Anxiety and Anxiety Disorders

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14.1 Vignettes

1. An emergency psychiatric consultation was requested for a 48-year-old man who was admitted to the coronary care unit (CCU) with massive myocardial infarction (MI). He was reported to be acutely agitated, and he wanted to sign out against medical advice. The reason for consultation was to determine the patient's competence to sign out. When the consultant arrived in the CCU, a number of staff members were surrounding the patient as he attempted to exit the cubicle. He shouted, "I want to get out! You cannot hold me here!"

   The consultant told him, "I am a psychiatrist, and I am here to help you. I think it might be possible for you to leave if you wish, but I need to speak with you first."

   "Not here, not in this room!" replied the patient.

   "OK, would it be OK if we talked in the waiting room?"

   The patient agreed. He was placed in a gurney and wheeled to the waiting room.

   The consultant said, "Since you became quite anxious and flushed, I would like the nurse to give you a sedative to help you relax as we talk." Lorazepam 1 mg IV was administered, which calmed the patient considerably. In the interview, the consultant learned that the patient became panicky when he was rushed into the particular cubicle in the CCU, as it was the same cubicle in which his father

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had died of an MI some 4 months prior to the patient's own admission. The patient was convinced that he would die in that cubicle just as his father did. When the patient was offered another cubicle, he gladly accepted it without any hesitation. He recovered uneventfully.

2. A 73-year-old woman was admitted for pain in the lumbar area associated with a mass found on a computed tomography (CT) scan. She had a history of major depression in the past but was currently on no medications. A psychiatric consultation was requested as the staff thought the patient was depressed. The patient denied current depression, but admitted to having insomnia and panicky feelings. She was a retired executive, who had "always been on top of things." The patient felt quite apprehensive and out of control as she did not know what was happening to her physically. She stated that the doctors did not explain anything to her, saying only that they needed to do more tests. She was afraid to ask questions because she felt that the doctors were withholding information from her so as to not upset her. When the consultant asked her if she would like the doctors to explain to her exactly what they found and what they were planning to do, she agreed. It turned out that the doctors had not yet found the time to have an in-depth conversation with the patient simply because they had been busy with other patients, not because they were afraid of upsetting her. In fact, the mass turned out to be benign and the patient was discharged without any antidepressant or antianxiety medications.
3. Psychiatric consultation was requested for a 34-year-old man who had undergone a magnetic resonance imaging (MRI) scan and panicked while he was positioned in the narrow confines of the imaging apparatus. On examination, the patient turned out to have claustrophobia. As the MRI was a medical necessity, lorazepam 2 mg po was administered 30 min prior to the next scheduled MRI. Though apprehensive, he was able to complete the MRI scan.

14.2 Anxiety: General Considerations

14.2.1 The Function of Anxiety

The most prominent subjective features of anxiety are *fear, a sense of dread,* and *apprehension*. This fearful feeling is usually vague and diffuse, but it may also focus on a specific idea, such as fear of dying, or of cardiac arrest, or of having a serious disease such as cancer. It may also arise under specific situations, such as being in closed spaces, as in the final vignette cited above. Physiological changes are part of anxiety. They are mediated by activation of the sympathetic outflow and of the hypothalamic-pituitary-adrenal (HPA) system. Thus, the manifestations may include rapid pulse, increased blood pressure, excessive sweating, changes in bowel function, changes in appetite, trouble sleeping, and difficulty breathing. Subjective feelings of dread and fear accompanied by symptoms and signs of appropriate physiologic changes indicate the presence of anxiety. The brain structures associated with anxiety include the sensory and association cortices for processing the anxiety signal, the limbic system, particularly the amygdala and the anterior cingulate gyrus, the reticular activating system, and locus ceruleus (see Chap. 7).

Anxiety clearly has adaptive value both for the individual and in an evolutionary sense. Fear is essential in learning to avoid dangerous situations. Fear with associated physiologic arousal, when followed by resolution through mastery, such as successfully avoiding or overcoming the feared object, can also be associated with pleasure and euphoria, explaining thrill-seeking behavior. Genes coding for a low threshold for anxiety and fear, like a sensitive smoke detector, might have conferred survival advantage for our ancestors who needed to be fleet on their feet to avoid predators (see Chap. 7). In the modern age, individuals endowed with such genes might be diagnosed with a generalized anxiety disorder (Nesse 2001). Certain genetic polymorphisms, such as the serotonin transporter promoter gene

(5HTTLPR) short allele may code for a constitutional proneness for anxiety (Caspi et al. 2010; Ernst et al. 2013; Uher et al. 2011) (see Chap. 7).

Anxiety has an inverted U relationship with task performance. Too little anxiety results in little motivation and a lackluster performance, whereas too much anxiety leads to paralysis. Mild and transient, barely perceptible anxiety may arise when a stimulus has the potential to reactivate a long-standing psychological conflict that may result in overwhelming anxiety. Such anxiety, called *signal anxiety*, activates automatic psychological defense mechanisms (somewhat akin to a thermostat), such as denial, repression, projection, rationalization, and sublimation, that ward off the perception of the stimulus or its connections to the conflict.

14.2.2 Dysregulation of Anxiety

Anxiety is considered pathologic if it is uncontrollably excessive or persistent so as to affect one's functioning. Such dysregulation of anxiety may occur at several levels: genes, gene x environment interaction in childhood, and recent and current stress, both psychosocial and biological. The final common pathway brain dysfunction in the anxiety circuits underlies the anxiety syndrome (see Chap. 7).

14.3 Anxiety Syndromes

Anxiety disorders are the most common psychiatric condition. The 12-month prevalence estimate of anxiety disorders ranges from 4 to 17 %, and the lifetime prevalence ranges from 9 to 29 % (Somers et al. 2006). Anxiety disorders are more common in females than males (2:1 ratio). People seeking treatment for physical conditions have a higher than expected rate of anxiety disorders. A World Health Organization (WHO) study of 14 countries found a mean 1-month prevalence rate of 7.9 % of generalized anxiety disorder for patients presenting at a primary care clinic (Maier et al. 2000). Another recent WHO study of 17 countries found a positive linear relationship between the number of pain conditions and the rate of combined anxiety disorder (Gureje et al. 2008; Jordan and Okifuji 2011)

A childhood diagnosis of separation anxiety disorder significantly increases the risk of any later anxiety disorder (Kossowsky et al. 2013).

14.3.1 Secondary Anxiety Symptoms and Syndromes

In the consultation-liaison (CL) setting, secondary anxiety syndromes are quite common and should be considered first in diagnosing the anxious patient. Anxiety may be secondary to the stress of hospitalization itself, to the apprehension associated with a serious diagnosis or with procedure such as surgery, or to the biochemical changes secondary to the biochemical changes caused by the medical disease or by the drugs to treat the disease. Patients' lack of information concerning the illness and proposed treatment is another very common cause of anxiety. See Table 7.1 in Chap. 7 for a list of medical diseases that may underlie psychiatric syndromes.

Anxiety symptoms are particularly common in endocrine/metabolic disorders, such as hyperthyroidism, Cushing's syndrome, hypoglycemia, and hypocalcemia. They may also occur in certain neoplasms, particularly pheochromocytoma and carcinoid tumors as well as tumors of the CNS. Delirium and drug withdrawal states are almost always associated with anxiety. Pain is also an important concomitant of anxiety.

The stress of a serious medical disease or of hospitalization tends to heighten the underlying personality traits of an individual. Thus, a patient who has an anxious personality will experience even greater anxiety and may develop general anxiety or phobic symptoms, and an obsessive-compulsive personality may develop heightened obsessive-compulsive symptoms.

Differential Diagnosis of Anxiety Syndromes

1. Secondary Contributing Factors
   (a) Substances (adverse effects, intoxication, withdrawal)
      - Prescribed Drugs
      - Recreational Substances
   (b) Medical Diseases
2. Primary Anxiety Disorders

14.3.2 Primary Anxiety Disorders

Once secondary anxiety has been either ruled out or considered as a contributing but not primary factor, the presence of primary anxiety syndrome should be considered. Primary anxiety syndrome usually antedates the illness for which the patient is being treated, though it may be exacerbated by the illness or the stress of hospitalization.

DSM-5 classifies anxiety disorders as below:

Separation Anxiety Disorder
Selective Mutism
Specific Phobia
  Animal
  Natural environment
  Blood–injection–injury
  Fear of blood
    Fear of injections and transfusions
    Fear of other medical care
    Fear of injury
  Situational
  Other
Social Anxiety Disorder (Social Phobia)
Panic Disorder
Agoraphobia
Generalized Anxiety disorder
Substance/Medication-Induced Anxiety Disorder
Anxiety Disorder Due to Another Medical Condition
Other Specified Anxiety Disorder
Unspecified Anxiety Disorder

14.3.2.1 Separation Anxiety Disorder (SAD)

Predominantly a disorder of childhood and adolescence, this is characterized by developmentally inappropriate and excessive fear or anxiety concerning separation from the person(s) to whom the patient is attached. There is often recurrent excessive distress in anticipation of separation, persistent and excessive worry about losing the attachment figure, persistent and excessive worry about an untoward event (e.g., accident, abduction) that may cause a loss or separation, persistent reluctance to go out away from home for fear of separation, persistent or excessive fear of being alone, repeated nightmares involving the theme of separation, and repeated physical symptoms when separation from an attachment figure occurs or is anticipated. According to DSM-5, at least three of the above, and a duration of 4 weeks for children and adolescents and of 6 months for adults as well as clinically significant distress or impairment in social, academic, occupational, or other important functioning is required for the diagnosis.

According to DSM-5, the 12-month prevalence for adults is 0.9–1.9 %; in children, 4 %, and in adolescents, 1.6 %. Separation anxiety disorder is the most prevalent anxiety disorder in children under 12 years of age.

Separation anxiety disorder has high comorbidity with other anxiety disorders, obsessive-compulsive disorder, as well as depression and bipolar disorder.

Twin and family studies show a genetic contribution to SAD. Behavioral inhibition, which is a heritable temperamental characteristic, seems to be predictive of anxiety disorders in later childhood. (Hanna et al. 2006) Genetic influences may be greater for girls while shared environmental influences may be greater for boys. SAD seems more common in the siblings of children who have SAD and in the offspring of women who have anxiety or depressive disorders. Offspring of parents who have panic disorder have been shown to have a threefold increased risk of SAD, while offspring of parents who have panic disorder plus major depressive disorder have more than a tenfold increased risk.

Childhood anxiety disorders, particularly SAD, exhibit many of the respiratory abnormalities characteristic of adult panic disorder (Battaglia et al. 2009). These and other findings suggest that certain childhood anxiety disorders may share pathophysiologic features with adult panic disorder and that parents who have panic disorder may transmit a diathesis for some forms of anxiety that is observable in the respiratory system (Aschenbrand et al. 2003). In addition to genetic factors, developmental factors such as insufficient habituation, and the lack of safe environment and parental coping mechanisms of avoidance may contribute to the development of SAD.

14.3.2.2 Selective Mutism

Children with selective mutism do not initiate speech or respond to others when spoken to. Such children will speak with immediate family members at home but often not even in front of close friends or relatives (DSM-5). Children with selective mutism often refuse to speak in school, resulting in academic impairment. This condition may be accompanied with excessive shyness.

Selective mutism is a relatively rare condition, with prevalence of less than 1 %.

The onset is usually before age 5, and the course is variable, with most "outgrowing" the condition but many with social anxiety may continue to experience it.

Comorbidities include other anxiety disorders, especially social anxiety. Others include enuresis, encopresis, obsessive-compulsive disorder, depression, premorbid speech and language abnormalities, developmental delay, and Asperger's disorders (Wong 2010).

14.3.2.3 Specific Phobia

Specific phobias consist of marked and persistent fear that is excessive or unreasonable, cued by the presence or anticipation of a specific object or situation such as particular animals, heights, thunder, darkness, flying, being in closed spaces, urinating or defecating in public toilets, eating certain foods, undergoing dental work, the sight of blood or injury, and the fear of exposure to specific diseases. The onset is usually in childhood or early adulthood. The seriousness of the condition depends on how easy it is for the patient to avoid the phobic situation. Disease phobias (e.g., HIV/AIDS, radiation sickness) and needle phobias are common in CL settings. The phobic object may be a conditioned stimulus to fear.

Specific phobias are relatively common, up to 10 % of general population. Functional neuroimaging using symptom provocation paradigms show abnormal activations in brain areas involved in emotional perception and early amplification, mainly the amygdala, anterior cingulate cortex, thalamus, and insula. The insula, thalamus, and other limbic/paralimbic structures are particularly involved in specific phobias with prominent autonomic arousal. Emotional modulation is also impaired after exposure to phobic stimuli, with abnormal activations reported for the prefrontal, orbitofrontal, and visual cortices. Other cortices and the cerebellum also appear to be involved in the pathophysiology of this disorder (Del Casale et al. 2012).

DSM-5 lists the following specific phobias.

Animal (e.g., ailurophobia—cats, arthrophobia—insects, arachnophobia—spiders, ophidiophobia—snakes, misophobia—germs)
Natural environment (e.g., acrophobia—height, aquaphobia—water)
Blood-injection-injury
  Fear of blood
  Fear of injections and transfusions
  Fear of other medical care
  Fear of injury
Situational (e.g., claustrophobia—closed space, aviophobia—flying)
Other

14.3.2.4 Social Anxiety Disorder (Social Phobia)

Social phobia is characterized by marked and persistent fear of one or more social or performance situations in which the person is exposed to unfamiliar people or to possible scrutiny by others. In children, the anxiety must occur in peer settings and not just in interaction with adults. Individuals with social phobia fear that they will act in a way that will be humiliating or embarrassing, and consequently they avoid such social situations. The social situations must almost always provoke fear or anxiety to be diagnosed with this condition.

The phobia may be restricted to eating in public, to public speaking, or to encounters with the opposite sex, or it may be generalized, that is, involving almost all social situations outside the family circle. The onset is usually in childhood or adolescence, and it is more common in females.

About 7 % of the population have full social phobia, while up to 24 % have symptoms of social phobia. In a recent survey, about 9 % of adolescents in the USA had social phobia. There are more females with diagnosed social phobia, though the symptoms may be equally distributed between the sexes (Burstein et al. 2011; Merikangas et al. 2002).

The prevalence decreases with age, reaching in adults 2–5 % (DSM-5). However, those afflicted with the condition develop increasing impairment if left untreated (Hidalgo et al. 2001).

DSM-5 describes the syndrome of *taijin kyofushoI* (in Japan and Korea) as a culture-related diagnostic issue. This syndrome is characterized by the fear that the individual makes *other* people uncomfortable, e.g., "My gaze upsets people so they look away and avoid me" In societies with high collectivistic orientation, there may be higher social anxiety but lower prevalence of social anxiety disorder.

Behavioral inhibition and fear of negative evaluation are underlying traits of social anxiety disorder. Childhood abuse and maltreatment increases the risk of social anxiety disorder. First degree relatives of social anxiety disorder are two to six times at greater risk of developing the disorder (Hidalgo et al. 2001) (DSM-5).

14.3.2.5 Panic Disorder

In panic disorder, there are recurrent attacks of intense anxiety under unpredictable circumstances. A panic attack is an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes (DSM-5). There is often a sudden onset of palpitations, sweating, chest pain, choking sensations, dizziness, nausea, chills, chest pain or discomfort, and feelings of unreality (depersonalization or derealization). There is also a secondary fear of dying, losing control, or going mad. These attacks usually peak within 10 min and usually result in the patient's hurried exit from the place in which the attack occurs. A panic attack is often followed by a persistent fear of having another attack. Frequent and unpredictable panic attacks produce fear of being alone or going into public places where escape may be difficult (panic disorder with agoraphobia).

There is a remarkable similarity between the physiological and behavioral response to a conditioned fear stimulus and a panic attack which are mediated by a "fear network" in the brain that is centered in the amygdala and its interaction with the hippocampus and medial prefrontal cortex (Dresler et al. 2013; Gorman et al. 1989, 2000). There is evidence of decreased 5-hydroxytryptamine 1A (5-HT_{1A}) receptors in anterior cingulate, posterior cingulate, and raphe nuclei in panic disorder patients (Neumeister et al. 2004).

The onset of panic disorder is usually in early to middle childhood, affecting about 1–3 % of the population but as high as 7 % in an urban population (Goodwin et al. 2001; Pilowsky et al. 2006; Weissman et al. 1997). It occurs more commonly among females and is often associated with depression and increased suicidal ideation (Goodwin et al. 2001). Both heritable factors and stressful life events, particularly in early childhood, may be responsible for the onset of panic disorder.

Cardiac symptoms such as chest pain and palpitations, as well as mitral valve prolapse, hypertension, and cardiomyopathy, share significant comorbidity with panic disorder. In the respiratory subtype, there is often increased sensitivity to carbon dioxide (Amaral et al., 2013; Freire et al., 2010). There is also significant comorbidity between panic disorder and chronic obstructive pulmonary disease, irritable bowel syndrome, and migraine headache. There may be common pathophysiological mechanisms that may explain the association between panic disorder and comorbid medical illnesses, such as autonomic dysregulation of cardiac activity and smooth muscle tone and dynamic abnormalities of the coronary microvasculature (Zaubler and Katon 1996).

14.3.2.6 Agoraphobia

Agoraphobia is intense fear or anxiety triggered by real or anticipated exposure to a wide range of situations including at least two of (a) using public transportation, e.g., buses, planes, (b) being in open spaces e.g., parking lots, marketplaces ("agora" in Greek means "market"), (c) standing in line or being in a crowd, (d) being outside of home alone. Patients typically have thoughts of something terrible happening and that it would be difficult to get out, and panic-like symptoms may develop. The fear, anxiety, or avoidance must be out of proportion to the actual danger posed by the situation.

Approximately 1.7 % of adolescents are diagnosed with agoraphobia every year and females

are twice likely to have agoraphobia according to DSM-5. Prevalence in people over 65 years of age is 0.4 %. A high percentage of agoraphobic patients (30–50 %) also have panic attacks. The onset is before 35 years in 60 % of cases, and the course is chronic and persistent, and there is a high rate of comorbidity with other psychiatric disorders.

14.3.2.7 Generalized Anxiety Disorder (GAD)

In this syndrome, there is excessive anxiety and worry or apprehensive expectation about many events and activities. The symptoms may include nervousness, shakiness, muscular tension, sweating, light-headedness, palpitations, and stomach discomfort. There may be vague apprehension and forebodings of dreadful accidents or illness happening to them or to loved ones. Generalized anxiety disorder affects about 2.9 % of the adult population, is more common in women, and is often associated with chronic stress. Up to 10 % of the primary care population may have GAD (Lieb et al. 2005). In a recent study, 12 % of a large veteran population had GAD, and 40 % of patients with PTSD had comorbid GAD (Parmentier et al. 2013). GAD is associated with significant disability.

In GAD, there is evidence of dysregulation of central fear circuitry that includes components of the anterior limbic network (ALN) and involves connections between the amygdala and the ventromedial prefrontal cortex, ventrolateral prefrontal cortex, along with the rostral insula and subgenual and rostral anterior cingulate cortex. The ALN is innervated by multiple systems whose neurochemistry has been implicated in anxiety disorders. Serotonergic neurons, which originate from the median raphe nuclei innervate many of the individual components of the ALN and these structures (e.g., amygdala, ACC) contain numerous serotonin receptors. Similarly, structures such as the amygdala and hippocampus are densely coated with receptors for the inhibitory neurotransmitter γ-amino-butyric acid (GABA). In adolescents with GAD, viewing fearful faces caused increased activation of the amygdala, ventral prefrontal cortex, and ACC compared to healthy subjects. There was also less "negative coupling" between the VLPFC and amygdala, suggesting a failure of either modulatory or compensatory functions of the VLPFC (Strawn et al. 2012).

14.3.2.8 Anxiety-Related Physical Symptoms/Psychophysiologic Syndromes

This does not translate into a specific DSM-5 anxiety disorder diagnosis, but some patients manifest more prominent physical symptoms than the subjective feelings of anxiety. Only by careful questioning does one discern that the symptoms are associated with stress or stressful situations. Common such physical symptoms are palpitations, choking sensation, sweating, frequency of urination, nausea, vomiting, and constipation. Less common but more serious conditions include hyperventilation syndrome, irritable bowel syndrome, neurodermatitis, asthma, and fainting (Culpepper 2009). Any physical symptom associated with a physical disease may become exaggerated or exacerbated by anxiety, for example, tremors, seizures, COPD, migraine, and back pain. There is a bidirectional relationship between anxiety, hypertension, and coronary disease (Player and Peterson 2011).

Under DSM-5, many anxiety-related somatic symptoms would qualify for the diagnosis of somatic symptom disorder.

14.4 Management and Treatment of Anxiety Syndromes

In general, anxiety, regardless of cause, may be reduced by the use of antianxiety drugs, cognitive behavioral techniques, and environmental means. In secondary anxiety syndrome, the underlying cause should be identified and treated in conjunction with management of anxiety per se.

General pharmacologic treatment for anxiety involves the use of γ-aminobutyric acid (GABA) agonists such as benzodiazepines, selective serotonin reuptake inhibitors (SSRIs), and antipsychotic drugs. Benzodiazepines are useful for immediate relief of anxiety, especially situational anxiety. SSRIs are useful for treatment and attenuation of anxiety on a long term basis, as their

antianxiety effects are manifest weeks after beginning treatment. For severe anxiety, especially when associated with dissociative or psychotic symptoms, antipsychotic drugs such as perphenazine or quetiapine may be useful. Beta-blockers such as propranolol may be used for physiologic symptoms such as palpitation, and especially for performance anxiety. For performance anxiety, such as public speaking, propranolol 10 mg po 30 min prior to the performance may be quite effective. Antihistaminics, such as hydroxyzine, may be used for the sedative effect in anxiety disorders. Tricyclic antidepressants, for example imipramine and amitriptyline, and monoamine oxidase inhibitors (MAOIs) may also be used in place of SSRIs.

General nonpharmacologic treatments include cognitive-behavioral therapy (CBT), reassurance, supportive psychotherapy, relaxation training, mindfulness training, and self-hypnosis.

14.4.1 Separation Anxiety Disorder

Cognitive-behavioral therapy and psychoeducation of family is the treatment of choice for SAD (Bogels et al. 2013; Schneider et al. 2011, 2013). SSRIs, clomipramine, and tricyclics may also be useful (Lehman 2002; Seksel and Lindeman 2001). Benzodiazepines may be used judiciously, especially short-acting ones in the morning to allow the child to go to school (Hanna et al. 2006).

14.4.2 Selective Mutism

Treatment includes individual cognitive-behavioral therapy, family therapy, and psychotherapy with antidepressants (e.g., SSRIs) and antianxiety medications. Integrated behavior therapy for selective mutism has also been developed (Bergman et al. 2013).

14.4.3 Specific Phobias

Most phobias respond robustly to in vivo exposure, but it is associated with high dropout rates and low treatment acceptance. Response to systematic desensitization is more moderate. Virtual reality may be effective in flying and height phobia. Cognitive therapy is most helpful in claustrophobia. D-Cycloserine has been used effectively in conjunction with psychotherapy for specific phobias (Choy et al. 2007). Other psychotherapeutic techniques include relaxation training, flooding, and exploratory psychotherapy.

14.4.4 Social Anxiety Disorder

The drugs of choice are selective serotonin-reuptake inhibitors (SSRIs) including fluvoxamine, sertraline, paroxetine, citalopram, escitalopram, and fluoxetine, and the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine and duloxetine. Benzodiazepines, such as clonazepam and alprazolam, also are used frequently to treat anxiety disorders. Clonazepam is an efficacious treatment for social phobia. These drugs may interfere with exposure to feared situations that often is a part of cognitive behavioral therapy (CBT) for social phobia.

Monoamine oxidase inhibitors (MAOIs), such as phenelzine sulfate, are among the most efficacious treatments for social phobia. MAOIs, however, may have pressure responses to tyramine containing food and sympathomimetic drugs. Gabapentin seems to be effective only at higher doses. β-Adrenergic blockers do not seem to be efficacious for social phobia when administered on a regular dosing schedule, but they may have a role in the management of anxiety experienced occasionally in performance situations (Jorstad-Stein and Heimberg 2009). Propranolol 10 mg po 30 min prior to performance, such as public speaking, may be particularly effective.

Behavioral therapy, guided exposure, CBT with social skills training, and group therapy have been shown to be effective (Hofmann 2010).

CBT package (ie, psychoeducation, cognitive restructuring, and exposure) with an additional social skills training module may be particularly efficacious (Halaby et al. 2013; Hidalgo et al. 2001). CBT group therapy for social anxiety is also well established (Jorstad-Stein and Heimberg 2009).

Interpersonal therapy and psychodynamic psychotherapy may also be utilized. A recent study showed that both CBT and psychodynamic therapy were effective, but CBT had a higher remission rate (36 % vs. 26 %). The response rates were 60 % and 52 % respectively, and were comparable to those with pharmacotherapy (Leichsenring et al. 2013).

More recently, psychotherapeutic techniques such as motivational interviewing, mindfulness training, and acceptance and commitment therapy (ACT) have been utilized. In ACT, attempt is made to reduce experiential avoidance of fearful situations by helping socially anxious patients to accept and endure the negative experiences (i.e., develop greater "psychological flexibility"), rather than resort to avoidance and escape strategies (Eifert and Forsyth 2005; Mahaffey et al. 2013).

D-Cycloserine (DCS), a partial agonist of the NMDA receptor, has been shown to augment learning and memory, and doses of DCS received shortly after exposure facilitate extinction to feared stimuli in animals. Short-term dosing of DCS in social anxiety patients was found to be more effective than placebo in enhancing the effect of exposures. Patients who received DCS before exposures reported less social anxiety than patients who received placebo Patients who received DCS also reported improvement in their perception of their speech (Guastella et al. 2008; Hofmann et al. 2013a, b; Otto et al. 2007; Smits et al. 2013; Yaka et al. 2007).

14.4.5 Panic Disorder

Antidepressant drugs (SSRIs, tricyclics, and MAOIs) and high-potency benzodiazepines have been shown to be effective for panic disorder with or without agoraphobia. Commonly used SSRIs include fluoxetine, paroxetine, and sertraline, and high-potency benzodiazepines include alprazolam and clonazepam. Alprazolam is effective in treating the acute panic attack, but has a high potential for tolerance and abuse. Venlafaxine and mirtazapine have also been found to be effective in reducing anxiety in panic disorder (Andrisano et al. 2013).

Panic disorder has been subtyped into two subtypes based on differential responses to CO_2 challenge. Patients who showed prominent respiratory symptoms (respiratory subtype) were more sensitive to CO_2 challenge, had a significantly longer illness duration, had more severe panic and phobic symptoms, and were more likely to be heavy smokers than were patients without respiratory symptoms (Biber and Alkin 1999). Clonazepam may be especially useful in treating patients with the respiratory subtype of panic disorder (Nardi et al. 2013).

Cognitive-behavioral therapy is effective, particularly in combination with pharmacotherapy (de Carvalho et al. 2010; McHugh et al. 2009; Schmidt and Keough 2010). The cognitive component may include, for example, reevaluating the symptoms as being due to anxiety and not due to a heart attack, and the behavioral component may include *exposure and response prevention;* that is, the patient is exposed to a panic-producing situation and the patient learns to "ride out" the panic until it passes.

14.4.6 Generalized Anxiety Disorder

Generalized anxiety disorder is a chronic illness, and a realistic goal of treatment is to reduce anxiety symptoms sufficiently for functioning, not total elimination. In general, a combination of pharmacotherapy and cognitive behavioral therapy is effective in GAD (Wetherell et al. 2011, 2013).

Evidence suggests the efficacy of the SSRIs (e.g., sertraline, fluvoxamine, fluoxetine, paroxetine) and the SNRIs, venlafaxine and duloxetine in treating GAD. Buspirone, a 5-HT1A partial agonist, seems less effective (Mavranezouli et al. 2013; Strawn et al. 2012). Imipramine, hydroxyzine, valproate, and pregabalin are also effective, and the antipsychotic mood stabilizers, risperidone, olanzapine, ziprasidone, and aripiprazole may also reduce symptoms (Huh et al. 2011).

Psychoeducation, CBT, supportive psychotherapy, relaxation training, meditation, and self-hypnosis may be useful in GAD. All forms of CBT, including individual, group, and family/parental formats of CBT have been shown to be

effective for GAD. Interpersonal therapy, motivational interviewing, and acceptance-based behavioral therapy (ABBT) may also be effective (Garfinkle and Behar 2012)

14.4.7 Anxiety-Related Physical Symptoms and Psychophysiologic Syndromes

Treatment of the physical symptoms associated with anxiety should be geared to both the physical symptoms and the underlying anxiety. Thus, paper-bag rebreathing to reduce the hypocapnea is an effective treatment for *hyperventilation syndrome*, and anticholinergic drugs may be effective for *irritable bowel syndrome*. The effective use of non-deceptive placebo for irritable bowel syndrome has been reported (Kaptchuk et al. 2010).

Benzodiazepines or antidepressants may be used to control/reduce anxiety. In psychophysiologic syndromes, there may be excessive physiologic arousal in the presence of only moderate anxiety, and such arousal may be treated with antianxiety agents. There is no evidence that prolonged use of moderate to large doses of benzodiazepines to control such physical symptoms results in tolerance and the need for more benzodiazepines. The pharmacologic and psychotherapeutic measures described for GAD are also applicable for psychophysiologic syndromes (Dekel et al. 2013).

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