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Review article

Understanding the role of adjunctive nonpharmacological therapies in management of the multiple pathways to depression

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ABSTRACT

Major depressive disorder (MDD) is a common disorder with a lifetime prevalence of 16.2% and the fourth highest cause of disability globally. It is hypothesized to be a syndromatic manifestation of multiple pathological processes leading to similar clinical manifestation. MDD is associated with at least three categories of peripheral hormone-type factors including neurotrophic factors, proinflammatory cytokines, and processes that impair regulation of the hypothalamic-pituitary-adrenocortical axis. Neuroimaging studies have identified functional abnormalities including subcortical systems associated with reward and emotion processing, medial prefrontal and anterior cingulate cortical regions and the lateral prefrontal cortical systems involved in cognitive control and voluntary emotion regulation. Studies investigating the effects of psychotherapy and pharmacotherapy on functional brain measures show normalization of brain function with return to euthymia. Nevertheless, approximately 50% of patients with MDD will not respond sufficiently and 60 to 70% will not achieve full remission with first-line pharmacotherapy, therefore clinicians strive to improve patient responses through the use of adjunct therapies. This review discusses recent research in the various biological processes associated with MDD as well as recent data in support of the use of adjunctive non-pharmacological therapies including psychotherapy, bibliotherapy, Internet therapy, "natural" or herbal approaches, exercise therapy, and somatic therapies.

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1. Introduction

1.1. Epidemiology of MDD

Major depressive disorder (MDD) is a seriously disabling public health problem worldwide (Kessler et al., 2003). It is the fourth highest cause of disability with over 150 million people estimated to be suffering from depression (World Health Organization [WHO], 2003). MDD is a common disorder with a lifetime prevalence of 16.2% and a prevalence of 3–10% in the general population (Kessler et al., 2003; World Health Organization [WHO], 2003). It is twice as common among women as among men (Kessler et al., 2005; Weissman and Olfson, 1995) and in medically ill populations, the prevalence of MDD has been reported to be approximately 20–30%. It is associated with increased health care costs, reduced compliance, and increased morbidity and mortality (Clarke et al., 1991; Gehi et al., 2005; Strain and Blumenfield, 2008). Furthermore, the prevalence of metabolic syndrome in patients with MDD has been found to be as high as 48% (Heiskanen et al., 2006; John et al., 2009; Richter et al., 2010; Teixeira and Rocha, 2007). Therefore, the need to evaluate the relationship that exists between MDD and metabolic syndrome is essential in order to achieve an efficacious treatment strategy for the patient.

1.2. Pathophysiology of MDD

MDD is believed to be a syndromatic manifestation of multiple pathological processes that lead to a similar clinical manifestation. The pathophysiology of MDD is associated with at least three main categories of peripheral hormone-type factors including neurotrophic factors and other growth factors, proinflammatory cytokines, and processes that appear to impair regulation of the hypothalamic-pituitary-adrenocortical (HPA) axis (Kupfer et al., 2012). Evidence supporting the role of neurotrophic factors in the pathophysiology of depression comes from studies demonstrating that stress, a precipitating factor in depression, has been shown to reduce both neurogenesis as well as the expression of neurotrophic factor genes in the brain (Duman, 2004; Nibuya et al., 1995). Moreover, treatment with antidepressants promotes neurogenesis and neurotrophic factor gene expression (Malberg et al., 2000; Nibuya et al., 1995). The most widely studied neutrophic factor implicated in depression is brain-derived neurotrophic factor (BDNF). BDNF levels have been shown to be abnormally low in patients suffering from MDD, increase significantly following a course of antidepressant treatment, and correlate significantly with changes in depression scores (Brunoni et al., 2008; Sen et al., 2008).

Proinflammatory cytokines are also implicated in the pathophysiology of depression (Dantzer et al., 2008). Innate immune cytokines are believed to be involved in all pathophysiologic processes related to depression including neurotransmitter metabolism, neuroendocrine function, synaptic plasticity, and regional brain activity (Dantzer et al., 2008; Raison et al., 2006). Elevated levels of innate immune cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF)-alpha, as well as their soluble receptors, have been found in peripheral blood and cerebrospinal fluid (CSF) of patients with MDD (Raison et al., 2006). Raison et al. (2009) demonstrated that peripherally administered interferon (IFN)-alpha can gain access to the brain in humans and trigger an inflammatory response in the CNS as measured by elevations in IL-6 and MCP-1 in CSF. Furthermore, increased levels of IL-6 were associated with decreased levels of the serotonin metabolite, 5-HIAA, and decreases in the latter were correlated with depression. The antidepressant bupropion has been shown to decrease levels of TNF-alpha, IFN-gamma, and IL-1 beta (Brustolim et al., 2006).

A study conducted by Motivala and colleagues (2005) investigated whether or not immune activation occurs in patients with MDD, through investigating the relationship between MDD and serum levels of inflammatory risk factors (soluble intercellular adhesion molecule [sICAM], monocyte chemotactic protein [MCP-1], interleukin-6 [IL-6], and IL-6 soluble receptor [IL-6sR]). Serum levels of these markers were taken following sleep onset and it was found that nocturnal serum levels of IL-6 and sICAM were significantly higher ($p<0.05$) in patients with MDD, versus control, therefore indicating the association of specific inflammatory markers with MDD patients (Motivala et al., 2005).

Impaired regulation of the HPA system is a consistent finding in acute episodes of depression (Horstmann et al., 2009). It is believed that an imbalance of glucocorticoid (GR) and mineralocorticoid receptors in depressed individual's results in impaired negative signaling of GRs on corticotrophin releasing hormone (CRH) and vasopressin (AVP) neurons, leading to hypersecretion of CRH and AVP. Hypersecretion of these two hormones gradually shifts the activity of the HPA system to a higher set point, resulting in continuous HPA hyperdrive in depressed patients. Most patients with acute depression demonstrate an exaggerated plasma corticotrophin (ACTH) and cortisol response to the combined dexamethasone-corticotrophin-releasing hormone test, a sensitive measure of altered regulation of the HPA system (Ising et al., 2007). The response attenuates and gradually normalizes with successful antidepressant therapy (Holsboer, 2000). High HPA responses that persist are associated with a less favorable prognosis (Horstmann et al., 2009).

1.3. Neuroimaging studies

Neuroimaging studies of MDD have identified specific functional abnormalities in several neural systems including: (1) subcortical systems involved in reward and emotion processing (e.g., amygdala, ventral striatum); (2) medial prefrontal and anterior cingulate cortical regions involved in automatic or implicit regulation of emotion and processing of emotion; and lateral (3) prefrontal cortical systems involved in cognitive control and voluntary regulation of emotion (e.g., ventrolateral prefrontal cortex and dorsolateral prefrontal cortex) (Phillips et al., 2008). In a review of 30 studies investigating the effects of psychotherapy and 33 studies investigating the effects of pharmacotherapy on functional brain measures, normalization was observed (Quide et al., 2012). Psychotherapy in particular increased the activity and recruitment of frontal areas (top-down effect), especially in the anterior cingulate cortex, whereas pharmacotherapy tended to decrease the over-activity of limbic structures (bottom-up effect). The majority of studies using neuroimaging to identify predictors of outcome and measures that change in response to different