

CHAPTER 15. ANXIETY DISORDERS

15.1 ANXIETY DISORDERS: INTRODUCTION AND OVERVIEW

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Anxiety disorders are among the most prevalent psychiatric condition in the United States and in most other populations studied. Further, studies have persistently shown that they produce inordinate morbidity, utilization of health care services, and functional impairment. Recent studies also suggest that chronic anxiety disorder may increase the rate of cardiovascular-related mortality. Hence, clinicians in psychiatry and other specialities must make the proper anxiety disorder diagnosis rapidly and initiate treatment.

From a neurobiological perspective, study of anxiety disorders is now seen as compelling. Although validation of animal models of many psychiatric disorders, including depressive disorders, eating disorders, bipolar disorders, and schizophrenia is difficult, constructing animal models of fear and anxiety that appear relevant to human psychopathological states is relatively straightforward. This tool for understanding the neuroanatomy and molecular biology of anxiety promises new insights into etiology and more specific (and thus more effective) treatments in the next decade.

At the same time, the treatments currently available for anxiety disorders are among the most effective in clinical medicine. Pharmacological, cognitive-behavioral, and psychodynamic approaches have all proved useful in combating anxiety disorder. For many conditions (e.g., panic disorder), most patients should expect substantial relief from their symptoms in a relatively brief period.

Another fascinating aspect of anxiety disorders is the exquisite interplay of genetic and experiential factors. While there is little doubt that abnormal genes predispose to pathological anxiety states, evidence clearly indicates that traumatic life events and stress are also etiologically important. Study of

the anxiety disorders thus presents a unique opportunity to understand the relation between nature and nurture. This arena should show little regard for purely biological versus psychological explanations about pathogenesis or therapeutics. Rather, anxiety disorder research aims at presenting a view of human function under pathological conditions that integrates multiple sources of theory and information.

The sections that follow review progress in our understanding of panic disorder with and without agoraphobia, social phobia, generalized anxiety disorder, specific phobia, and posttraumatic stress disorder. Each section is intended to provide an up-to-date assessment of the field at the time of its writing.

EPIDEMIOLOGY

Ewald Horwath and Myrna Weissman review epidemiological data and studies on the anxiety disorders. Few published studies have appeared that specifically use the fourth edition of *Diagnostic and Statistical Manual of Mental Disorder* (DSM-IV) criteria; hence, most studies of interest involve the older third edition of DSM. Third edition of DSM (DSM-III) and revised third edition (DSM-III-R) criteria sets. This is not expected to make a substantial difference because most changes from DSM-III to DSM-IV have been relatively minor. The data presented demonstrate that anxiety disorders are highly prevalent and that rates of illness are fairly uniform across cultures. In most cases, women are more likely to have anxiety disorder than men, a phenomenon that still begs for adequate explanation. Of particular interest is the finding that social phobia is more common in women than men. Early textbooks gave the opposite view, but that turned out to be a mistake based on overgeneralization of populations seeking treatment rather than community-based studies. While women are about twice as likely to have social phobia as men, men appear more likely to seek treatment. One might speculate that as more women enter the workforce and assume performance roles, they will increasingly find that social phobia symptoms interfere with career success and seek treatment at higher rates.

Horwath and Weissman argue that the data do not substantiate that agoraphobia without panic attacks is nearly as common as an initial glance at available epidemiological studies might suggest. Rather, follow-up studies indicate that panic attacks were missed in such patients or that they actually suffer from other phobic disorders. This remains controversial, and the primacy of the panic attack in leading to agoraphobia remains a subject of investigation (using DSM-IV criteria in the future, one hopes).

CLINICAL FEATURES

The phenomenology of anxiety disorders is reviewed extensively by Daniel Pine. Here, the DSM-IV criteria are used. Some of the differences between DSM-IV and earlier versions are interesting. For example, no longer is a specific number of panic attacks necessary in a specific period of time to meet criteria for panic disorder. Rather, the attacks must be recurrent and at least one attack must be followed by at least 1 month of anticipatory anxiety or phobic avoidance. This recognizes for the first time that although the panic attack is obviously the seminal event for diagnosing panic disorder, the syndrome involves a number of disturbances that go beyond the attack itself. Furthermore, isolated panic attacks

without functional disturbance are not uncommon, occurring in approximately 15 percent of the population.

Social phobia has received increasing research and clinical attention in recent years. It is now clear that this condition is not uncommon and that it significantly impairs work and social function. Social phobia is also associated with high rates of substance abuse and, like all anxiety disorders, with depression. One challenge is deciding where to draw the line between social phobia and performance anxiety. Rates of speech phobia may exceed 50 percent in the population, but it is unclear whether such fear and avoidance of public speaking warrants a psychiatric diagnosis and what the appropriate clinical approach should be. On the other hand, generalized social phobia is clearly a serious condition that warrants clinical attention.

Pine notes significant alteration in criteria for posttraumatic stress disorder between DSM-III-R and DSM-IV. The criteria for the earlier version suggest that anyone exposed to particular traumatic events would be expected to develop posttraumatic stress disorder. Furthermore, the qualifying traumas were considered “outside of the range of ordinary human experience.” Two things changed this view. First, clearly fairly ordinary traumatic events can produce posttraumatic stress disorder and there is no adequate definition of “outside the range of ordinary human experience.” Second, only a subset of people exposed to the same traumatic event actually develop posttraumatic stress disorder. The number of previous traumatic events, the severity of the events, and certain precipitating factors such as previous psychiatric illness all seem to increase the likelihood that an individual exposed to severe traumatic stress will actually develop posttraumatic stress disorder. Hence, the DSM-IV criteria make no statement about the commonality of the required traumatic events but stipulate that they must involve a threat of death or physical injury.

What has emerged is a clear picture of separate anxiety syndromes under the rubric of anxiety disorder. These can be reliably diagnosed, but clearly substantial comorbidity exists among them, and each is frequently complicated by depression and substance abuse. Increasingly, investigators are attempting to define common denominators among the mood and anxiety disorders and to discern whether certain childhood conditions specifically predispose to any adult disorders.

GENETICS

Many studies have shown that anxiety disorders tend to run in families. For most medical conditions, this would suffice to conclude that abnormal genes must be etiologically relevant. However, it is not difficult to conceive that growing up with anxious parents or siblings might influence the development of anxiety in any individual. Therefore, family studies are only leads that prompt genetic investigators to attempt to determine whether any anxiety disorders are indeed inherited.

Abby Fyer accomplishes two things in her chapter on genetic aspects of anxiety disorders. First, she instructs the reader about the current techniques used to attempt to disentangle genetic and environmental influences for anxiety disorders. Then she reviews several types of studies that have

already been published. What emerges is a clear picture that genetics has something to do with anxiety disorders but that no anxiety disorder is likely to be the result of a simple Mendelian abnormality. That is, there probably is no specific “gene” for panic disorder or social phobia or generalized anxiety disorder. Fyer's review indicates that what is inheritable is a susceptibility to develop anxiety disorder. It is not even entirely clear at this point whether this susceptibility predisposes to the development of a specific anxiety disorder (e.g., panic) or to any one of the anxiety disorders. Further, it is not entirely clear to what extent these genetic influences overlap between susceptibility to anxiety disorder and to depression.

One compelling hypothesis is that individuals inherit a temperament like shyness, hyperactive autonomic nervous system responses, or behavioral inhibition. Then, depending on a variety of life circumstances, these genotypes are expressed as specific phenotypes—one or more of the anxiety disorders themselves. It may also be that more powerful “anxiety genes” require less environmental stress to be expressed.

Modern understanding of molecular genetics makes the above notion entirely plausible. Although the actual genes an individual receives cannot be altered by experience, most genes are only variably expressed. Every cell in the human body contains all of the approximately 100,000 genes in the human genome. A liver cell, for example, has all the same genes as a neuron in the brain's frontal cortex, but the liver cell does not sprout axons and dendrites or generate neural impulses. The genes for these functions are not expressed in the liver cell. Clearly a variety of environmental influences activate latent genes through complex biochemical process, and these operate in the central nervous system. Hence, it is likely that genetic susceptibility to an anxiety disorder becomes an actual anxiety disorder when some set of environmental influences causes anxiety proneness genes to become active.

NEUROBIOLOGY

Attempts are now being made to link the extensive data on the biology of the fear response in animals to observations in humans with anxiety disorder. Two interesting leads are provided from the preclinical literature. First, conditioned fear in animals depends absolutely on normal function of the central nucleus of the amygdala (CNA). This work, pioneered by neurobiologists such as Joseph LeDoux, Trevor Robbins, and Michael Davis, has elegantly shown that afferent projections from the CNA during fear reactions in animals activate autonomic nervous system centers of the brain that reproduce most of the behavioral and physiological manifestations of the acute anxiety response. Second, studies in rodents and nonhuman primates indicate that early separation distress changes function of the hypothalamic-pituitary-adrenal axis that endures throughout the life span of the affected animal.

Gregory Sullivan and Jeremy Coplan review what is now known about the neurobiology of human anxiety. Studies in panic and posttraumatic stress disorders are now extensive. Since the original finding that sodium lactate infusion can induce panic attacks in patients with panic disorder, many substances have shown similar panicogenic properties including the noradrenergic stimulant yohimbine (Yocon), carbon dioxide, the respiratory stimulant doxapram (Dopram), and cholecystokinin. Disordered

serotonergic, noradrenergic, and respiratory systems are clearly implicated in panic disorder, and the condition appears to be caused both by a genetic predisposition and traumatic separation distress. More recently, neuroimaging studies revealed that patients with panic disorder have abnormally brisk cerebral vascular responses to stress, showing greater vasoconstriction during hypocapnic respiration than normal controls.

Studies of patients with posttraumatic stress disorder have revealed a downregulated hypothalamic-pituitary-adrenal axis with reduced secretion of cortisol, presumably a result of chronically increased production of corticotropin releasing factor. Studies also suggest that the hippocampus may show neuronal degeneration in patients with posttraumatic stress disorder, probably as a result of increased central glucocorticoid effects. Because the hippocampus is critical for memory function, this could explain any loss of memory for the original traumatic event in these patients.

To date, there is no coherent biology for social phobia. Generalized anxiety disorder has also been inadequately studied, with most interest focused to date on possible abnormalities in the central benzodiazepine receptor and its associated site for binding of the inhibitory neurotransmitter γ -aminobutyric acid (GABA). Further research is needed into the biology of these two very common illnesses.

Overall, neurobiological studies, particularly with respect to panic disorder and posttraumatic stress disorder have elucidated a specific set of neurotransmitter and central nervous system abnormalities that can now be addressed with more-specific treatment approaches. For the first time, treatment research can finally be guided to some degree by an understanding of basic pathological mechanisms within the brain.

PSYCHODYNAMIC ASPECTS

Glen Gabbard provides a modern understanding of the psychodynamic aspects of anxiety disorder. One can only admire the insights he derives from Freud's seminal work on the subject, *Inhibitions, Symptoms, and Anxiety*. It is fascinating to recognize that some findings of current neurobiologists substantiate many of Freud's original ideas. For example, the existence of an unconscious memory system for anxiety responses is well substantiated by work demonstrating that the amygdala subserves the fear response without any reference to conscious memory. Gabbard shows the development of Freud's theories through subsequent psychodynamic writers, including Melanie Klein and Heinz Kohut, and demonstrates how psychodynamic concepts of anxiety disorder are indeed fully consonant with observations from neuroscience. For example, he points out that panic attacks may not be entirely "out of the blue" phenomena but are likely to be related to "meaningful stressors" in the patient's life. This view accords with modern ideas about fear conditioning. He also discusses childhood precursors to panic disorder, again finding much in common with preclinical scientists who show that early separation distress in infant animals produces an "anxiety prone" adult animal.

Similarly, in his discussion of phobias, Gabbard draws on the exciting work of Jerome Kagan and

colleagues at Harvard University who have identified a state in young children called “behavioral inhibition to the unfamiliar.” This temperamental disposition can apparently be altered by a variety of powerful life experiences. This gives credence to the idea that psychodynamic treatments may be able to alter genetically mediated personality traits.

Although no controlled trials of psychodynamic therapy for anxiety disorders exist, only the rare psychiatrist does not use these techniques even when prescribing medication or using cognitive-behavioral therapy to treat anxiety disorder. When large scale studies are mounted to test the efficacy of psychodynamic treatments for anxiety disorders they are expected to reveal an effective treatment approach.

SOMATIC TREATMENT

Medication to treat anxiety is centuries old if one includes alcohol. As Laszlo Papp details, somatic treatments have gone through many incarnations. Until recently, most antianxiety medications were developed empirically rather than on the basis of known organic pathology. Benzodiazepines remain one of the most often prescribed class of drugs for anxiety, but whether they address any actual brain abnormality or work nonspecifically is not known.

One of the great challenges in prescribing medication to patients with anxiety disorder is their known sensitivity to even relatively minor adverse effects. Because anxious patients generally maintain fear of physical sensations, medication adverse effects are sometimes viewed catastrophically. Hence, as Papp discusses, most treatment should be started at relatively low doses of the selected medication, with slow titration to a fully therapeutic dose. On the other hand, evidence clearly shows that anxiety disorders are, in general, chronic illnesses that often require long-term therapy. Thus the medication selected must be well tolerated and safe even if the patient must continue to take it for a prolonged period to prevent relapse.

Antidepressant medication is increasingly seen as the medication treatment of choice for the anxiety disorders. More specifically, drugs with primary effects on the serotonin neurotransmission system have become first-line recommendations for panic disorder, social phobia, obsessive-compulsive disorder, and posttraumatic stress disorder. Evidence also now exists that such medications are also effective for generalized anxiety disorder. Although they generally take longer to work than benzodiazepines, the selective serotonin reuptake inhibitors such as fluoxetine (Prozac), sertraline (Zoloft), paroxetine (Paxil), fluvoxamine (Luvox), and citalopram (Celexa), as well as venlafaxine (Effexor) and nefazodone (Serzone) are probably more effective than benzodiazepines and easier to discontinue. Increasingly, benzodiazepines are used only for the temporary relief of extreme anxiety as clinician and patient wait for the effects of antidepressants to take hold. Longer-term administration of benzodiazepines is reserved for patients who do not respond to, or cannot tolerate, antidepressants. Monoamine oxidase inhibitors are given only to anxiety disorder patients who do not respond to trials with several medications.

Placebo-controlled trials leave little doubt, as Papp notes, that newer antidepressants are effective for anxiety disorders. Because they work fairly quickly and have fewer adverse effects than tricyclic drugs and monoamine oxidase inhibitors, a low threshold for prescribing them to anxious patients should be maintained. However, most clinicians believe that the best result for anxiety disorder patients comes with combination of medication with one or more types of psychotherapy.

COGNITIVE-BEHAVIORAL APPROACHES

One remarkable recent advance in therapeutics for anxiety disorders is the rigorous testing of cognitive and behavioral psychotherapies. Although many claim that it is difficult to submit psychosocial treatments to experimental investigation, scientists have developed the capacity to apply excellent research designs including randomization and blinded assessment to cognitive behavioral therapy. As Lawrence Welkowitz describes, the result has been documentation that cognitive-behavioral therapy is effective for most anxiety disorders.

A large number of studies have now shown that cognitive-behavioral therapy of various types is effective for panic disorder. The response rate after acute treatment is comparable to that achieved with tricyclic drugs or benzodiazepines. Furthermore, some, but not all, studies indicate that once a patient with panic disorder has completed this therapy, the response may be long-lived. Many different techniques are incorporated into standard cognitive-behavioral packages for panic disorder, including breathing retraining, deconditioning, cognitive restructuring, relaxation, exposure, and psychoeducation. It is not clear which among these is critical for favorable outcome. Studies are also needed to determine if some kind of maintenance, or booster, therapy would help prevent symptomatic relapse.

At least one group has shown that cognitive-behavioral therapy is effective for social phobia, and many studies have documented its benefits for obsessive-compulsive disorder. Studies also report favorable outcome with patients suffering from generalized anxiety disorder or posttraumatic stress disorder. These treatments may be given as first-line approaches to patients who refuse or cannot tolerate medication or in combination with medication. The latter approach may be particularly effective, but empirical justification for it is lacking.

Not only has cognitive-behavioral research provided another effective way to treat anxiety disorders, it has also heartened psychotherapists in general because it proves that one can demonstrate scientifically that psychotherapy works. This should be considered just as exciting a development as anything generated by the neuroscience community. One intriguing challenge for research will be understanding how the psychosocial treatments affect central nervous system processes. Indeed, some imaging studies already suggest that psychotherapy may alter abnormal patterns of brain activation, but much more work is required in this area.

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