Anxiety Disorders and Medical Comorbidity: Treatment Implications

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This chapter identifies medical illnesses with high co-occurrence with anxiety disorders and offers an analysis of implications for treatment of both types of conditions. We concentrate on medical conditions with high associations to anxiety and panic by aspects of symptomatology, specifically neurological disorders (fibromyalgia, epilepsy, cerebral palsy), non-cardiac chest pain, diabetes, gastrointestinal illness (irritable bowel syndrome, gastroesophageal reflux disease), and cardiovascular and respiratory illnesses (asthma).

Comorbid Neurological, Pain, and Anxiety

Fibromyalgia Symptoms of anxiety depression are cardinal for individuals with fibromyalgia (FM). FM is a chronic neurological disorder characterized by pervasive musculoskeletal pain and tenderness, with secondary symptoms including fatigue, memory impairment, and gastrointestinal disorders, among others [1]. It occurs in up to 4% of the general population, with women being the majority of individuals diagnosed [2]. A large percentage of individuals with FM meet diagnostic criteria for at least one anxiety or depressive disorder, making the treatment of FM a complex task [2]. Specifically, 27–60% of patients with FM report a current anxiety disorder, with 62% reporting lifetime diagnoses of any anxiety disorder [3]. Research indicates that anxiety in FM patients is associated with higher levels of perceived pain and more severe symptom [4, 5]. Because FM symptoms and associated psychiatric symptoms can substantially reduce daily functioning, the illness is of significant economic burden. Among chronic pain conditions, FM is associated with the most unemployment, financial disability, and days off [2, 6]. Because there is no cure, physicians and patients focus on managing and coping with existing pain.

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Y.-K. Kim (ed.), *Anxiety Disorders*, Advances in Experimental Medicine and Biology 1191, https://doi.org/10.1007/978-981-32-9705-0_15

The first line of treatment for FM patients with comorbid anxiety is antidepressants or psychotherapy [7]. It is widely accepted that cognitive, behavioral, and affective factors play a pivotal role in the level of pain, psychological distress, and impairment associated with chronic pain conditions [5]. Cognitive factors such as catastrophizing, pain-related fear or anxiety, attentional bias toward threatening or general negative cues, and helplessness all contribute to how a patient experiences and copes with their chronic pain [5, 8, 9].

Cognitive behavioral therapies (CBT) are frontline psychological treatments for chronic pain, including fibromyalgia [10], with findings of controlled trials providing supporting treatment benefits for comorbid pain and anxiety [11, 12]. For instance, in a controlled trial by Garcia and colleagues [12], the authors examined the differential efficacy of CBT, a muscle relaxant (cyclobenzaprine), combined treatment, or a waitlist control condition. The CBT and combined group conditions resulted in significantly greater long-term improvements in anxiety compared to the drug-only or control condition [13]. Other variations of CBT, including CBT-Insomnia, CBT-Pain, and their hybrid (CBT-IP), showed mixed success for reducing anxiety [13, 14].

Interventions aimed at facilitating change in attentional biases also show promise for reducing pain, anxiety sensitivity, and pain-related fear and anxiety. In a small, double-blind, controlled trial, 17 women with FM received an attentional modification group (AMP) or an active, placebo control group [8]. Participants in the AMP group completed two weekly 15-min sessions over 4 weeks targeting attentional biases toward catastrophizing and pain-related anxiety. AMP resulted in significantly greater reductions for pain, anxiety sensitivity, and pain-related fear supporting attention modification as a viable psychological treatment option [8]. Mindfulness-based stress reduction and Acceptance and Commitment Therapy (ACT) provide good grounds for treating comorbid chronic pain, fibromyalgia, and anxiety [15, 16]. For example, comparing 12 weeks of ACT to a waitlist control, Wicksell and colleagues showed significant reductions in anxiety in FM patient [17]. Additionally, a variety of intervention strategies including guided imagery/hypnosis, attachment-based compassion therapy, and meditation have shown success in controlled trials for reducing pain and psychological distress [18–20]. Lastly, studies have highlighted the efficacy of biofeedback broadly within neurological disorders, some focusing directly on its effect within FM populations [21, 22]. For example, EEG biofeedback, compared to escitalopram, resulted in greater anxiety and depression reductions, with gains being maintained throughout follow-up [22]. The initial evidence for neurofeedback intervention for comorbid fibromyalgia syndrome and affective symptoms is promising and inspired further research [23].

Epilepsy Epilepsy is a rare but highly debilitating neurological disorder. Epilepsy is characterized by unprovoked seizures with a wide range of symptoms. Epidemiological research has found anxiety disorders to be more than twice as likely in patients with epilepsy compared to the general population, with some studies reporting anxiety disorders in up to 30% of epileptic patients [24, 25]. Comorbid anxiety and epilepsy reduce health-related quality of life [26, 27].

Increasing seizure control with medical procedures, such as epilepsy surgery or medication, is the first line of treatment [25]. Once seizure control is improved, second-line treatments targeting anxiety can be employed. Antidepressants, such as buspirone and selective serotonin reuptake inhibitors (SSRIs), are commonly used to treat comorbid epilepsy and anxiety disorders [25], though special attention and monitoring are required to seize the elevated risk of inducing or exacerbating seizures. A 2017 Cochrane review [28] found that psychological treatments including CBT or ACT were beneficial for individuals with epilepsy, though only one of the five studies included anxiety as outcome measures. Overall, those studies reported significant reductions in anxiety levels post-intervention [28]. Apart from reducing anxiety, CBT and ACT have shown promise in reducing depression and improving quality of life, for people with epilepsy, particularly when combined with antidepressants [29–32]. For instance, Macrodimitris and colleagues [33] tested a ten-session group CBT pilot trial for epilepsy and comorbid depression or anxiety and observed significant improvements in anxiety, depression, and negative automatic thoughts. The generic CBT protocol targeting anxiety and depression was well accepted and provided evidence reducing affective symptoms. Following up with a controlled trial, Gandy and colleagues [34], however, failed to demonstrate significant improvements in anxiety when comparing CBT to a waitlist control for patients with epilepsy. An uncontrolled prospective ACT intervention involving 60 patients with epilepsy found the treatment had medium to large positive effects on several psychological outcomes, including anxiety, at 6-months follow-up [31]. Comparing mindfulness-based therapy (MT) and social support in drug-resistant patients with epilepsy also resulted in significantly greater reduction anxiety and depression symptoms and frequency of seizures in the MT group [35]. Lastly, preliminary results for biofeedback for epilepsy show promise, providing a low-cost and easy-to-implement therapy approach for seizure control [36–38].

Cerebral Palsy Cerebral palsy (CP) refers to a group of developmental disorders defined by impairment in motor function, muscle tone, balance, and coordination. CP is associated with varying degrees of functioning across domains (i.e., speech, cognitive functioning, eating). Research indicates that adults with CP are at a 40% increased risk of being diagnosed with an anxiety disorder, with the risk even higher for those without intellectual disability [39]. Mothers of children with CP also reported elevated levels of parenting stress [40], and up to 30% report experiencing affective symptoms at clinical levels [41]. Both are negatively associated with parenting satisfaction and child quality of life [42]. In a study involving 31 caregivers of children or adolescents with CP parents' ratings of their characteristics and children's behavior problems, parenting depression, stress, and state anxiety were significantly related to children's quality of life [43]. As a result, interventions targeting parent-child relations and parenting strategies are becoming more common.

Roux and colleagues [44] investigated the effects of a nine-session group family intervention (Stepping Stones Triple P; SSTP) on child behavior problems, parenting styles, parent-child conflicts, and parental satisfaction. Fifty-two families with a

child diagnosed with autism spectrum disorder, CP, Down syndrome, or intellectual disability were randomized into a waitlist group or immediate treatment conditions, designed to facilitate positive parenting strategies, children's competence, positive relationships, and behavior management. The authors found significant improvements in child behaviors, relationship quality, and parental satisfaction [44]. Another controlled study involving 67 parents of children with CP compared the differential effects of SSTP, SSTP+ACT (Acceptance and Commitment Therapy) and a waitlist control on improvements in quality of life, functional performance, parenting style, and behavioral and emotional problems [45, 46]. Compared to the waitlist, the SSTP + ACT group demonstrated improved quality of life and functional performance as well as decreased behavioral problems and parental psychological symptoms, over-reactivity, and verbosity. SSTP alone was associated with decreased behavioral problems and emotional symptoms [45, 46].

However, there is relatively limited literature focused on psychotherapy, specifically targeting anxiety in people with CP. Three case studies, one involving systematic desensitization, one biofeedback relaxation training, and the other involving CBT, discuss that the suitability of these interventions for CP is far from providing adequate evidence for their efficacy [47–49]. Additionally, two controlled studies involving interventions for individuals with CP indicate that mindfulness yoga interventions and horse therapy could be beneficial for various physical, behavioral, and cognitive outcomes, though neither study discusses anxiety as an outcome [50, 51].

Non-cardiac Chest Pain

Non-cardiac chest pain (NCCP) is experienced as a squeezing, pressure-like, or burning substernal sensation which radiates to the spine, neck, left arm, or jaw [52]. NCCP is difficult to distinguish from malign cardiac chest pain. Consequently, it is a highly prevalent symptom reported within emergency departments and primary care clinics, with an incidence rate of 20–25% [52, 53]. Medical literature cites multiple causes of NCCP, both biological (e.g., gastrointestinal reflux disease, microvascular ischemia) or psychological (e.g., abnormal pain perception, passive pain coping strategies) [54]. Though NCCP is a benign condition with an excellent prognosis [55–57], it is often chronic and is associated with high disability and cost [58]. Research has shown higher prevalence rates of psychiatric disorders within NCCP, with up to half of the patients eventually meeting diagnostic criteria of an anxiety disorder, including generalized anxiety disorder, panic disorder, and social phobia [59, 60]. Inaccurate interoceptive sensitivity, or hypervigilance of somatic sensations, is hypothesized to play an important role in the development of anxiety, particularly within these populations. White and colleagues [61] found that patients with NCCP and comorbid anxiety or depression symptoms were prone to hypervigilance of their cardiorespiratory symptoms. This inaccurate and oversensitive perception, particularly with cardiac anxiety (the fear of sensations associated with the heart), has been linked to excessive healthcare-seeking behaviors [62]. NCCP is associated with exceedingly high healthcare costs (up to 315 million dollars

annually), likely due to the various invasive procedures, incorrect diagnoses, and failed treatments associated with assessing and treating chest pain [63, 64]. Thus, interventions targeting symptom differentiation and relieve are of high priority.

Treatment for NCCP varies depending on the etiology of the pain (i.e., biological or psychological). The majority of patients who seek medical attention for chest pain are eventually diagnosed with medically based disorders such as gastroesophageal reflux disease or esophageal motility disorders and thus treated with medications, minor procedures, or surgery. However, those whose chest pain has no biological or medical explanation are thought to benefit from psychotherapy.

A 2015 Cochrane review [65] concluded that CBT-type interventions are beneficial for individuals with NCCP. By restructuring anxiogenic thoughts, providing education about symptom origination, and exposing patients to feared bodily sensation, CBT aims to reduce distress produced when experiencing non-cardiac chest pain [66, 67]. Specifically, in the studies that included anxiety as an outcome variable (four CBT interventions, two relaxation interventions, one cardiac rehabilitation, and one coping skills training), psychological conditions indicated significant improvements over control conditions [65]. Spinhoven and colleagues [68] compared the efficacy of 12 weeks of CBT, paroxetine (a selective serotonin reuptake inhibitor), or placebo in reducing pain, anxiety, and heart-related anxiety for 69 individuals with NCCP. Analyses indicated that CBT was superior to paroxetine and placebo in reducing pain, while both CBT and paroxetine were superior in reducing heart-related anxiety compared to placebo [68]. Jonsbu and colleagues [66] did not observe significant improvements in the frequency of bodily symptoms in a brief three-session CBT-controlled trial for NCCP. However, there was a reduction in avoidance and catastrophic interpretation of those symptoms, which may be the more significant finding for psychologically based NCCP [66]. Finally a recent, large controlled study demonstrate short-term success (at 3 months) but failed to show long-term (1-year) improvements in psychological health, including anxiety, in a brief BT intervention for NCCP [69].

An alternative treatment approach for NCCP is relaxation training. For example, Lahmann and colleagues [70] assigned sufferers to either functional relaxation (FR) or an enhanced medical care control group. The intervention was 6 weeks in duration during which the FR treatment group received ten group sessions focused on creating awareness of various bodily sensations by physical movements and breathing [65, 70]. FR group resulted in significantly greater anxiety and somatization symptom reductions compared to the control group [70]. Furthermore, a study recognizing the unique needs of NCCP, particularly within an emergency department, pilot tested a brief self-help psychoeducational intervention for NCCP patients with elevated anxiety [71]. The psychoeducational materials included (1) information regarding potential causes of NCCP, (2) coping techniques for stress and pain management, and (3) directions on how to implement coping techniques. The trial provided a strong preliminary signal for need, feasibility, and acceptability [71]. Other forms of psychosocial interventions for NCCP include hypnosis, coping skills training, and guided breathing [65, 72, 73].

Lastly, pharmacological treatments designed to reduce symptoms of anxiety and depression, as well as the perception of pain, are tested, but results are mixed [68, 73]. Comparing sertraline to placebo resulted in significant reductions in daily pain, but not depressive symptoms [74]. In a study by Keefe et al. [73], sertraline only did not result in reductions in anxiety. However, the combination of coping skill training (relaxation, imagery, distraction, activity-rest cycling, pleasant activity scheduling, and cognitive restructuring) was successful.

Comorbid Diabetes and Anxiety

Diabetes has become a rising health concern, with a prevalence of 8.3% in the population [75]. Diabetes complications include cardiovascular disease, circulatory difficulties, kidney failure, and amputations [76]. Clinical anxiety has been diagnosed in up to 40% of diabetes patients and is linked to worse glycemic control [77–80]. Numbers may be even higher due to healthcare professionals overlooking anxiety symptoms and attributing distress to patients having maladjustment to their diabetes diagnosis [81]. Like in other chronic somatic disorders, comorbid anxiety disorders can exacerbate disease symptoms by interfering with treatment adherence, such as having a fear of injection and needles may interfere with glycemic control [82, 83].

Symptom overlap between diabetes and anxiety, especially panic, is common and is associated with greater distress, disease worsening, and a greater burden on the healthcare system [84]. For example, feelings of tingling and numbness in the extremities are a common symptom of both panic disorder [85] and diabetes [76]. Hypoglycemia or low blood sugar can lead to shakiness, sweating, and rapid heartbeat [81], symptoms that mimic the ones of a panic attack [86]. Phobic fears include fear of needles and injection [83, 87]. Patients with comorbid diabetes and blood-injection-injury phobia [85] are more likely to have macrovascular complications and insulin non-compliance [88]. Lastly, a specific diabetes-related fear, fear of hypoglycemia, can cause patients to maintain levels above the recommended dose [84, 89].

Interventions targeting the complex interaction of diabetes-related health and affective disorders are of great interest and need. One major goal of psychotherapeutic treatment of diabetes is to improve glycemic control by helping patients manage their medications and be more adherent to better healthier lifestyles [90]. A meta-analysis on psychosocial interventions for comorbid mental health disorders and diabetes has found that a combination of lifestyle and psychosocial interventions (problem-solving, cognitive-behavior therapy, and social support) are efficacious in reducing physical or mental health symptoms, but possibly not both [91]. Psychosocial interventions that included education and skills training had better outcomes on glycosylated hemoglobin (HbA1c) [91]. A recent meta-analysis on psychosocial interventions (ranging from CBT to illness management interventions) concluded that psychosocial interventions specifically appear to reduce anxiety symptoms short-term, but not long-term, and failed to improve self-efficacy of diabetes management [92].

Results from CBT trials show promise in reducing HbA(1c), anxiety, and prevention of hypoglycemic states compared to a treatment-as-usual control group [93]. Several other psychotherapeutic intervention modalities are recommended as diabetes treatment augmenters. For instance, techniques to enhance mindfulness and nonjudgmental approach (components of ACT) resulted in normalizing glycated hemoglobin and improving coping strategies [94], but more controlled studies are needed [95, 96]. Combining CBT and motivational enhancement therapy has also shown promise in glycemic control management [97], so has motivational interviewing [98] and problem-solving therapy [99]. The latter, a pilot trial, led to reductions in psychological distress and normalization in glycemic markers.

Comorbid Gastrointestinal and Esophageal Disorders and Anxiety

Gastrointestinal (GI) and esophageal symptoms like diarrhea, abdominal distress, and nausea are commonly reported by anxiety sufferers especially those diagnosed with generalized anxiety disorder and panic disorder [100–104]. Historically, medical and psychological models independently examined GI symptoms. Current research acknowledges more strongly a brain-gut connection or axis, where psychosocial stressors and anxiety may negatively impact the gastrointestinal biome and exacerbate existing biological vulnerabilities [105–108]. Stress and the endocrine response of corticotropin-releasing factor (CRF) has been proposed to affect IBS through multiple pathways including CRF role in colon secretion, visceral hypersensitivity, hypervigilance, and effects of CRF on low-grade activation of the immune system cells in the GI tract caused by inflammation [109, 110].

An example of this interaction is irritable bowel syndrome (IBS), a condition highly comorbid with anxiety disorders [107]. Primary symptoms of IBS include high levels of recurrent abdominal pain, present at least 1 day per week over at least 3 months. IBS is associated with changes in bowel habits, including diarrhea, constipation, or both [111, 112]. Epidemiological studies indicated that 10–25% of the population suffers from IBS, with twice as many women than men [113]. Likewise, more than half of those with IBS have been reported to have a comorbid psychiatric disorder, with the most common being depression (25%), panic disorder (21–46%), and generalized disorder (25%) [107, 114–117]. Lee et al. [118] found that IBS was 4.7 times more common in GAD than in non-patients.

Targeted intervention is of high relevance and need due to the documented heightened comorbidity, high costs in the utilization of healthcare services, and negative impact on patients' overall work productivity [119–121]. Four primary psychotherapeutic interventions for IBS have been studied: cognitive behavioral therapy (CBT), relaxation techniques, hypnosis, and psychodynamic therapy [122, 123]. A recent meta-analysis by Laird et al. [124] of 41 controlled trials of psychological interventions for IBS showed that CBT, hypnosis, psychodynamic, and relaxation were beneficial in improving mental health symptoms, including anxiety and depression. Except for relaxation techniques, interventions also increased

improvements in daily functioning. CBT was the most studied modality (21 studies compared to less than 5 for their other modalities) showing the most evidence for its efficacy in improving daily functioning and reducing avoidance behavior likely due to teaching exposure-based techniques. In support, systematic exposures in an Internet-delivered CBT dismantling study were associated with greater GI symptoms and anxiety decrease than CBT without [125]. Results on long-term effects (12-month follow-up) are mixed with some showing enduring effects [123, 126], while others such as gut-directed hypnotherapy do not [127].

Treatment options tailored to targeting anxiety specific to IBS symptoms, coined gastrointestinal (GI)-specific anxiety [128–130], have also been studied. GI-specific anxiety is linked to increased hypervigilance, poor coping responses, and increased pain sensitivity [128] and can lead to symptom exacerbation [131]. Targeting hypervigilance and hypersensitivity to visceral sensations through exposure-based interventions is, therefore, a promising approach [107, 124]. In a meta-analysis on CBT-controlled trials for IBS, Altayar et al. [132] found reductions in IBS symptom severity, IBS quality of life, and abdominal pain, as did a recent meta-analysis on the effects of antidepressants, relaxation therapy, multicomponent psychological therapy, hypnotherapy, and dynamic psychotherapy [133]. The psychological interventions of CBT, hypnotherapy, multicomponent psychological therapy, which included a mix of relaxation, thermal biofeedback, and cognitive therapy techniques, were more efficacious in reducing symptoms than control therapy conditions [133].

Challenges to treatment engagement in IBS sufferers can be due to lack of motivation or denials that their symptoms are connected with their psychosocial functioning [108, 134]. Therefore, clinicians and medical providers should establish good patient rapport and provide clear education on the interaction of mental health and IBS to increase treatment participation and adherence [135].

As an alternative to psychotherapy, psychotropic medications are investigated for functional gastrointestinal disorders (FGID). Tricyclic antidepressants and SRRI show promise in lowering pain and anxiety symptoms in patients with FGID [136, 137]. Despite greater efficacy over placebo, caution should be used before administering antidepressants as shown in a recent meta-analysis due to intolerability issues [138]. Corticotropin-releasing hormone antagonist also shows promise in reducing inflammation [139] and anxiety and depression [110], yet no large-scale trials are published yet.

Combined medication and drug treatments can also be considered. In a recent controlled trial for patients with nonerosive reflux disease, Li et al. [140] found the combination of GI medication (omeprazole and domperidone) and CBT was more efficacious in reducing self-report gastroesophageal reflux and quality of life than medication or CBT alone. Anxious or depressed symptoms were equally lower in CBT only or the combined treatment compared to medication only.

Lastly, research on treating psychological distress in gastroesophageal reflux disease (GERD), a condition where stomach content begins to leak back into the esophagus, causing discomfort or pain, has garnered interest. GERD, a diagnosis confirmed by endoscopic esophageal mucosal damage or erosion [141, 142], poses

a heavy burden on the healthcare system with seven million visits a year attributed to GERD and reflux esophagitis [143]. First-line medical treatments, including proton pump inhibitors, pharmacology, and behavioral changes like weight loss and diet [144], have high numbers of non-responders (40%) [145–148]. Psychogastroenterology highlights the integration of psychological interventions and GI interventions [149], as psychosocial stressors appear to worsen symptoms of GERD [148]. Emerging psychosocial interventions include relaxation [150], diaphragmatic breathing [151], and speech therapy [152]. These treatments show promise for reducing reflux, GI and GERD symptoms, and stress, but objective 12 measures of acid exposure are often lacking. CBT for excessive supragastric belching, a condition related to GERD, found relief in both objective symptoms of GI as well as overall increased quality of life [153]. The sessions consisted of psychoeducation about the disease, identification of physical sensations, restructuring maladaptive thinking patterns about their belching, diaphragmatic breathing, and mouth opening/tongue position to better control belching.

Comorbid Cardiorespiratory Disorders and Anxiety

Decades of research support the heightened prevalence of anxiety disorders, particularly panic disorder, within individuals with respiratory and cardiovascular diseases [154–156]. With more than 80% of panic sufferers complaining of such physical symptoms as chest pain, tachycardia, or dyspnea [157, 158], PD is associated with substantial health decrements [159] and ranked among the top three mental and physical illnesses associated with perceived health decrements [160–162].

Cardiovascular Disorders Interactions between psychological stress and activation of the cardiovascular system have long been a focus of research [163–165]. Epidemiological studies report consistent links between anxiety disorders and cardiovascular disease, including cerebrovascular events, such as strokes [166], coronary heart disease (ischemic heart disease, myocardial infarction, angina pectoris), chronic heart failure [167], and hypertension [112, 155, 168–172]. Heart racing or palpitations are central symptoms in both cardiovascular illness conditions and anxiety. Notably, they are also the most prominent and widely reported physical symptoms in panic disorder (PD) [173]. Dysfunctional activity of the autonomic nervous system and hypothalamic-pituitary-adrenal axis, which affects the cardiovascular system, is implemented in both anxiety and depression [156, 174, 175]. Consequently, studies highlight the bidirectional nature of cardiovascular illness augmenting the vulnerability for a subsequent anxiety disorder and vice versa. In support of the earlier, hypotensive compared to normotensive individuals have elevated rates of PD, and PD onset was typically followed diagnosis [176]. Likewise, discrete cardiac events such as myocardial infarctions (MI) are associated to increased risk of posttraumatic stress disorder (PTSD), worsened adverse illness management outcomes, and subsequent major cardiac events and mortality [177]. In a recent 2019 study, 54% of cardiac disease patients met criteria for severe depression [178]. However,

there is also an elevated risk for anxiety disorders, with 19% meeting criteria severe-to-very severe anxiety [178] and the manifestations of cardiovascular illness, including mortality from cardiac events [179, 180]. Reversely, several longitudinal studies show that panic onset before the age of 21 years relates to a 1.3-fold risk for subsequent hypertension [181] and panic sufferers had a 1.5-fold risk of atrial fibrillations in one study [182] and a 2-fold risk of subsequent cardiovascular illness in another [183]. Finally, postmenopausal women with PD were at more than the fourfold risk for developing coronary heart disease [184].

Cardiac rehabilitation represents the first-line treatment for coronary heart disease (CHD). It is a multicomponent treatment incorporating health education, physical exercise, and diet but also includes psychosocial (e.g., CBT, hypnotherapy, stress management such as relaxation, coping and problem-solving skill training) and psychopharmacological interventions. CHD and anxiety disorders share contributing factors that strongly link to problematic health behaviors, such as physical inactivity, smoking, and obesity.

Development of catastrophic thoughts and fear of dying following illness onset and subsequent avoidance behavior further fuel sedentary lifestyle, and foster symptoms at benign levels of physical activity. Furthermore, somatizing medical patients likely present with a lower threshold for experiencing subtle bodily sensations as aversive and fear-provoking (heart-focused anxiety), particularly if the sensation mimics those of serious medical conditions [156]. Stress resulting from heart-focused anxiety may, in turn, increase the occurrence of angina attacks and the probability of cardiac death as discussed above. Notably, while CHD patients predominantly report physical symptoms, they rarely fear them or have a sense of catastrophe. By contrast, chest pain experiences in NCCP are dominated by catastrophizing thoughts. Palpitation, the most common reason for cardiologist referrals, is indeed only weakly related to arrhythmia and is largely asymptomatic as are heart rate symptom perceptions.

Furthermore, preventative cardiac treatments such as the use of implantable cardioverter defibrillators (ICDs) to treat life-threatening ventricular fibrillation can, in and of themselves, increase the risk for clinical anxiety. The painful and uncontrollable shocks are linked to adverse psychological outcomes, with up to 20% of ICD users developing severe anxiety and panic [185, 186]. Strikingly, rates of PD and agoraphobia are 60% for those with more than two electrical discharges per year compared to 10% for one discharge [187].

Based on the latest Cochrane study [188] on the effects of p*sychological* interventions for coronary *heart* disease, no effect was found for reduced total deaths (any cause), risk of cardiac surgery, or having another heart attack. However, they showed significant reductions in stress, depression, and anxiety [188]. Particularly promising was the small but significant effect for cardiac mortality. Similarly, a recent meta-analysis on patients with myocardial infarction [189] attested to the benefits of exercise-based cardiac rehabilitation on alleviating anxiety and depression symptoms. Findings from CBT-based trials demonstrate anxiety reductions up

to 60% in patients with ICDs [190] as well as for CHD more generally, including acute coronary syndrome, atrial fibrillation, and postmyocardial infarction [191]. A controlled trial testing anxiety-focused CBT for comorbid generalized anxiety disorder and chronic heart failure sufferers resulted in significant reductions in anxiety and unplanned hospital admissions [192]. Finally, promising new interventions are under investigation, such as the UNWIND study which is examining the benefits of exercise and escitalopram in anxious patients with coronary heart disease [193].

Asthma Strong and consistent associations have been found between asthma and anxiety disorders [112, 194], in particular, panic disorder, panic attacks, generalized anxiety disorder, and phobias [195–199], with prevalence rates for anxiety disorders of up to 45% in asthmatic samples [200]. Self-reported respiratory disease is associated with a 70% greater likelihood of panic attacks [195]. Sixty-three percent of asthma patients presenting to the emergency room for acute exacerbations suffered from an anxiety disorder [201], a phenomenon which is likely due to the frightening nature of asthma symptoms such as extreme dyspnea, chest tightness, or feelings of suffocation. Among the anxiety disorders, PD has often presented a specifically strong association with asthma [202], with prevalence rates up to 24% of adults and 4.7% of children/adolescents [112, 203]. Childhood asthma symptoms are associated with increased levels of shyness/anxiety [204] and predict later-life development of panic disorder and agoraphobia [198, 205]. The illness may lead to subsequent anxiety/panic through the emotional burden of chronic illness and excessive monitoring of illness-related symptoms that are interpreted as impending signals of physical catastrophe (e.g., shortness of breath interpreted as respiratory arrest) [206]. Early adulthood PD increases odds by more than six times for asthma later in life, possibly through additional problematic health behaviors, such as smoking, lack of physical activity, or dysfunctional dietary habits leading to obesity [207].

A substantial body of evidence suggests that comorbid anxiety complicates the management of asthma and is a risk factor for greater asthma morbidity, independent of objective measures of pulmonary function [200, 208]. Strong negative emotions and stress contribute to bronchoconstriction [209–212] and airway inflammation [213, 214], thereby exacerbating asthma. Asthma exacerbations lead to symptoms greatly feared by comorbid panic sufferers, thus exacerbating panic attacks. Anxiety and asthma comorbidity are associated with mutual complications in diagnosis and management. Similar symptoms may cause errors in diagnosis and treatment, leading to additional costs for the healthcare system [215, 216]. Asthma patients with higher anxiety levels are more likely to use healthcare providers, hospitalization, and emergency visits [217–219]. Comorbidity has been associated with reduced quality of life [220, 221] and elevated medication use [222].

Although medication is undisputedly the first line of treatment for asthma patients, some (e.g., oral corticosteroids, β-agonists [205]) provoke the very symptoms anxious patients fear, thus exacerbating anxiety. Likewise, psychotropic medication for anxiety can cause respiratory side effects that can complicate asthma

symptoms. Thus, psychosocial interventions that are equally effective as psychotropic medication in managing anxiety may be preferable.

On the other hand, caution is warranted since psychosocial interventions for anxiety carry other risks for the asthma patient. For example, CBT for anxiety often includes interoceptive exposure exercises, such as voluntary hyperventilation, that would lead to bronchoconstriction [223, 224]. Similarly, slow abdominal breathing training without control of PCO_2 levels, a common technique included in CBT, can lead to hyperpnea or hyperventilation [225]. The efficacy of relaxation for asthma patients also is debated [226, 227] since it may encourage bronchoconstriction through enhancing parasympathetic activity.

Despite the repeated calls for standardized and evaluated interventions for comorbid asthma and anxiety [112, 196, 228], interventions remain remarkably absent, even though anxiety symptoms are viewed as modifiable risk factors. There have been attempts to improve self-management behaviors [229, 230], such as self-monitoring (symptom and peak flow diaries), allergen and trigger avoidance, and correct use of medication [231–235]. Interventions, including CBT, yoga, scriptography, and biofeedback techniques [226, 236], have been devised that target aspect of asthma pathophysiology, with assumptions derived from biobehavioral and psychophysiological models of the disease. While efficacies ranges from limited [237] to promising [238, 239]; most interventions have failed to address anxiety direct.

Notwithstanding, a few interventions are targeting comorbid asthma and anxiety. In a small trial, the investigators (Ross et al. [240]) found that an 8-week group treatment that combined CBT for panic disorder with asthma education led to reductions in panic and anxiety that endured for 6 months, in addition to short-term improvements in morning PEF and asthma-related quality of life. Lehrer et al. [224] tested the benefits of a multimodal intervention for comorbid asthma and panic disorder, combining panic control therapy [241] with asthma education, smoking reduction, and assertiveness training. Findings of the uncontrolled pilot study reported promising reductions in panic and asthma symptoms, improvement in asthma quality of life, and decreased albuterol use. The intervention resulted in clinically significant reductions in panic and asthma symptoms and albuterol use as well as improved asthma stability and quality of life. Similarly, Yorke et al. [242] tested the feasibility and acceptability of group CBT in severe asthma, which provided a moderate signal for utility due to the high attrition. Given the particularly high comorbidity of asthma and PD in Latinos [200], Feldman and colleagues [243] developed a culturally adapted behavior psychophysiological therapy. The 8-week treatment was comprised of CBT for panic disorder, asthma education, differentiation between panic and asthma symptoms, and heart rate variability biofeedback. A control group received music and relaxation therapy (MRT). While both interventions showed improvements in anxiety and asthma outcome measures, only CBT led to improvement in adherence to inhaled corticosteroids. Finally, respiratory training using biofeedback of capnometry to reduce hyperventilation may likely benefit both panic symptomatology [244, 245] and asthma outcomes [246], but evidence has yet to be established.

Conclusion

This chapter examined the link between comorbid anxiety and medical illness through the physical character of its symptoms. They overlap with the symptomatology of a range of chronic somatic illnesses and the presence of maladaptive cognitions and behaviors. Because of the highly complex nature of bodily sensations, attempts to assign "typical" versus "nontypical" symptoms to medical or psychiatric diagnoses are overly simplistic. Strictly speaking, the diagnostic nomenclature (DSM-5) prohibits a diagnosis of PD if the origin of the symptoms is the direct cause of a medical condition. However, given that anxiety and panic/fear symptoms mimic those of several a critical medical condition, differential diagnosis is far from straightforward. The most common factor identified in research on nonspecific, medically unexplained symptoms is the persistence of bodily perceptions paired with catastrophic beliefs about the nature of these symptoms. While several promising interventions for comorbid anxiety and medical conditions have emerged, research and dissemination of evidence-based, tailored interventions with an impact on both psychiatric and chronic disease health are still in its infancy.

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