Problems in Family Practice

Anxiety Disorders

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The Diagnostic and Statistical Manual of Mental Disorders (DSM-III) has expanded descriptions of anxiety and includes new categories with definitive diagnostic criteria. It has also eliminated its previous psychodynamic and psychoanalytic approach to psychopathology. The new anxiety classifications reflect the growth of knowledge in neurochemistry, especially cell-membrane binding sites and specific pharmacologic actions of certain drugs. Many research conclusions have become questionable as a result in large part of their reliance upon the obsolete versions of DSM (I and II). Among major findings in research on anxiety are its relatively common incidence, especially in family practice, and its relationship to secondary depression and increased association with physical disorders, particularly if the anxiety disorder is of long duration. Family and genetic studies have revealed a high incidence of anxiety within families, though there is little evidence of heritability. The pathophysiology of anxiety is only beginning to be studied productively. Research in drug therapy and psychotherapy have supported the need for both therapeutic modalities in most circumstances.

At some time everyone experiences the emotion of anxiety. When it results from the anticipation of an unpleasant event, it is a normal phenomenon. If there is no apparent precipitating circumstance or if the response is excessive or handicapping, it is abnormal.

This paper presents a clinically oriented overview of anxiety disorders as identified in the third edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-III).[1] In 1952 the American Psychiatric Association created DSM-I to bring a common glossary to the confusion of diagnostic terms previously in use. It reflected the Adolf Meyer school of personality reaction to psychosocial and biological factors. DSM-II, pub-

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lished in 1968, implied no particular theoretical framework; however, it did utilize Freud's classification of the neuroses.

In 1974 the American Psychiatric Association initiated a task force to coordinate the classification changes that were to be included in DSM-III with the revision of the *International Classification of Diseases* (ICD-9). The final product, published in 1980, reflected major changes. Some of these new features are expanded descriptions, definitive diagnostic criteria, additional new categories, exclusion of several time-honored categories, and an increased commitment to reliance on data. An atheoretical approach to etiology was adopted. Clinical manifestations are not used as the prime basis of classification. A descriptive approach to manifestations is present throughout. No assumption that each mental disorder is a discrete entity with sharp boundaries is made. Each disorder is associated and described in terms of the distress (unpleasant symptoms) or disability (impaired function) that it produces. Explicit criteria and definitive content are specified in order to enhance diagnostic reliability across the broad spectrum of professionals who might utilize DSM-III. Disturbances of interpersonal relationships are not dealt with.

The separate identifiable classification of "neurotic disorders" used in DSM-I and DSM-II no longer exists. They are now included as part of the affective, anxiety, somatoform, dissociative, and psychosexual disorders. Prior to DSM-III, when anxiety was the chief characteristic, anxiety was grouped under one of the neuroses. With DSM-III, where anxiety is experienced directly, it falls under the syndrome of the anxiety disorders. As an example, the DSM-II designation of anxiety neurosis has been separated in DSM-III into panic disorder and generalized anxiety disorder. The rationale for the change is the compelling evidence that panic disorder has a differential treatment response (imipramine) as compared with other disorders in which anxiety is prominent.

Recent advances in neurochemistry and psychopharmacology have profoundly influenced concepts concerning etiology and, therefore, the classification of many mental disorders. The DSM-III reflects this through a marked change in disease categories. This is especially true of its section on anxiety disorders.

Greater uniformity is now possible in a literature whose nomenclature has been so variable as to often make comparisons of studies irrelevant, if not impossible.

Prevalence

Rees[2] indicates that anxiety may be a frequent accompaniment of any medical or surgical condition, and it is prominent in the expression of many psychiatric disorders. Anxiety is an important presenting feature of acute toxic confusional states. It plays a prominent role in the disability of phobias, obsessive-compulsive disorders, many depressive episodes, as well as somatoform and psychosexual disorders. But equally important, it may occur independently of other disorders.

Data from national surveys are only partially useful. They do not focus on the specific DSM-III diagnostic entity of anxiety disorders; rather, they measure the full range of neuroses. Interpolation is usually necessary because of the ubiquity with which the term *anxiety* is used and the less exact diagnostic criteria that were previously applied.

The National Ambulatory Medical Care Survey for 1977[3] indicates that "mental disorders accounted for 24.5 million patient visits." Over one half of these (12.5 million) were classified as "neuroses." This diagnostic category was the sixth most common and accounted for 2.2 percent of visits for all causes, both physical and mental.

The Virginia Study of Marsland et al[4] analyzed the health care problems of 88,000 patients who presented to 118 family physicians over a period of two years. The problems of 526,196 patient visits were coded and analyzed. Mental illness, personality disorders, and psychoneuroses accounted for 5 percent of all visits. Anxiety neurosis was specifically responsible for 1.57 percent of these visits. Stewart,[5] in his review of the study, felt that this and many other categories, including alcoholism, depression, neuroses, and "physical disorders of presumably psychogenic origin," were underreported.

Marks and Lader[6] state that among psychiatric outpatients, 6 to 27 percent suffered from anxiety states (anxiety neurosis). In a normal population they indicate a prevalence of 2 to 4.7 percent in Britain and the United States. They make the further point that 10 to 14 percent of patients seen in cardiology practice suffer from anxiety states.

Berger[7] refers to over 8,000 tons of benzodiazepines being consumed in 1977 in this country

alone. The National Institute of Drug Abuse stated that 51 million people were given tranquilizers in that same year. More money was spent for them than for antibiotics or antihypertensives or antipsychotics.

Hasday and Karch[8] found that 7.3 percent of all prescriptions from a family practice center were for benzodiazepines. Kirchner et al[9] noted anxiety, in general, to be the third most common disorder seen at a family practice center in New Orleans.

Classification and Clinical Features

The more common anxiety disorders will be described in terms of their diagnostic criteria according to DSM-III.

Panic disorders usually last several minutes or (rarely) hours. Recurrence and unpredictability are characteristic. The classic features are a sudden onset of intense apprehension and a feeling of impending doom with a fear of doing something uncontrollable or of dying or of going crazy, accompanied by dyspnea, palpitations, parasthesias, choking, sweating, faintness, trembling, and shaking. Onset is usually in adolescence or early adult life and may last several weeks before disappearing, recurring, or becoming chronic. Hypoglycemia or pheochromocytoma should be ruled out.

Generalized anxiety disorders are unremitting and persist for at least one month. Mild depressive symptoms are commonly associated. Signs are notable in three categories:

1. Motor tension is increased with apparent restlessness, fidgeting, twitching, easy startle, strained facies.

2. Autonomic hyperactivity is apparent with sweating, chills, dry mouth, frequent urination, diarrhea, flushing, pallor, tachycardia, tachypnea.

3. Cognitive signs suggest apprehension, excessive vigilance, difficulty in concentrating, irritability, impatience, distractability.

Obsessive-compulsive disorders are characterized by recurrent and persistent ideas, images, or impulses that invade the consciousness, are perceived as senseless or unpleasant, but result in acts that are performed repeatedly without purpose and usually in a stereotyped fashion. No pleasure occurs, but tension is relieved. The subject knows that the act is senseless, excessive, and desires to resist, but to no avail. Obsessions and compulsions are a significant source of stress and interfere with social or role function. They usually have their onset early in life. Although symptoms may change in intensity, the course is usually chronic. Attempts at treatment often result in alcohol or drug abuse.

Agoraphobia without panic is characterized by marked fear of being alone or of being in a public place from which escape might be difficult or help not available in case of a sudden incapacitation. Normal activities are increasingly restricted as the avoidance behavior dominates the individual's daily life. Agoraphobia usually begins in early adult life. Periods of complete remission sometimes occur. The object of dread may change daily. Some become housebound. Others suffer social or occupational inconveniences such as avoiding crowds or elevators. Depression commonly results from a prolonged course.

Agoraphobia with panic is the recurrence of panic attacks resulting in development of anticipatory anxiety regarding such attacks. The individual reacts by reluctance or refusal to enter a variety of situations.

Social phobia results from an irrational desire to avoid the scrutiny of others. It is a persistent fear that the individual may act in a manner that will result in humiliation or embarrassment. Anticipatory anxiety forces the avoidance. The distress is recognized as excessive and unreasonable. Avoidance of public lavatories or eating in public are common examples. The irrational fear generates anxiety that impairs performance, which produces justification for the avoidance behavior. A vicious cycle is set in motion.

Usually only one social phobia occurs at a time. It is chronic and usually begins in early adolescence. Inconvenience is common; incapacity is rare. Those afflicted are prone to alcohol and prescription drug abuse.

Simple phobias (specific phobias) refer to objects such as animals or situations such as heights or closed spaces. Other characteristics are similar to social phobias except that panic attacks result more often, and treatment is sought by patients when panic attacks do occur.

Posttraumatic stress disorders (acute, chronic or delayed) are characterized by symptoms of insomnia, hyperalertness, exaggerated startle response, and excessive autonomic arousal that are produced recurrently following a psychologically

traumatic event which is outside the range of usual human experience. The event would evoke significant symptoms of distress in most people. Stressors responsible for this disorder include earthquakes, military combat, rape, airplane crashes, and fire. Re-experiencing the event may reduce the individual's involvement with the outside world or result in impaired memory or difficulty concentrating or irritability. Impairment is variable, as is the course.

Atypical anxiety disorder is a catchall category for an anxiety disorder that does not meet the criteria of the previously described conditions.

Family and Genetic Studies

Panic, phobic, and obsessive-compulsive disorders are each more common among family members of individuals with these disorders than in the general population. DSM-III indicates that the evidence does not support a more definitive statement. A variable degree of reactivity of the autonomic nervous system has consistently been found to be a heritable and measurable trait by the animal experimentalist, the physiologist, and the psychologist.[10]

The following reports represent the rather meager literature in the field of family and genetic studies of anxiety disorders. Miner's[11] review of genetic components in the neuroses included a description of a study by Slater[12] of 2,000 soldiers during World War II in whom a diagnosis of neurosis had been made. More than 50 percent of this sample had a positive family history of first-degree relatives with some form of psychopathology.

Noyes et al[13] studied family histories of their patients with anxiety by structured interview and blind diagnosis with a control group. Criteria for the diagnoses were closely comparable to DSM-III. One hundred twelve patients and a similar number of controls were used. He found the morbidity risk among female relatives was 24 percent for female patients and 13 percent for male patients.

Crowe et al[14] studied a subset of Noyes' patients to learn the incidence, specifically, of panic disorder. He found a 41 percent risk for first-degree relatives of patients with a diagnosis under the rubric of anxiety disorders. Among controls, the incidence was only 8 percent.

Corey and Gottesman[10] pooled the findings of a number of studies including Noyes et al. They found an overall prevalence of 15 percent in first-degree family members of patients. If both parents were so diagnosed, the prevalence was 40 percent. When one parent was affected, the rate fell to 25 percent. It was concluded that the risk to first-degree relatives increases as a function of family loading.

In their review article, Marks and Lader[6] comment on the study of monozygotic twins by Slater and Shields.[15] Co-twins showed a 50 percent concordance rate for anxiety, while 65 percent showed marked anxiety traits. Among fraternal twins, only 4 percent showed concordance, whereas 13 percent revealed anxiety traits. These studies were done in England over the time frame of 1948-1964, and were based on a sample of patients hospitalized for a psychiatric disorder. Generalizations from the study are difficult because of the sample chosen and the classifications of anxiety employed.

Another review of twin studies by Corey and Gottesman[10] examined obsessive and phobic states. They concluded that concordance is very high for monozygotic twins even in studies from different cultures and wide geographic differences. This was also true in those very few twins who were found to be raised apart.

In a reanalysis of the existing data regarding identical twins with little, some, or much contact with one another, Farber[16] included a reanalysis of data regarding fearfulness, anxiety, and neurosis. The author analyzed the data descriptively, and the results were based on only a handful of examples. There was some suggestion in the data that psychological components indicating anxiety arousal exist among twins reared apart. The basis for heritability may be in the physiology of anxiety and autonomic arousal mechanisms.

Analysis and comparisons concerning a number of these studies done over the years are not tenable, since significant variations in terminology, diagnostic criteria, and sample characteristics exist. The literature repeatedly avers to the likelihood of a familial relationship between panic disorder or generalized anxiety disorder and depression, alcoholism, phobias, and obsessions.[6,10,11,13]

Because many suspect a pedigree relationship between anxiety disorders and mitral valve prolapse (MVP), several studies have tried to elucidate a heritable segregation of these two. MVP has

been shown to be transmitted as an autosomal dominant disorder. Crowe et al[14] studied a series of patients with panic disorder in collaboration with the Department of Cardiology at Iowa University Hospital. Their preliminary data indicate a link with MVP, but they could not conclude that the combination was one disease. Those with the combination had the unique finding of impaired exercise tolerance tests.

Kane et al[17] studied patients with an established diagnosis of MVP. An attempt was made to determine whether they were at high risk for developing anxiety disorders. Self-evaluation scales and structured interviews (not blind interviews) were utilized to establish anxiety in conformity with DSM-III criteria. They found that the majority of patients with MVP do not have increased anxiety. At the same time, more people with MVP experienced panic attacks than those with no valvular involvement.

Gorman et al[18] studied 20 patients with panic disorder, 15 of whom had associated agoraphobia. All were undergoing treatment with imipramine. Ten were found to have MVP by standard criteria including echocardiography. They conclude that panic disorder patients have an especially high incidence of MVP, but MVP is not sufficient to account for the panic attacks. They suggest that it may play a provocative role or be linked to panic disorder through a common disturbance of the autonomic nervous system.

Another possible heritable mechanism may be found in the recent reports of benzodiazepine receptor sites being demonstrated throughout the central nervous system. A deficiency state or altered protein structure is postulated.

Pathophysiology

With the discovery of cell membrane receptors and specific binding sites for endorphins and benzodiazepine binding sites,[19] the relationship between neurophysiology and behavior is becoming a major focus of current research.

Several amino acids are now recognized to have prominent roles as neurotransmitters. Some amino acids (glutamic acid, aspartic acid, cystic acid, and homocystic acid) cause depolarization and thereby stimulate synaptic transmission. Other amino acids, such as γ-aminobutyric acid (GABA), glycine, taurine, and β-alanine, interfere with synaptic transmission. The rate of presynaptic or postsynaptic flow results from cell membrane receptors (macromolecules) binding with these amino acids or other chemical agents (called ligands). Binding sites (receptors) specific for benzodiazepines were identified in 1977[20] and appear to be exclusively localized to neurons. The number, affinity, and structure of the benzodiazepine receptors all appear to be susceptible to genetic or constitutional variability.[21] In the 1960s, recognition of receptors specific for opiates led to the search for and identification of endorphins and recognition of their function. The search is now on for endogenous anxiolytic agents,[22] which should naturally occupy these binding sites.

Benzodiazepines appear to function predominantly by enhancing the neuromodulator activity of GABA. Benzodiazepine and GABA receptor sites are closely situated on the same macromolecule. Both, directly and concomitantly, influence the flow of chloride ions (chloride channel) into the cell. Acceleration of this chloride flow diminishes the threshold of excitability of the neuron.[20] Deceleration of the flow increases the threshold of neuron excitability.

Significant research efforts are currently under way to relate molecular and cellular actions with behavioral and therapeutic consequences.[19,20,23] The resultant understanding of this type of drug action should markedly improve the indications for and expectations from their use.

Prognosis

DSM-III makes no reference to prognosis. It speaks of the "course" of each disease entity, but these statements are very general and mostly inconclusive.

In 1980 Noyes et al[24] reported a six-year follow-up of 112 patients with a similar number of surgical patients used as a control group. Their criteria were closely comparable to DSM-III criteria. Their conclusions were that 12 percent were completely free of symptoms, while 17 percent had mild symptoms without impairment, 39 percent were mildly impaired by symptoms, and 22 percent were moderately disabled. The remaining 10 percent were found to have an incorrect

initial diagnosis. When the initial symptoms lasted less than a year, the prognosis was best. These patients were those having the least severe or no symptoms at follow-up. Lower socioeconomic status was associated with a poorer prognosis. Secondary depression developed in almost one half of the anxious patients. The prevalence of peptic ulcer and hypertension were increased in the population, and the most commonly missed diagnosis was alcohol abuse.

Therapy

Drug Indications

Anxiety, within the context of the use of DSM-III, can no longer be considered a single entity, treatable by a minor tranquilizer. Instead, there are a number of distinctly identifiable diagnostic categories characterized by a cluster of signs and symptoms that require different treatment strategies. Diagnosis of a specific anxiety disorder may require a significant period of observation and often does not appear to be clear cut. Despite this lack of certainty, however, there are empirical indications for specific pharmacotherapy and psychotherapy.

Antidepressants such as imipramine and phenelzine sulfate specifically act to prevent the cognitive and motor symptoms that are most prominent in such disorders as agoraphobia with panic attacks. They may require up to eight weeks before maximal therapeutic effect is established. Ultimately anticipatory anxiety and avoidance behavior also show improvement, once the cycle of recurrent panic attacks is broken.

Anxiolytics bring rapid relief and are most effective where cognitive symptoms are severely disturbing, and motor and autonomic symptoms are less prominent as in generalized anxiety disorder. Tolerance to the benzodiazepines is almost never a problem, but dependence often occurs. In those with hepatic damage (often the elderly), the half life of benzodiazepines is often prolonged by a factor of two to three. Effective therapeutic levels for anxiety begin at a serum concentration of 400 ng/mL. Sedative and psychomotor changes often become manifest between 300 and 400 ng/mL, so that anxiolytic activity is not perceived without a degree of sedation. A few deaths have been reported at doses greater than 700 ng/mL; yet the margin of safety of benzodiazepines is recognized as being extremely high. Gross central nervous system intoxication usually requires a blood level in the range of 900 to 1,000 ng/mL.

β-Blockers such as propranolol are of greatest benefit when cognitive symptoms are low but autonomic and motor symptoms are high, as in stage fright and examination anxiety. They are often valuable prophylactically when the simple and social phobias are intermittent and of brief duration.

Obsessive and compulsive disorders generally respond poorly to drug therapy alone. They are less common but more disabling than the others. Phobic avoidance behavior that involves the content of the obsession is a major disability. Tricyclic antidepressants with behavior modification offer the greatest likelihood for improvement, whereas anxiolytics are ineffective.[25]

It is often necessary to combine drug therapies for short periods to cause symptom improvement. An example is the relief of anticipatory anxiety by benzodiazepines while awaiting an imipramine effect in preventing panic attacks. Also effective is the coadministration of a β-blocker and axiolytic to diminish autonomic symptoms of generalized anxiety disorder. Lower doses, less sedation (dependence), and more dramatic response may result.

Behavior modification, reassurance, and other forms of psychotherapy[26] are important ingredients in enhancing drug response in all of these conditions.

Psychotherapy

Psychotherapy for anxiety can take many forms, including behavior modification, family therapy, group therapy, biofeedback, hypnosis, and insight-oriented therapy, among others. The different forms involve many of the same procedures, including establishing rapport, giving support, thoroughly evaluating physical, cognitive, and autonomic components, establishing therapeutic goals, identifying and clarifying conflicts and solutions, and strengthening a patient's ego.

In 1975 Luborsky et al[27] reviewed comparative studies of outcome with various psychotherapeutic modalities. In addition, they analyzed reports comparing the efficacy of psychotherapy com-

bined with psychopharmacology with psychotherapy alone and drug therapy alone. Although these studies transcended the investigation of anxiety, they appear to be essentially applicable to this paper.

Using the criteria of enhancement of therapeutic goals in psychotherapy, the general conclusions of Luborsky et al were that in controlled comparative studies up to 60 percent of patients who go through any modality of psychotherapy gain from the experience. Different forms of psychotherapy are all equal in the proportion of patients who improve by treatment, drug therapy plus psychotherapy was demonstrated to be superior to psychotherapy alone, and drug therapy alone and a combination of drugs and psychotherapy were found to be equally effective.

Epstein and Vlak[28] recently reviewed research on the effectiveness of psychotherapy on anxiety as well as other psychiatric disorders. These authors find some support for the effectiveness of behavior therapy in the treatment of obsessive-compulsive disorders with any psychotherapeutic modality.

Sheehan et al[21] studied anxiety with manifestations of phobias, hysteria, and hypochondriasis. They compared three therapeutic modalities: (1) monamine oxidase inhibitor plus supportive psychotherapy, (2) tricyclic antidepressant plus supportive psychotherapy, and (3) placebo plus supportive psychotherapy.

Although dosages used were low, they were able to conclude that both drug regimens were superior to supportive psychotherapy plus placebo. They further comment: "It has not been demonstrated that any of the special technical maneuvers associated with traditional psychotherapy, whether psychoanalytical or behavioral, show an additive response to the drug effect beyond ensuring compliance to the drug regimen and offering hope and support."

Conclusions

In medical usage the term *anxiety* should indicate a symptom of a disease. In normal individuals, it is too often used interchangeably to designate fear.[7] Stress, mood alteration, and apprehension are components of everyday experience and normal living. Too often in the therapeutc process stress, mood alteration, and apprehension are regarded as "anxiety" by the physician. They do not respond specifically to anxiolytic agents, but are influenced by any agent with sedative qualities. No drug in this class will significantly improve performance in the normal individuals. All sedative-tranquilizers produce a dulled awareness that patients frequently interpret as a sense of improvement. There is a distinct physiological difference, however, between the "escape" of dulled senses and the specific neuromodulation mediated through GABA and benzodiazepine receptors.[20,27]

Pany et al,[29] in an analysis of the national patterns of psychotherapeutic drug use, found that over one half of the patients who received tranquilizers had no psychiatric problems. These patients were suffering from such somatic disorders as cardiovascular disease, peptic ulcer, painful arthritis, acute dermatitis, and other physical ailments. Berger[7] comments that although somatic disease or hospital admission is a strong reason for a patient to be concerned about the consequences, these are realistic fears. As such, they are inaccessible to the specific pharmacologic effects of anxiolytics. Any noted alteration is a sedative or placebo response. Tolerance and dependence are common; withdrawal produces a state of psychic (cognitive) tension unacceptable to the patient.

The anxiety disorders are thought to be another example of that kind of a disease entity wherein environmental factors are responsible for the expression of a genetic trait with variable penetrance.[10] Diversity of presenting complaints and varying response to therapeutic modalities ultimately mandate multiple visits and continuity of care for a successful outcome. For psychotherapy and pharmacotherapy to reinforce each other, a sense of rapport and dedication is required between the therapist and the patient.

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