New ways of predicting efficacy of antidepressants

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Major depressive disorder (MDD) is a neurobehavioral condition that is becoming increasingly prevalent in today's society. According to the World Health Organization, MDD is "amongst, and documenting..." (p. 61) and has a very complex pathophysiology. Until recently, a definitive answer had not been found; however, recent studies have suggested that a genetic susceptibility related to increased expression of the brain-derived neurotrophic factor (BDNF) and cognitive-emotional biomarkers may be key in the mechanism of this disorder.

A literature review of articles found in PubMed, CINAHL, Cochrane Library, and PsycINFO has shown that the last 16 years have focused on the hypothesis of MDD as a neurobehavioral disorder, with cognitive-emotional, antidepressant, and BDNF. The review found that MDD has a multitude of interconnected systems that interact and coexist, and it is not difficult to find a treatment option that works. However, cognitive-emotional biomarkers were able to predict the efficacy of antidepressants in the treatment of MDD. BDNF has also been decreased in patients with MDD and increased after treatment with certain medications. These systems may help better treatment response and an overall improvement of the burden of this disease.

**Key Terms:** brain-derived neurotrophic factor, serotonin, serotonergic, serotonergic hypothalamic, depressive disorder, serotonin and noradrenergic receptor subunits, and serotonin uptake inhibitors.

**Introduction**

**MDD**, according to Cai et al. (2015), "is a mood disorder characterized by prominent and persistent low mood, marked starchation, cognitive impairment, and social cognitive impairment" (p. 61). The Centers for Disease Control and Prevention (2016) states that almost 10% of adults ages 40-60 and more than 1 out of 20 Americans 12 years of age or older reported current depression. "Cognitive deficits are considered by many symptoms of depression that are associated with both substantial response to antidepressants and reduced remission rates" (Cassano, 2016, p. 1255). In the last decade, there has been an abundance of research showing that levels of neurotrophins found in the brain, may be involved in the pathophysiology of MDD and may predictably the efficacy of antidepressants and the remission of MDD.

The purpose of this review is to determine how BDNF and cognitive-emotional biomarkers factor into the pathophysiology of MDD, and how they can predictably the efficacy and outcome of certain antidepressants.

**Statement of the Problem**

According to Cai et al. (2015), "MDD can reduce the capacity of a patient to study, work, and engage in social activities" (p. 61). It also increase the risk of suicide and disability that has not been directly measured. The World Health Organization, in 2015, "is that about 23% of the burden of disease will be ranked next to that of ischemic heart disease, becoming the second most common cause of disability and death" (Cai, 2016, p. 279). The strategy of MDD has not been completely understood, according to Rinevskaya-Dzitakova et al. (2013), and many new hypotheses in the pathophysiology of MDD have been formulated. Antidepressant treatment only has an efficacy of 40-65%, a response rate of only 30%, and a high percentage of patients that do not show any improvement. Also, antidepressants increase the levels of these monoamine neurotransmitters in the central nervous system (CNS), but often take at least two weeks for them to take effect.

Not being a definitive mechanism by which these disorders works it makes it harder to find treatment options that are going to provide the efficacy and tolerability that these patients need. As more definitive mechanisms are discovered, treatment options can be more effective as they are tailored to the specific mechanism.

**Research Questions**

In adults with MDD, does BDNF play a role in the pathophysiology of MDD?

In treatment of adults with MDD, do cognitive biomarkers predict the efficacy and outcome of treatment and remission?

In treatment of adults with MDD, does BDNF predict the efficacy and outcome of treatment and remission?

**Literature Review**

**Pathophysiology of Major Depressive Disorder**

Monoamine deficiency hypothesis only partly explains the pathophysiology of MDD. Other hypotheses in the pathophysiology of MDD include inflammatory cytokines, hypothalamus-pituitary-adrenal axis, glutamate receptors, BDNF dysfunction, increased apoptosis, & vitamins D dysregulation. Rot et al. (2009) found that a polymorphism of BDNF affects the intracellular transport and secretion of BDNF and may increase apoptosis of neurons in the CNS and PNS. BDNF levels are decreased, an impairment in the brain, and there is only a small number of patients that actually reach remission. This suggests that there is no to the pathophysiology of depression.

**Cognitive & Emotional Biomarkers**

Cassano et al. (2016) found that both SNRIs and SSRIs reduced the effective symptoms in MDD, as well as significantly improved the global cognitive function. Both SNRIs and SSRIs improved executive function and verbal memory, however, this improvement was independent from the efficacy of affective symptoms.

Elkin et al. (2015) showed that remission rates with escitalopram treatment were higher for individuals predicted to reach remission with than those predicted to not reach remission and remission rates were higher if they received escitalopram versus sertraline or venlafaxine. Participants that were predicted to reach remission had slightly lower depressive severity, were more educated, and received a lower dose of escitalopram at week 5. The patients that were predicted not to reach remission had generally impaired cognitive functioning. Those predicted to reach remission were treated 2-3 months sooner than those that did not achieve remission (p. 279). According to Gyruk et al. A region in the right inferior parietal cortex predicts HRSD remission differentially by SRI treatment. Patients who did not reach remission had slightly lower depressive severity, were more educated, and received a lower dose of escitalopram at week 5. The patients that were predicted not to reach remission had generally impaired cognitive functioning. Those predicted to reach remission were treated 2-3 months sooner than those that did not achieve remission (p. 279). Gyruk et al. (2016) showed that remission was distinguished from nonremitters by greater pretreatment right inferior parietal cortex and lower pretreatment right inferior frontal cortex volumes. Gyruk et al., 2016, states that remitters to treatment were distinguished from nonremitters by greater pretreatment right inferior parietal cortex and lower pretreatment right inferior frontal cortex volumes.

Gyruk et al. (2016) found that remitters to treatment were distinguished from nonremitters by greater pretreatment right inferior parietal cortex and lower pretreatment right inferior frontal cortex volumes. Patients who did not reach remission had slightly lower depressive severity, were more educated, and received a lower dose of escitalopram at week 5. The patients that were predicted not to reach remission had generally impaired cognitive functioning. Those predicted to reach remission were treated 2-3 months sooner than those that did not achieve remission (p. 279).

Gyruk et al. (2016) showed that regions in the right inferior parietal cortex predicts HRSD remission differentially by SSRI treatment. The International Journal of Neuropsychopharmacology, 19, 111-118. http://dx.doi.org/10.1017/S146114571500099X

Critically, this meta-analysis showed the importance of SNRIs in the treatment of MDD, as serotonin and noradrenaline are involved in the pathophysiology of MDD. Gyruk et al. (2016) showed that regions in the right inferior parietal cortex predicts HRSD remission differentially by SSRI treatment. The International Journal of Neuropsychopharmacology, 19, 111-118. http://dx.doi.org/10.1017/S146114571500099X


**Literature Review**

Rot et al. (2009) stated that the pathophysiology of MDD has mainly been based on the monoamine-deficiency hypothesis. This hypothesis focuses on decreased levels of serotonin, norepinephrine, and dopamine being the cause of MDD. However, there are antidepressant medications to actually reduce all of these.

Gyruk et al. (2016) stated that neurotrophins, such as BDNF, regulate growth and apoptosis of neurons in the CNS and PNS. BDNF levels are decreased, an impairment in the brain, and there is only a small number of patients that actually reach remission. This suggests that there is no to the pathophysiology of depression.

Yang et al. (2016) stated that neurotrophin and neuroplasticity are involved in memory and learning, and if disturbed as with decreased BDNF levels, MDD may occur.

Gyruk et al. (2016) found that “response with antidepressant medication can be reliably predicted for outcomes with MDD by pretreatment performance on a standard battery of cognitive-emotional functions.”

Gyruk et al. (2016) showed that activation in the frontoparietal region of the brain is associated with improved executive function and verbal memory, however, this improvement was independent from the efficacy of affective symptoms.

Gyruk et al. (2016) showed that regions in the right inferior parietal cortex predicts HRSD remission differentially by SSRI treatment. The International Journal of Neuropsychopharmacology, 19, 111-118. http://dx.doi.org/10.1017/S146114571500099X

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