panic and anxiety symptoms.^{4,5} Adverse social factors in early years, such as exposure to stressful life events, attachment difficulties, parental loss and exposure to marital disharmony, contribute to the development of anxiety disorders.⁸ Risk factors for developing anxiety disorders also include social isolation, unemployment and poverty.⁴

In clinical situations, psychoanalytical therapies are sometimes used as a part of the treatment though the evidence base for these is scant. Some psychoanalytical theories have been based on ideas such as anxiety arising as a defence against underlying unconscious and unacceptable psychological conflicts and disturbances of interpersonal functioning. Phobic disorders have been thought to occur when anxiety is displaced on to a neutral stimulus, which can be easily avoided, as opposed to facing the unconscious conflict from which anxiety originates.⁴

— Pathophysiology

Dysfunctions of various neurotransmitters and receptors in the brain have been implicated in anxiety disorders. The three neurotransmitters primarily implicated in anxiety are gamma-aminobutyric acid (GABA), serotonin (5HT) and noradrenaline.

GABA is the main inhibitory neurotransmitter in the central nervous system. There

are two subtypes of GABA receptors, GABA_A and GABA_B. Benzodiazepines bind to the benzodiazepine site of the GABA_A-benzodiazepine receptor complex located on the postsynaptic neuron. Such binding augments the effect of GABA, leading to the opening of chloride ion channels, causing influx of the chloride ions into the cell resulting in neuronal membrane stabilisation. GABA may also influence anxiety levels by mediating the release of other neurotransmitters, such as cholecystokinin, and suppressing neuronal activity in the serotonergic and noradrenergic systems.

The role of 5HT and its receptor subtypes in mediating the symptoms of anxiety, panic and obsessions is complex. Specific attention has been drawn to the 5HT_{1A} and 5HT_{2C} receptor subtypes.⁴ 5HT released from the nerve terminal binds to the postsynaptic 5HT_{2C} receptor subtype, which mediates anxiety. 5HT_{1A} is an auto-receptor on the presynaptic neuron which, when stimulated, inhibits the release of 5HT from the presynaptic neuron into the synapse. Buspirone, a 5-HT_{1A} partial agonist, mediates its anxiolytic effect by decreasing serotonergic neurotransmission. It is further considered that 5HT_{2C} receptors have different effects on generalised anxiety and panic depending on the site of action in the brain.⁴

Dysregulations in the noradrenergic systems are hypothesised to occur in anxiety disorders. Noradrenaline modulates autonomic arousal mechanisms, including increased heart rate and respiration. This leads to a physiological cascade resulting in panic symptoms, such as paraesthesia, numbness and tightness in the chest.

GAD is associated with noradrenergic overactivity, serotonin receptor (5HT_{1A}, 5HT_{2C}) dysregulation and a decrease in the number of benzodiazepine sites on the GABA_A-benzodiazepine receptor complex.^{5,8} Given the response to treatment with selective serotonin reuptake inhibitors in OCD, serotonergic dysfunction is strongly implicated. Studies have shown there to be a decrease of 5-hydroxy indole acetic acid, a metabolite of serotonin, in the cerebrospinal fluid in OCD with clomipramine treatment.⁵ Further, a decrease of auto-receptor 5HT_{1D} in a certain part of the brain (orbitofrontal cortex), in response to treatment with selective serotonin reuptake inhibitors has been noted.⁸

Serotonin, noradrenaline, GABA, cholecystokinin and adenosine are thought to play a role in panic disorder.⁵ Cholecystokinin agonists and GABA antagonists are known to precipitate panic attacks.⁸ In PTSD, purported disturbances include noradrenergic overactivity, alpha-2 adrenergic receptor dysregulation and serotonergic dysregulation. Also, endogenous opiates are suspected to mediate the symptoms of emotional numbing and amnesia that can occur in PTSD.

Dysregulations in cortisol secretion and in the hypothalamic pituitary axis, which modulate stress responses, have been observed in anxiety disorders such as GAD and PTSD.^{8,9} Other substances implicated in anxiety include neuropeptide Y, tachykinins and glutamate.^{5,8}

Recent advances in brain neuroimaging techniques have significantly contributed to ongoing research aimed at understanding the possible anatomical sites of dysfunction in the brain in relation to anxiety disorders. The results so far are not conclusive but have helped to identify certain regions of the brain that may be implicated in the aetiology of anxiety disorders. For example, studies have shown alterations in the amygdala (part of the limbic system mediating anxiety and fear) and a reduced volume of hippocampus (the part of the brain dealing with learning and memory) in PTSD.⁹ Neuroimaging studies of GAD have suggested that there are dysregulations in parts of the brain such as the basal ganglia, several areas of the cortex and parts of limbic system and thalamus.¹⁰ In OCD, abnormalities in the orbitofrontal cortex and striatum (part of the basal ganglia) have been observed.⁸ Two major nuclei, the locus caeruleus and raphe nuclei in the brain stem are major mediators of norepinephrine and serotonergic systems respectively. The aforementioned neurotransmitters are abundant in these brain structures and hence involved in the pathophysiology of anxiety states.

— Diagnosis

The two classification systems widely used for the diagnosis of mental disorders are the “Diagnostic and statistical manual of mental disorders” (DSM-IV-TR)⁵ and “International classification of mental and behavioural disorders” (ICD-10).¹¹ Under these categorical classification systems, lists of symptoms are identified for each mental disorder. Anxiety disorders generally manifest with psychological, somatic and behavioural symptoms. Some of these are common to different anxiety disorders and others are distinctive to particular disorders.

Under these systems, a minimum number of symptoms or criteria essential for making each diagnosis is specified. For a diagnosis of any anxiety disorder to be made, it is considered essential that the symptoms should cause distress to the patient and/or cause impairment in their daily functioning, for example, in their social or occupational activities. Panel 2 highlights some of the clinical features of different anxiety disorders under these classification systems. For more precise details, readers are advised to consult the classification manuals mentioned above.

Approximately 62 per cent of patients with an anxiety disorder fulfil a diagnosis for another psychiatric disorder.³ Anxiety disorders mostly co-occur with depression and

substance misuse, including illicit drug and alcohol misuse or dependence. Commonly, patients use alcohol and drugs (particularly benzodiazepines) in an attempt to alleviate the symptoms of anxiety, which may progress into a dependence pattern. Co-existing personality traits, such as obsessive tendencies in patients with OCD and anxious-avoidant traits in patients with other anxiety disorders (such as phobic anxiety disorders) may also occur in this group of people.

Symptoms of anxiety can be directly caused by physical illnesses, thereby mimicking anxiety disorders, in addition to being co-morbid with physical illnesses. For example, conditions like hyperthyroidism, pheochromocytoma (tumour of the adrenal gland), hypoglycaemia and alcohol or drug withdrawal can cause anxiety symptoms. Many prescribed medicines can also cause anxiety symptoms. Anxiety disorders occur more frequently among patients with

Panel 2: Clinical features of anxiety disorders

Disorder	Clinical features
Generalised anxiety disorder	<ul style="list-style-type: none"> ■ Typically feel “free-floating” and excessive anxiety on most days for at least six months ■ Anxiety is not restricted to specific situations ■ Other co-existing symptoms can include palpitations, sweating, trembling, dry mouth, shortness of breath, chest or abdominal discomfort, a choking feeling, dizziness, fear of losing control or dying, feeling that oneself or the world is unreal, hot flushes or cold chills, numbness or tingling, muscle aches or tenseness, restlessness, tiredness, poor concentration, irritability, disturbed sleep
Obsessive-compulsive disorder	<ul style="list-style-type: none"> ■ Characterised by repeated intrusive obsessional thoughts, impulses, images, or compulsive acts ■ Sufferers describe these thoughts as distressing and excessive and often attempt to resist them ■ The thoughts are acknowledged by sufferers as their own and not imposed by external influences ■ Attempts to resist the thoughts lead to anxiety and carrying out the ritual relieves tension ■ Common obsessions include fear of contamination and sexual or aggressive ideas or impulses
Post-traumatic stress disorder	<ul style="list-style-type: none"> ■ Arises after an exceptionally threatening event, such as war, torture or rape ■ Sufferers have repeated intrusive flashbacks, memories or dreams of the traumatic event ■ Avoidance of situations that remind sufferers of traumatic event ■ Increased irritability, arousal, startling reactions and vigilance ■ Generally accompanied by sleep disturbances and poor concentration
Panic disorder	<ul style="list-style-type: none"> ■ Characterised by recurrent unexpected panic attacks which last several minutes ■ Can occur with or without agoraphobia ■ Typically described as a “crescendo-type” of anxiety ■ Characterised by symptoms such as palpitations, sweating, trembling, dry mouth, a choking feeling, shortness of breath, chest or abdominal discomfort, nausea, dizziness, unsteadiness, fear of losing control, fear of dying, numbness or tingling sensations and cold chills or hot flushes
Phobic anxiety disorders (including specific phobia, social phobia and agoraphobia)	<ul style="list-style-type: none"> ■ Manifests as excessive anxiety evoked by specific objects or situations ■ May be accompanied by panicky feelings, nausea, trembling or panic attacks ■ Sufferers acknowledge feelings as excessive and avoid precipitating situations ■ Specific phobias occur towards objects or situations such as blood, injury, animals, heights or flying ■ Social phobias involve fear of social situations, because of worries of acting in a manner that might be embarrassing or fears of ridicule by others ■ Agoraphobia involves fear of crowds or public places and commonly occurs with panic disorder

chronic medical illnesses like hypertension, chronic obstructive pulmonary disease, irritable bowel syndrome and diabetes than in the general population.⁸ This emphasises the need for a full assessment of the patient, including performing a physical examination and relevant investigations.

There are many rating scales that can be used in clinical settings to assess the severity and progress of anxiety disorders. It is important to select an appropriate scale, which is valid and reliable, for the disorder assessed. For example, the "Hospital anxiety and depression scale", originally designed for use in hospital settings, is a brief self-rated scale used to measure anxiety and depressive symptoms. It has two sub-scales, each containing seven items, one for symptoms of anxiety and the other for depressive symptoms. Each item is scored from 0 to 3 depending on the severity of the symptom, giving a maximum score of 21. Based on the total score, the interpretation would be "normal" (0–7), "mild" (8–10), "moderate" (11–14) or "severe" (15–21) symptoms. Some of the other scales available include the "Hamilton anxiety scale" and "Beck's anxiety inventory." The "Impact of event scale," which measures intrusive and avoidance symptoms can be used in PTSD. The "Yale-Brown obsessive compulsive disorder scale" measures the obsessive and compulsive symptoms in relation to the time occupied, interference with ordinary social activities, degree of distress, resistance and control. The "Fear questionnaire" and "Social phobia inventory" can be used for phobia.

Psychological treatments

Over the years there has been growing evidence of efficacy for the use of psychological treatments in anxiety disorders. The current evidence base supports the use of focused psychological treatments, such as cognitive behavioural therapy (CBT) including exposure therapy and response prevention. Such treatments focus on the "here and now" situation and target problems identified by the patient with the aid of the therapist. The treatment is structured, time-limited and involves active effort by the therapist and patient. The treatment sessions occur on a weekly basis and last for an hour. The number of sessions varies between eight and 12 but can be shorter or longer depending on the need. The patients are also given assignments to practice outside the sessions.

The basic premise of cognitive therapy is that thinking patterns, emotions and behaviour are linked. The aim is to identify these links in relation to the problem or problems, which cause distress to the patient and challenge the irrational and automatic negative beliefs by "socratic" questioning, thereby creating alternative ways of perception to alleviate distress.

Behavioural therapy may include systematic desensitisation or exposure to the anxiety-provoking stimulus (for example, in phobias), coupled with relaxation. This involves constructing a graded hierarchy of the situation that provokes the anxiety and systematically exposing the patient from the lowest anxiety-provoking situation to the highest one. This is coupled with relaxation techniques to inhibit anxiety in each exposure. Exposures can be carried out in the patient's imagination, in real life or a combination of both.

Response prevention is a technique used with exposure, for example, in OCD, when the patient is prevented from carrying out the compulsive behaviour after exposure. Eye movement desensitisation and reprocessing (EMDR) is a proven treatment in PTSD. This is a multistage treatment with CBT techniques. One of the stages involves asking the patient to visualise in their memory the traumatic image and emotions and simultaneously ask them to focus on finger movements performed in front of their face which last for a few minutes. This procedure is repeated until the image fades.

The National Institute for Health and Clinical Excellence guidelines, based on evidence, recommend individual CBT for panic disorder and GAD.¹² Trauma focused CBT or EMDR is suggested for PTSD.¹³ For OCD, CBT including exposure and response prevention is recommended.¹⁴ The importance of providing self-help written materials (bibliotherapy) based on tenets of CBT and support groups is emphasised for all disorders. Exposure therapy with systematic desensitisation is an effective treatment for phobias. It is pertinent to consider any preferences the patient has about their treatment since they will generally need to be motivated for psychological treatments to be successful.

Conclusion

Anxiety disorders are common but are often unrecognised and untreated. There are effective psychological and pharmacological treatments (described in the second part of this special feature, p119) that can alleviate the distress and morbidity caused by these disorders in a significant proportion of sufferers.

It is likely that multiple factors, including biological, psychological and social aspects, contribute to the aetiology of anxiety disorders. Further advances in research will hopefully further our understanding in this field and help tailor more specific treatments for these complex disorders.

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Counselling services

Often, a few moments of reassurance and compassion will go a long way to help anxious patients. For more specialised listening and counselling service, patients can be referred to national charities such as the National Phobic Society (website www.phobics-society.org.uk, telephone 0870 112 2325) or No Panic (website www.nopanic.org.uk telephone 0808 808 0545).