Perceiving Panic: Panic Disorder and Comorbid Medical Conditions

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Psychology

Panic Disorder (PD) is an anxiety disorder characterized by periods of intense and uncontrollable fear, often referred to as panic attacks. PD is developed through exposure to panic attacks that lead to anxiety and worry about future panic attacks. A vital component of PD is the physical nature of the panic symptoms. For this reason, comorbid medical conditions are important to analyze. There may be overlap between the symptoms of an individual's PD and medical conditions, or they may exacerbate each other. Individuals with PD are often more receptive to interoceptive cues. Consequently, individuals with PD are more likely to interpret these interoceptive cues as signals of a medical condition. This review will focus on the relationship between PD and medical conditions and analyze the prevalence of comorbidity. There has been research on PD comorbidity with respiratory disorders (Meuret, Kroll, & Ritz, 2017; Muller, Koen, & Stein, 2005), seizure disorder (Muller et al., 2005), Kluver-Bucy syndrome (Muller et al., 2005), mitral valve prolapse (Filho et al., 2011; Gulpek et al., 2004; Muller et al., 2005), cardiovascular disease (Meuret et al., 2017; Roy-Byrne et al., 2008), irritable bowel syndrome (Meuret et al., 2017; Roy-Byrne et al., 2008) and other gastrointestinal disorders (Stasi et al., 2017), diabetes (Meuret et al., 2017), fibromyalgia (Carta et al., 2018), joint hypermobility (Garcia-Campayo, Asso, & Alda, 2011; Gulpek et al., 2004), and asthma (Roy-Byrne et al., 2008). Understanding the relationship between PD and these medical conditions is vital for diagnosis and treatment.

Characteristics of Panic Disorder

A panic attack is an experience of intense fear that can be accompanied by a number of physical and mental symptoms, including chest pain, heart palpitations, shortness of breath, dizziness, and thoughts of losing control, going crazy, or dying (Bouton, Mineka, & Barlow, 2001). A person must experience unexpected panic attacks that do not occur because of any cues or triggers in order to meet criteria for PD. The individual must also develop substantial anxiety or worry about having future panic attacks and the implications of these panic attacks. This is an important distinction because many people experience panic attacks in response to stress but do not develop anxiety about having panic attacks and therefore do not meet the criteria for a PD diagnosis (Bouton et al., 2001). Based on data from the National Comorbidity Survey Replication, it is estimated that 4.7% of the U.S. population will experience PD at some time in their lives (National Institute of Mental Health, 2017).

The physical symptoms associated with panic attacks play a major role in perpetuating PD. If an individual with PD experiences breathlessness for any number of reasons they may interpret this as the onset of a panic attack. This thought may exacerbate these physical symptoms and eventually lead to a panic attack. In an attempt to break this cycle, many individuals with PD try to avoid the physical symptoms that occur during their panic attacks. For example, an individual may avoid physical exercise because it may cause breathlessness or other symptoms that they associate with their panic attacks. This avoidance only helps to maintain the PD because the individual does not learn to cope with these physical symptoms.

Many of the physical symptoms that occur during panic attacks are also present in the medical conditions that will be discussed in this paper. When an individual experiences these symptoms it may be difficult for them to determine if it is a representation of their medical

condition or the onset of a panic attack. The hypersensitivity to physical symptoms that individuals with PD exhibit, adds to the complexity of the interaction between these comorbid conditions.

There is a large body of evidence that anxiety is associated with high rates of medical symptoms and increased use of healthcare resources (Katon, Lin, & Kroenke, 2007; Marciniak et al., 2005; Simon & VonKorff, 1991). Anxiety disorders are strongly associated with chronic medical conditions (Härter, Conway, & Merikangas, 2003; Sareen et al., 2006), indicating the importance of research on the connection between anxiety and medical conditions.

Interoception in Panic Disorder

Interoception is defined as the sense of the internal state of the body. Individuals with PD have an increased interoceptive sensitivity, or a hypervigilance to physical symptoms. The ultimate goal of interoceptive cues is to maintain homeostasis throughout the body, but they are also theorized to play a role in feeling emotions (Meuret et al., 2017). For example, the ability of an individual to sense their own heartbeat is thought to amplify emotions, specifically sensations of anxiety and fear. Individuals that suffer from PD show an increased interoceptive sensitivity for somatic symptoms, which makes them more likely to make catastrophic misappraisal about their own body sensations (Garfinkel & Critchley, 2013). As previously noted, cardiac symptoms are commonly experienced during panic attacks, but are also commonly catastrophized as symptoms of a heart attack (Chambless, Beck, Gracely, & Grisham, 2000). For example, an individual with PD may experience heart palpitations and jump to the conclusion that they are having a heart attack, which in turn increases their panic response. For individuals with a comorbid heart condition it may be difficult to differentiate between harmless panic symptoms, and symptoms of their heart condition. Several studies have illustrated this hypervigilance to

panic symptoms. Two studies found that individuals with high anxiety sensitivity and frequent panic response were able to perceive their heartrate with greater accuracy than healthy controls (Richards & Bertram, 2000; Zoellner & Craske, 1999). Another study revealed that individuals with panic attacks were more likely to feel anxious in response to an increase in heartrate, but did not differ from controls in the number of heartrate increases (Pauli, Marquardt, Hartl, & Nutzinger, 1991). This finding suggests that the subject's interpretation of their visceral arousal is a major component of the panic response cycle.

Cardiovascular Illness and Panic Disorder

Heart palpitations or a "racing heart" is the most widely reported physical symptom of panic disorder, which raises suspicions of a link between panic disorder and cardiovascular illness. Past research has demonstrated the importance of psychological factors in cardiovascular illness, with stressful or traumatic experiences increasing cardiac events. An association has been revealed between anxiety disorders and coronary heart disease and hypertension, as well as cerebrovascular events, including strokes (Emdin et al., 2016; Meuret et al., 2017; Roy-Byrne et al., 2008). Large, nationally representative studies within the United States have found that individuals with PD are up to 2 times more likely to be diagnosed with coronary heart disease than individuals without PD (Goodwin, Davidson, & Keyes, 2009). There is, however, limited research on the role of PD specifically in association with cardiovascular disease. This warrants a need for further research that is focused on PD rather than anxiety disorders as a whole. One study found an increased rate of PD (13%) in hypertensive primary care patients, in which the PD developed after the hypertension diagnosis (Davies et al., 1999). More research is needed to determine the timeline of diagnoses among other cardiovascular illnesses and PD. A treatment for life-threatening ventricular fibrillations, implantable cardioverter defibrillators, delivers

shock to the individual. This treatment, although effective, has negative psychological outcomes including PD. One study found that within individuals undergoing this treatment and experiencing more than two electrical shocks per year, the prevalence of PD with agoraphobia was 62% (Meuret et al., 2017). Within individuals that only experienced one electrical discharge per year, the prevalence rate of PD with agoraphobia was 10%. Several studies have demonstrated that PD patients have an increased risk of developing various cardiovascular illnesses including a 1.3-fold risk of developing hypertension (Stein et al., 2014), a 1.5-fold risk of atrial fibrillation (Cheng et al., 2013), and a fourfold risk of developing coronary heart disease (Smoller et al., 2007).

There are several mechanisms that may play a role in the link between PD and cardiovascular illnesses. Problematic health behaviors that are often present in individuals with PD have been discussed as a contributor to this link, including lack of physical activity, obesity, and smoking (Meuret et al., 2017). Prescriptions of selective serotonin reuptake inhibitors that are often given to patients with PD can contribute to obesity and subsequent development of cardiovascular illnesses. There are also pathways in which cardiovascular illness may lead to subsequent development of PD. The emotional consequences of cardiovascular illness, including catastrophic thoughts and fear of dying, may lead to a development of anxiety or PD in individuals that are susceptible (Meuret et al., 2017). As discussed earlier, cardioverter defibrillator treatment can also increase the likelihood for an individual to develop PD. Although this treatment may be effective, the side effect of developing PD may cause patients to discontinue treatment. Understanding the link between PD and cardiovascular illness, and the mechanisms that are involved, is vital to the development of effective treatments.

Respiratory Conditions and Panic Disorder

Individuals with asthma have an increased prevalence rate of PD. A range of samples have suggested that the comorbidity rate is between 7% and 45% (Meuret et al., 2017). This clearly identifies a need for further research to more accurately define the prevalence of comorbidity between PD and asthma. Among pediatric patients (aged 5 to 11) with asthma the prevalence rate of comorbid PD was 14.9%, with other anxiety disorders following behind with a prevalence rate of 8.1% for separation anxiety, 5.4% for agoraphobia, and 4.1% for generalized anxiety disorder (Goodwin et al., 2009). Although asthma is the most commonly researched, PD is associated with an elevated prevalence of respiratory disease in general, including chronic bronchitis, COPD, and emphysema. However, this elevation in the rate of comorbidity is also seen in other mental illnesses including major depression, social anxiety disorder, and substance abuse (Patten & Williams, 2007).

Research has revealed that the association between PD and respiratory illness is bidirectional. Respiratory illness during childhood leads to an increased risk of PD diagnosis later in life. For example, one study found that asthma during early adulthood was associated with the development of PD 20 years later (Hasler, Gergen, Kleinbaum, Ajdacic, & al, 2005). This same study also found that PD during early adulthood was associated with developing asthma later in life. These findings support the bidirectional association between PD and respiratory illness, but it is important to understand the mechanisms that underlie this association.

Similar mechanisms that play a role in cardiovascular illness comorbidity, may also play a role in the comorbidity between PD and respiratory conditions. As described above, problematic health behaviors including lack of physical activity, obesity, and smoking are also

relevant to respiratory illnesses. For example, individuals with PD often avoid exercise due to the uncomfortable physical symptoms, but this exercise avoidance not only exacerbates the PD it also increases the risk of respiratory complications due to a sedentary lifestyle (Lucas & Platts-Mills, 2005). Smoking and obesity contribute to this increase in risk by causing airway damage and inflammation (Lugogo, Kraft, & Dixon, 2009). Sustained states of stress and anxiety can also generate inflamed airways, which can be exacerbated by anticipatory anxiety about future attacks (Battaglia & Ogliari, 2005). Anxiety and stress can facilitate respiratory infections as well, which can lead to the development of a respiratory illness.

There are several mechanisms in which respiratory illness can lead to subsequent PD. The emotional burden of chronic illness can lead to stress, anxiety, and even catastrophizing that may contribute to the development of PD. The symptoms that are associated with respiratory illness may be misinterpreted. For example, breathlessness is a common symptom among respiratory illnesses and is also one of the most common symptoms associated with PD. Individuals with respiratory illnesses may also be more attuned to a suffocation alarm that can lead to hyperventilation, which is also common in PD (Klein, 1993). Several medications for respiratory illness, including bronchodilators and oral corticosteroids, can induce symptoms similar to those observed during the onset of a panic attack (Brown et al., 2004; Lehrer et al., 2008).

Functional Gastrointestinal Disorders and Panic Disorder

There are 28 functional gastrointestinal disorders (FGIDs), of which irritable bowel syndrome (IBS) is the most common and well-studied (Roy-Byrne et al., 2008). Individuals with IBS typically have visceral hyperalgesia, an exaggerated pain response to intestinal activity (Drossman, 2006; Jarcho & Mayer, 2007). Similar to the increase in interoception that is seen in

PD, individuals with IBS have an increased awareness of digestive discomfort. Stress reactivity is also an important feature of IBS (Drossman, 2006; Jarcho & Mayer, 2007) and is characteristic of many anxiety and mood disorders. IBS is associated with higher levels of neuroticism, anxiety sensitivity, visceral anxiety, and worry compared to those without IBS (Hazlett-Stevens, Craske, Mayer, Chang, & Naliboff, 2003). IBS has high rates of comorbidity with other illnesses, suggesting that individuals with IBS are hypervigilant to symptoms (Whitehead et al., 2007). IBS has been linked to PD, with individuals with IBS having a prevalence rate for PD between 3.8% and 31% (Walker, Roy-Byrne, & Katon, 1990), although a more recent study has estimated that 4.4% of individuals with IBS also have a comorbid PD diagnosis (Janssens, Zijlema, Joustra, & Rosmalen, 2015). More research is needed to get a more accurate prevalence rate, but it is clear that among individuals with PD the rate of IBS is over twice that of those without PD (Lydiard, 2005).

Visceral pain signals, stress response, mood, anxiety, and gastrointestinal function are processed within the same neural pathways (Grundy et al., 2006), suggesting that these pathways may play a role in the comorbidity between PD and IBS. The hypothalamic-pituitary-adrenal (HPA) axis and subsequent corticotropin-releasing factor (CRF) play a major role in these pathways (Roy-Byrne et al., 2008). Severe or prolonged stress can lead to CRF hyperactivity and the release of pro-inflammatory cytokines and catecholamines, which can result in excessive inflammatory activity (Chang, 2006; Dinan et al., 2006). There is evidence for HPA abnormalities and pro-inflammatory activity in IBS and PD, suggesting that CRF dysregulation may act as a link between the two disorders (Chang, 2006). IBS and PD have similar mechanisms of onset and symptoms including anticipatory anxiety, nausea, and abdominal distress (Meuret et al., 2017). Patients with IBS and patients with PD have similar illness

prognoses, while individuals that have both have exacerbated versions of each disorder. One study found that anticipatory anxiety was higher in comorbid patients than in patients with PD alone (Sugaya et al., 2013). Catastrophic interpretations of IBS symptoms may contribute to PD development or maintenance (Meuret et al., 2017). Because IBS and PD have overlapping symptoms and mechanisms, they can both be treated with antidepressants, anxiolytics, and cognitive-behavioral therapy (Roy-Byrne et al., 2008).

Chronic Pain and Panic Disorder

Pain is a perceptual experience that can be altered by a number of factors including cognition, emotion, behavior, and social influences. Pain is designed as an adaptive process to avoid physical harm, but chronic pain no longer provides this adaptive quality (Roy-Byrne et al., 2008). The most common chronic pain disorders include chronic spinal pain, rheumatoid arthritis, fibromyalgia, and migraines. Chronic pain can lead to a slew of emotional distress including anger, guilt, depression, fear, social withdrawal, and anxiety (McWilliams, Cox, & Enns, 2003). These emotions can contribute to the experience of chronic pain, and chronic pain patients have higher rates of anxiety symptoms, specifically panic symptoms (Means-Christensen, Roy-Byrne, Sherbourne, Craske, & Stein, 2008). In two National Comorbidity Surveys the percentage of chronic pain patients with comorbid PD was 4.8% and 6.5% (McWilliams et al., 2003; Von Korff et al., 2005). Comorbidity rates are particularly high in chronic pain patients that experience chest pain or negative cardiac symptoms (Beitman et al., 1989; Katon et al., 2007). It is unclear whether PD typically precedes chronic pain or vice versa. Within a population of 146 injured workers with chronic pain, all but one of the patients had an anxiety disorder before the onset of their chronic pain (Asmundson, Jacobson, Allerdings, & Norton, 1996). Another study with a sample of 90 chronic lower back pain patients found that

23% of the patients previously had an anxiety disorder (Kinney, Gatchel, Polatin, Fogarty, & Mayer, 1993). More research is needed to determine the temporal pattern between chronic pain and PD specifically.

Pain and fear are both associated with physiological arousal. They are adaptive mechanisms, but can have detrimental effects when prolonged (Roy-Byrne et al., 2008). There is some literature to support the use of cognitive-behavioral therapy for individuals with chronic pain (Devine EC, 2003; Hoffman, Papas, Chatkoff, & Kerns, 2007; Morley, Eccleston, & Williams, 1999). Graded exposure has been used to reduce fear and pain intensity, and to increase physical activity in individuals with chronic pain (de Jong, Vlaeyen, Onghena, Cuypers, et al., 2005; de Jong, Vlaeyen, Onghena, Goossens, et al., 2005; Woods & Asmundson, 2008). Antidepressants are also beneficial to chronic pain patients (Saarto & Wiffen, 2007). These treatments are promising for individuals with comorbid PD and chronic pain, due to the overlap in effective treatment methods.

Diabetes and Panic Disorder

Within diabetic patient samples 1.3% to 8.9% have comorbid PD (Fisher et al., 2008; Grigsby, Anderson, Freedland, Clouse, & Lustman, 2002). However, one study found that the prevalence of PD is higher among patients with Type I diabetes than patients with Type II diabetes (de Ornelas Maia, Braga, Brouwers, Nardi, & de Oliveira e Silva, 2012). Individuals with diabetes and a comorbid PD or anxiety disorder exhibit poorer blood glucose levels and an increase in pain, symptom burden, diabetic complications, and overall disability (Smith et al., 2013).

PD and diabetes have a considerable amount of symptom overlap. One potential mechanism of the bidirectional association of PD and diabetes is the hypoglycemic episodes that mimic panic symptoms and can lead to a conditioned fear response. During a hypoglycemic episode an individual may feel faint, a symptom that is also characteristic of PD. This can lead to a panic response and subsequently a conditioned fear response. One survey of 244 diabetic patients who have experiences hypoglycemic episodes found that 74% were also diagnosed with agoraphobia, a conditioned fear response (Costea, Ionescu-Tîrgovişte, Cheţa, & Mincu, 1993). The conditioned fear response contributes to both the development and maintenance of panic. HPA axis dysregulation may be a mechanism for the comorbidity of PD and diabetes (Meuret et al., 2015). HPA axis activation without the presence of a threatening stimuli is characteristic of PD, and can lead to elevated levels of glucocorticoids, which initiates insulin resistance that is seen in diabetes (Rafacho, Ortsäter, Nadal, & Quesada, 2014). Negative health behaviors that are associated with PD may have an influence on the development and maintenance of diabetes. These include sedentary behavior, obesity, smoking, and poor sleep (DeFronzo et al., 2015).

Mitral Valve Prolapse and Panic Disorder

The association between mitral valve prolapse and panic disorder is debated within the research community because there are mixed results of the prevalence rate of the comorbid disorders. Mitral valve prolapse is an abnormality, affecting 3% to 5% of the adult population (Devereux, 1995; Freed et al., 1999), in which the two flaps of the mitral valve do not close evenly. Mitral valve prolapse and PD share many symptoms including chest pain, palpitations, dyspnea, dizziness, fatigue, and anxiety, and are both more common in women (Gulpek et al., 2004). Some studies suggest that the rate of mitral valve prolapse in PD is as great as 20% to 50% (Muller et al., 2005). A more recent study, with a sample size of 50, found no significant

difference in prevalence rate with 2.4% of PD patients also diagnosed with mitral valve prolapse and only 1% of the control group diagnosed with mitral valve prolapse (Filho et al., 2011). There is a need for more research on the prevalence of PD and mitral valve prolapse with larger sample sizes and a more standardized criterion for mitral valve prolapse diagnosis. PD and mitral valve prolapse may both be affected by dysregulation of the autonomic nervous system, including an increase in heart rate variability (Sullivan et al., 2004; Yeragani, Tancer, & Uhde, 2003). PD treatments have been found to be effective for mitral valve prolapse by reducing symptoms like hyperventilation that can contribute to heart rate variability (Sullivan et al., 2004).

Joint Hypermobility Syndrome and Panic Disorder

Joint hypermobility syndrome is a common, hereditary, connective tissue disorder that has been associated with PD and mitral valve prolapse (Garcia-Campayo et al., 2011; Muller et al., 2005). One of the first studies to look at the association between joint hypermobility and PD found that 67.7% of PD patients also had joint hypermobility syndrome (Martin-Santos, Bulbena, Porta, Gago, & al, 1998). Unlike other comorbid conditions, the temporal sequence is obvious because joint hypermobility syndrome is present from early childhood, while PD does not typically develop until early adulthood (Garcia-Campayo et al., 2011). One study aimed at understanding the role of mitral valve prolapse in the association of PD and joint hypermobility syndrome found that joint hypermobility syndrome was found in 59.5% of PD patients with mitral valve prolapse, and in 42.9% of PD patients who did not have mitral valve prolapse (Gulpek et al., 2004). This study suggests that mitral valve prolapse affects the prevalence of joint hypermobility syndrome in PD patients. Many of the symptoms and disorders discussed in this paper are also associated with joint hypermobility including asthma, cardiac dysfunctions, digestive problems, and pain disorders (Garcia-Campayo et al., 2011). The only suggested

mechanism for the association between joint hypermobility syndrome and PD is a genetic mutation, DUP25, on chromosome 15 that has been significantly associated with PD, social anxiety disorder, and joint hypermobility disorder (Gratacòs et al., 2001). However, another study did not find DUP25 in any of their patients with joint hypermobility syndrome and PD (Tabiner et al., 2003). More research is needed to determine the mechanisms that contribute to the association between joint hypermobility syndrome and PD.

Diagnosis and Treatment Implications

The overlap of symptoms between PD and comorbid medical conditions may cause errors in diagnosis and treatment, which may lead to additional healthcare costs (Greenberg et al., 1999; Potokar & Nutt, 2000). At the onset of symptoms many individuals turn to primary care settings where there is limited time and resources for comprehensive testing. Healthcare professionals may also overlook comorbid disorders after one diagnosis is made based on the presented symptoms (Meuret et al., 2017). Not only is there a bidirectional association between PD and medical conditions, but they can also exacerbate one another. For example, asthma is exacerbated by the presence of comorbid PD, this exacerbated asthma subsequently leads to symptoms that are feared by PD patients and therefore exacerbate the panic attacks that PD patients experience (Meuret, Ehrenreich, Pincus, & Ritz, 2006).

Comorbid treatment poses a challenge as treatment of one disorder may exacerbate the other disorder. Cognitive-behavioral therapy, that is often used to treat PD, includes voluntarily experiencing the symptoms of a panic attack which may cause issues for individuals with a comorbid medical illness. For a patient with comorbid PD and respiratory illness, it would be problematic to use cognitive behavioral therapy that requires voluntary hyperventilation because this would induce bronchoconstriction (Meuret et al., 2006). Cognitive-behavioral therapy may

be an effective treatment many comorbid PD and medical conditions. The breathing exercises that are often taught during cognitive-behavioral therapy are beneficial for individuals with comorbid respiratory illnesses because they can teach individuals how to reduce hyperventilation (Meuret, Wilhelm, Ritz, & Roth, 2008).

Future Research

There is still much to be discovered about the association between PD and medical conditions. Further research with larger sample sizes is needed to pin down more accurate prevalence rates for the comorbid disorders. Longitudinal studies are necessary to determine the temporal sequence of disorder onsets. Understanding which disorder preceded the other may help elucidate the mechanisms of onset. There is a need for neurological studies to determine the pathways that are involved in PD and the comorbid medical condition. Examining biological mechanisms will also help to illuminate the factors that contribute to this onset of conditions. There is little research on treatment for these comorbid disorders. Treatments are typically aimed at one of the comorbid disorders but ignores the other. Cognitive-behavioral therapy is effective for treating PD and some medical conditions but must be adapted to treat other medical conditions. Therapies and medications that are useful in treating PD must be evaluated as treatments for the comorbid medical illnesses. There is also a need for a more effective method of diagnosing these comorbid conditions. Many of these illnesses go undiagnosed because one diagnosis is already determined. More research is needed to understand the complex interaction of PD with comorbid medical conditions, but progress is currently underway.

Conclusion

Panic disorder has a complex array of comorbid medical conditions with an overlap in symptoms and mechanisms of onset. The physical nature of PD contributes to the hypervigilance towards physical symptoms that may overlap with comorbid medical illnesses. PD patients often interpret their physical symptoms as dangerous, especially if they are symptoms that overlap with their medical condition. It is important for PD patients, as well as their healthcare professionals, to parse out symptoms that are panic related and symptoms that are due to their medical illness. Our understanding of PD and comorbid medical conditions is still limited, therefore progress within this field is needed.

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