Depression

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Prevalence and Comorbidity

Depression frequently co-occurs with functional illness. As many as two-thirds of patients with functional illness have some comorbid psychiatric disease, with a history of depression being the most common [1]. Lifetime comorbidity of Major Depressive Disorder (MDD) in adults with functional illness has been estimated to be anywhere from 35% to 86%, with a current prevalence of 22–40% [2–5]. This strong comorbidity is seen across all domains of functional illness: from functional pain to movement disorders to voice dysfunction.

Numerous studies have documented the high rates of depression in patients with movement and paretic expressions of Functional Neurological Disorders, with the lifetime prevalence of MDD estimated at 35–42% in this population [4]. A review of 31 articles reporting psychiatric comorbidities in individuals with psychogenic non-epileptic seizures (PNES) found that—although the reported prevalence varies from study to study—some groups showed depression in almost 4 out of every 5 individuals [2]. These exceptionally high rates of depression are also seen in people with functional pain, as 90% of patients with fibromyalgia show depressive symptoms at some point in their lifetime, with 50–86% of individuals experiencing a major depressive episode [3, 6]. Indeed, the odds of patients with fibromyalgia having depression are roughly three times higher than the healthy population, even when controlling for important socio-demographic characteristics [5]. Functional voice dysfunction is similarly impacted; a study of 61 individuals with functional dysphonia found that 57% of the group met clinical criteria for a mood disorder, and patients had significantly higher depression scores than healthy, matched controls [7].

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Depression as a Risk Factor for Functional Illness

Clearly, functional illness and depression are strongly tied to one another. Indeed, not only is there a strong comorbidity, but the presence of depression can affect the severity of a functional illness. For instance, depression scores have been found to positively correlate with the severity of functional motor symptoms [8]. The question becomes, then, to what extent do depression and functional illness influence one another? Does depression precede or precipitate functional illness, or vice versa? Or are these two sets of symptoms linked to a common underlying mechanism which causes and/or modifies the severity of both in tandem? While there are no definitive answers to these questions—the causality of the relationship between depression and functional illness has yet to be fully discovered—there are observations and models that are beginning to explore the potential mechanisms of this comorbidity.

There is evidence for a genetic connection between depression and functional disorders, in that genetic factors may predispose certain individuals to develop both depression and functional symptoms in response to precipitating events such as injury or psychosocial stressors [3]. For instance, a polymorphism in the serotonin transporter (5-HHT) gene has been implicated in both MDD and fibromyalgia [9, 10], and MDD is predicted nearly equally by the presence of familial MDD or fibromyalgia, reinforcing the biological link between the two [11]. Functional pain and depression have also both been associated with the consequences of an abnormally persistent stress response, leading to disturbed cortisol levels and their effects on neurotransmitter systems, especially the hypothalamic–pituitary–adrenal axis [3, 12]. Gracely and colleagues [3] suggest that depression and functional pain likely share a mutual predisposition through a combination of genetic and environmental factors. However, they argue that the differing response of depression and fibromyalgia to certain pharmacological treatments indicates that they are "mediated by largely independent mechanisms with mutual modulation of specific symptoms" [3].

Functional illness is often explained using a biopsychosocial model in which characteristics such as depression may act as predisposing or triggering factors and may contribute to the chronicity of functional symptoms [13–15]. A link between depression and functional illness has also been suggested with regard to underlying deficits in emotional processing. It is well known that MDD is characterized by the presence of disturbed emotional processing [16], and it has been proposed that this deficit may also result in some individuals experiencing emotions more somatically; for instance, producing physical tension that impacts the voice leading to functional dysphonia [17, 18]. Under this model, high stress situations may produce both depression and functional symptoms in individuals with deficits in emotional processing.

Impact of Depression on Prognosis

The influence of comorbid depression on treatment outcomes is difficult to ascertain, and studies have produced conflicting results. For instance, some studies have observed that the presence of depression correlates with favorable prognosis in

patients with functional motor symptoms [19, 20], with one recent study finding that higher depression scores actually predicted better clinical outcomes [21]. However, not all reports concur with this observation, and other studies have found comorbid depression to be associated with poor clinical outcomes [22, 23].

Treatment

Functional illnesses often require an integrated multidisciplinary approach to treatment which targets the presenting symptoms with an understanding that neurological and psychological symptoms influence one another and may even share an underlying etiology [1, 15]. As we have seen, depression and low mood can influence prognosis, so it is important to consider these symptoms in treatment selection. Where a straightforward presentation of depression is identified, treatment according to established guidelines for depression may be appropriate [24]. However, the selection of therapeutic intervention must also take into account comorbidities, so clinical judgement should be used to maximize efficacy in treating depression while avoiding the potential exacerbation of functional symptoms [1]. Furthermore, a physician's approach to treatment is important; patients may benefit simply from validation and normalization of their concerns, and effective communication with the patient as well as between treating physicians may aid in treatment adherence and with the efficacy of interventions such as psychotherapy [25].

Medication

Antidepressant medications for the treatment of functional illness or depression and anxiety will be discussed in more detail in other sections. Here we discuss certain general considerations when selecting pharmaceutical treatments for functional symptoms in the face of comorbid depression. Evidence is scarce with regards to pharmaceutical intervention specifically for depression in functional illness, as there are few randomized controlled trials assessing the efficacy of any given antidepressant [1, 26, 27]. As such, pharmacological therapy is often primarily guided by the predominant symptoms that accompany functional complaints [1, 24, 28].

With regard to functional pain, tricyclic antidepressants (TCA), such as amitriptyline, have frequently been employed for their ability to improve both pain and depression. Serotonin–norepinephrine reuptake inhibitors (SNRIs), such as duloxetine, are also useful for this dual purpose. It is interesting to note that the dosage of TCAs used to treat pain is often much lower than that employed in the treatment of depression, and pain relief is usually achieved in a much shorter time compared with changes in depression symptoms [3, 29, 30]. These observations, paired with reports of independent symptom improvement with SNRIs, suggest the presence of independent mechanisms underlying these two disorders [3, 31]. Care should be taken in the use of opioids or cannabinoids for the treatment of functional pain, as they may exacerbate depression [13].

Psychotherapy

Psychological therapies are one of the most prevalent and effective forms of intervention in the care of depression [32, 33], and psychotherapies have also proven useful for reducing symptoms of functional illness. For instance, a variety of psychotherapies, including psychodynamic psychotherapy, mindfulness-based interventions, and group psychoeducation, have all been shown useful in the management of functional movement disorders [34–36]. O'Neal and Baslet [1] recommend having patients keep a diary of the things which precipitate their symptoms, helping create new behaviors to break unconscious patterns which may be leading to the expression of functional symptoms, and teaching strategies to reduce the tendency to express distress through physical symptoms.

Cognitive behavioral therapy (CBT) is a form of psychotherapy that involves efforts to pinpoint irrational or distorted thinking, identify emotions associated with this thinking, and restructure these thought patterns to affect positive changes in mood and behavior [37]. CBT is widely used in the treatment of depression, and its use in conjunction with pharmacotherapy is significantly more effective than medication alone [37, 38]. CBT is also beneficial in the treatment and management of functional illnesses and may even be superior to standard medical care in reducing symptom burden in certain populations [1]. In relation to functional disorders, CBT may focus on identifying thought patterns that are reinforcing symptoms while introducing stress management techniques and beneficial behavioral responses [1].

Given the widespread use of CBT for the treatment of depression and its demonstrated efficacy for both depression and certain functional symptoms, CBT represents a very promising modality for the unified treatment of comorbid psychiatric and functional symptoms. One study found that CBT alone and CBT + sertraline in combination were effective in reducing functional seizure frequency, but patients who received CBT alone reported a greater improvement of secondary outcomes including depression [24, 39]. Indeed, for patients with episodic symptoms, such as functional seizures, CBT has been suggested as the preferred treatment modality [1].

Brain Stimulation

Non-invasive brain stimulation, including repetitive transcranial magnetic stimulation (rTMS), has shown some early promise in the treatment of symptoms associated with functional illness. For instance, stimulation of motor cortex can reduce pain, whereas temporal–parietal junction stimulation may improve psychogenic seizure frequency [40, 41]. rTMS for the treatment of MDD typically targets the dorsolateral prefrontal cortex, and there is preliminary evidence to indicate that this target site is also effective at alleviating depression in individuals with comorbid functional pain [40]. Thus, although it is too early to establish optimal stimulation parameters in functional illness, rTMS and other non-invasive stimulation techniques—such as transcranial direct current stimulation (tDCS)—may represent an effective treatment alternative [24].

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