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# New Ways of Predicting Efficacy of Antidepressants

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## Abstract

Major depressive disorder (MDD) is a neuropsychiatric condition that is becoming increasingly prevalent in our country. According to Cai, Huang, and Hao (2015), MDD is “common and devastating” (p. 61) and has a very complex pathophysiology. Until recently, a definitive etiology had not been found, however, new evidence has suggested that Brain-derived neurotrophic factor (BDNF) and cognitive-emotional biomarkers may be a key into the mechanism of this disorder.

A literature review of articles found in PubMed, CINAHL, Cochrane Library, and PsychINFO within the last ten years focused on the hypotheses of the pathophysiology of MDD, cognitive-emotional biomarkers, and BDNF. The review found that MDD has a multitude of interconnecting systems that highlight its mechanism, and this is why it is so difficult to find a treatment option that works. However, cognitive-emotional biomarkers were able to predict the efficacy of certain antidepressants in the treatment of MDD. BDNF was also found to be decreased in patients with MDD and increased after treatment with certain medications. These systems may help predict better treatment response and an overall improvement of the burden of this disease.

**Key Terms:** brain-derived neurotrophic factor, sertraline, venlafaxine, venlafaxine hydrochloride, depressive disorder, serotonin and noradrenaline reuptake inhibitors, and serotonin uptake inhibitors

## Introduction

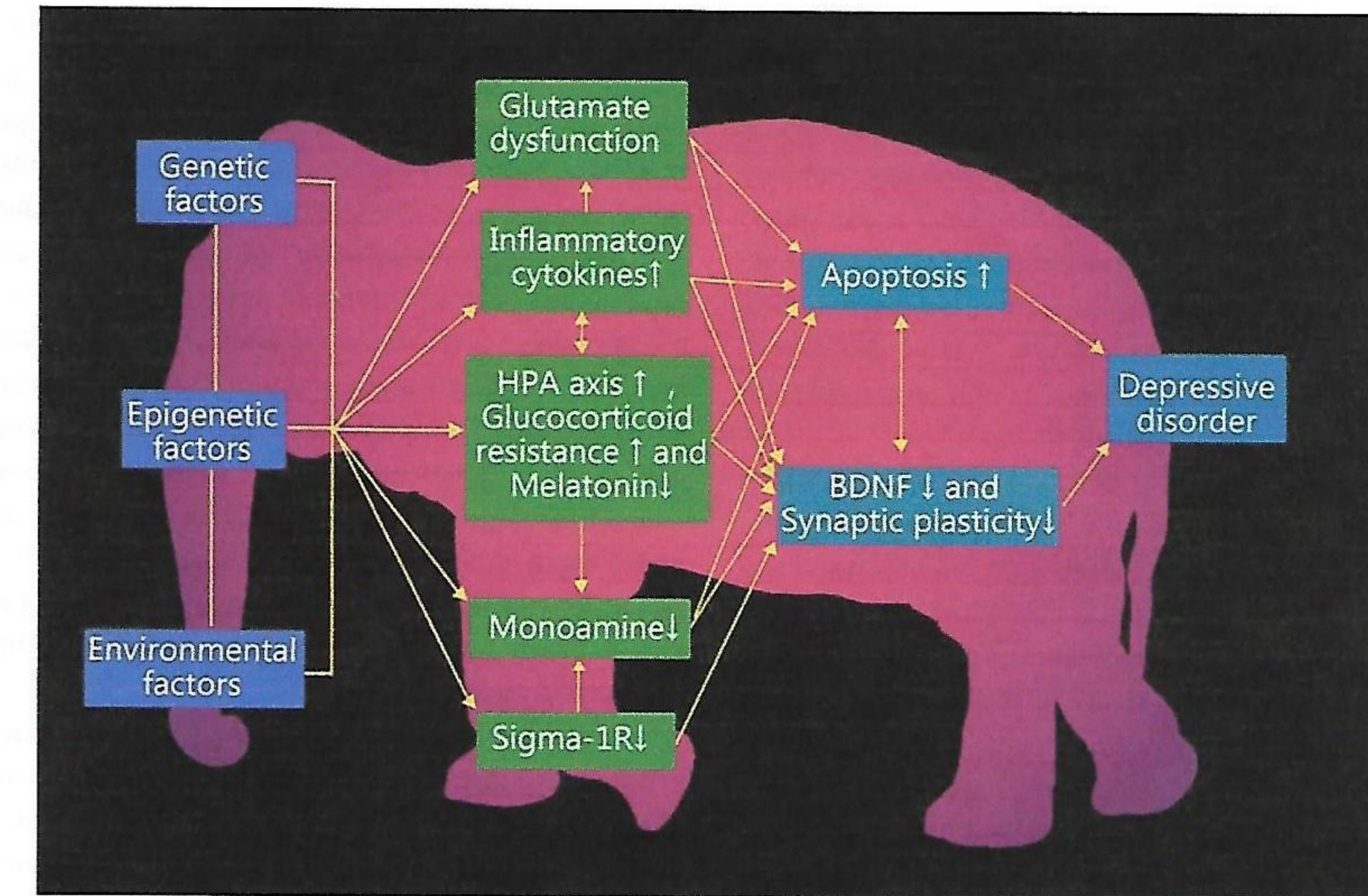
- MDD, according to Cai et al. (2015), “is a mental disorder characterized by prominent and persistent low mood, mental retardation, cognitive impairment, volitional decline, and somatic symptoms” (p.61).
- The Centers for Disease Control and Prevention (2016) states that almost 10% of adults aged 40-59, and more than 1 out of 20 Americans 12 years of age and older reported current depression.
- “Cognitive deficits are considered as key symptoms of clinical depression that are associated both with suboptimal response to antidepressants and reduced remission rates” (Castellano, 2016, p.1295).
- In the last decade, there has been an abundance of research showing that levels of neurotrophins, such as BDNF in the brain, may be involved in the pathophysiology of MDD and may accurately predict the efficacy of antidepressant medications and the remission of depression.
- The purpose of this review is to determine how BDNF and cognitive-emotional biomarkers factor into the pathophysiology of MDD, and if they can accurately predict 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 skills” (p.61). It can also increase the risk of suicide and disability rate and has a very high recurrence rate.
- According to the World Health Organization, there were 300 million patients with MDD in 2015. “It is estimated that by 2020, the disease burden caused by MDD will be ranked next to ischemic heart disease, becoming the second most common cause of disability and death” (Cai, 2015, p.61).
- The etiology of MDD has not been completely understood, according to Ristevska-Dimitrovska et al. (2013), and many new hypotheses in the pathophysiology of MDD have been formulated.
- Antidepressant treatment only has an efficacy of 60-65%, a remission 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 it often takes at least two weeks for them to take effect.
- Not having a definitive mechanism by which this disease works 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?



Schematic of the pathogenesis of depression. The pathogenesis of depression is complex. Like the proverbial blind men exploring an elephant, different hypotheses have been proposed for the etiology and pathogenesis of depression. It is important to have an integrated view of the mechanisms. Genetic and stress vulnerabilities interplay to initiate a cascade of neurobiological changes that disrupt a dynamic system. The decrease BDNF with associated synaptic plasticity and increased apoptosis may play an important role in the onset and maintenance of depression, and may be considered as a common pathway in various hypotheses of depression. Cai, S., Huang, S., Hao, W. (2015) New hypothesis and treatment targets of depression: an integrated view of key findings. Neuroscience Bulletin, 31 (1), 61-74. <http://dx.doi.org/10.1007/s12264-014-1486-4>

## Literature Review

- Pathophysiology of Major Depressive Disorder**
  - Monoamine-deficiency hypothesis only partly explains the pathogenesis of MDD.
  - Other hypotheses in the pathophysiology of MDD include inflammatory cytokines, hypothalamus-pituitary-adrenal axis, glutamate receptors, BDNF dysfunction, increased apoptosis, & vitamin D dysregulation.
  - Rot et al. (2009) found that a polymorphism of BDNF affects the intracellular transport and secretion of BDNF and may increase depression vulnerability.
  - There is a multitude of interconnected systems involved in the pathophysiology of MDD.
- Cognitive & Emotional Biomarkers**
  - Castellano et al. (2016) found that both SSRIs and SNRIs reduced the affective symptoms in MDD, as well as significantly improved the global cognitive function. Both SSRIs and SNRIs improved executive function and verbal memory, however, this improvement was independent from the efficacy of affective symptoms.
  - Etkin et al. (2015) showed that remission rates with escitalopram treatment were higher for individuals predicted to remit with escitalopram than for those predicted to not remit 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 8. The patients that were predicted not to reach remission had generally impaired cognitive functioning. Those predicted to not remit with escitalopram remitted at a lower rate if they received escitalopram compared with venlafaxine and sertraline.
  - Gyruk et al. (2016) found that that remitters to treatment were distinguished from nonremitters by greater pretreatment right dorsolateral prefrontal cortex (DLPFC) activation. “MDD patients who remitted were distinguished by relatively normal levels of DLPFC activation pretreatment, which attenuated posttreatment” (Gyruk, 2016, p.279). Patients who did not reach remission showed DLPFC hypoactivation at both pretreatment and posttreatment. A “failure to engage the DLPFC region may be a general marker of nonresponsiveness to treatment” (p.279), as stated by Gyruk et al. A region in the right inferior parietal cortex predicts HRSD remission differentially by SSRIs compared to SNRIs. Regarding effects of medications, Gyruk et al. found that “remitters specifically to SSRIs showed correspondingly normal levels of inferior parietal activation, which also attenuated posttreatment, while nonremitters to SSRIs showed parietal hypoactivation. Thus, SSRI and SNRI responders showed opposing patterns of activation in the parietal cortex”.
- Brain Derived Neurotrophic Factor**
  - Begni et al. (2016) proposed that BDNF is a very complex neurotrophin.
  - Ide et al. (2015) stated that “BDNF is highly expressed in the cortex, hippocampus, limbic structures, cerebellum, and the olfactory bulb” (p.120).
  - When BDNF is secreted, it binds to certain receptors & initiates a series of downstream signaling cascades which leads to prevention of cell death & neuronal differentiation.
- BDNF as a Target for Treatment Intervention**
  - Wolkowitz et al. (2011) found that serum BDNF levels were significantly lower in patients with MDD vs. healthy controls. This study also found that BDNF levels increased over the course of antidepressant treatment and that subjects with initially higher serum BDNF levels showed a larger antidepressant response to sertraline and escitalopram after 8 weeks of treatment.
  - Matriciano et al. (2009) showed that BDNF levels were lower in depressed patients versus healthy controls. A significant increase in BDNF serum levels after 5 weeks of treatment with sertraline and after 6 months of sertraline and venlafaxine were present. All three antidepressants were effective in relieving depression symptoms after 5 weeks and 6 months, despite their different effects on serum BDNF levels.
  - Ristevska-Dimitrovska et al. (2009) found that antidepressant treatment increased serum BDNF levels in depressed patients that were close to the healthy controls. In the integrated study, lower levels of BDNF were shown while depressive symptoms were evident.
  - Cattaneo et al. (2010) found that the BDNF serum and mRNA leukocyte levels showed a significant decrease in the MD patients compared to controls, as well as increased the level past baseline with escitalopram treatment. The drug treatment improved symptoms and significantly decreased MADRS scores.
  - Ghosh et al. (2015) found that plasma BDNF levels increased in MDD patients after 12-week treatment with both desvenlafaxine and fluoxetine.
  - Kurita et al. (2012) found that in the remission group, the MADRS scores reduced significantly over the course of treatment and the BDNF levels increased significantly with clinical improvement. Patients in the non-responder group did not show much difference in the MADRS scores, however, the plasma BDNF levels were still significantly decreased during the syndrome’s 8-12-week period.

## Discussion

- Both Cai et al. (2015) and Rot et al. (2009) stated that the pathophysiology of MDD has been mainly 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 acutely increase all of these neurotransmitters in the brain, and there is only a small number of patients that actually reach remission. This suggests that there is more to the pathogenesis of depression.
- Begni et al. (2016) stated that neurotrophins, such as BDNF, regulate growth and apoptosis of neurons in the CNS and PNS. If BDNF levels are decreased, an impairment of brain development and brain plasticity will occur.
- Yang et al. (2016) stated that neurogenesis and neuroplasticity are mechanisms involved in memory and learning, and if disrupted as with decreased BDNF levels, MDD may occur.
- Etkin et al. (2015) found that “response with antidepressant medication can be reliably predicted for outpatients with MDD by their pretreatment performance on a standardized test battery of cognitive and emotional function”.
- Gyruk et al. (2016) showed that activation in the frontoparietal region of the brain predicted remission with antidepressant treatment, particularly SSRIs.
- Overall, the review of literature showed that BDNF levels were decreased in patients with MDD. It also showed that these BDNF levels increase over time with antidepressant treatment with certain medications. These results may offer a tremendous gain in the treatment of adults with MDD and may finally be able to help find treatment options for patients that will work.

## Applicability to Clinical Practice

- In clinical practice, MDD is a disease process that will be encountered many times in a provider’s career.
- Based on cognitive and emotional tests performed before antidepressant treatment, studies were able to predict treatment response to certain SSRIs and SNRIs.
- BDNF is decreased in patients with MDD and certain antidepressants are able to increase this level. Some studies showed that a higher BDNF level showed a larger antidepressant response.
- If providers are able to predict whether certain medications will work before starting them, this can alleviate a large amount of stress and frustration.
  - Cognitive and emotional tests performed prior to antidepressant treatment may be an option to predicting if a medication will work.
  - Also, measuring BDNF levels before and during the course of treatment may help providers predict if antidepressant treatment will work much sooner than has previously been possible.

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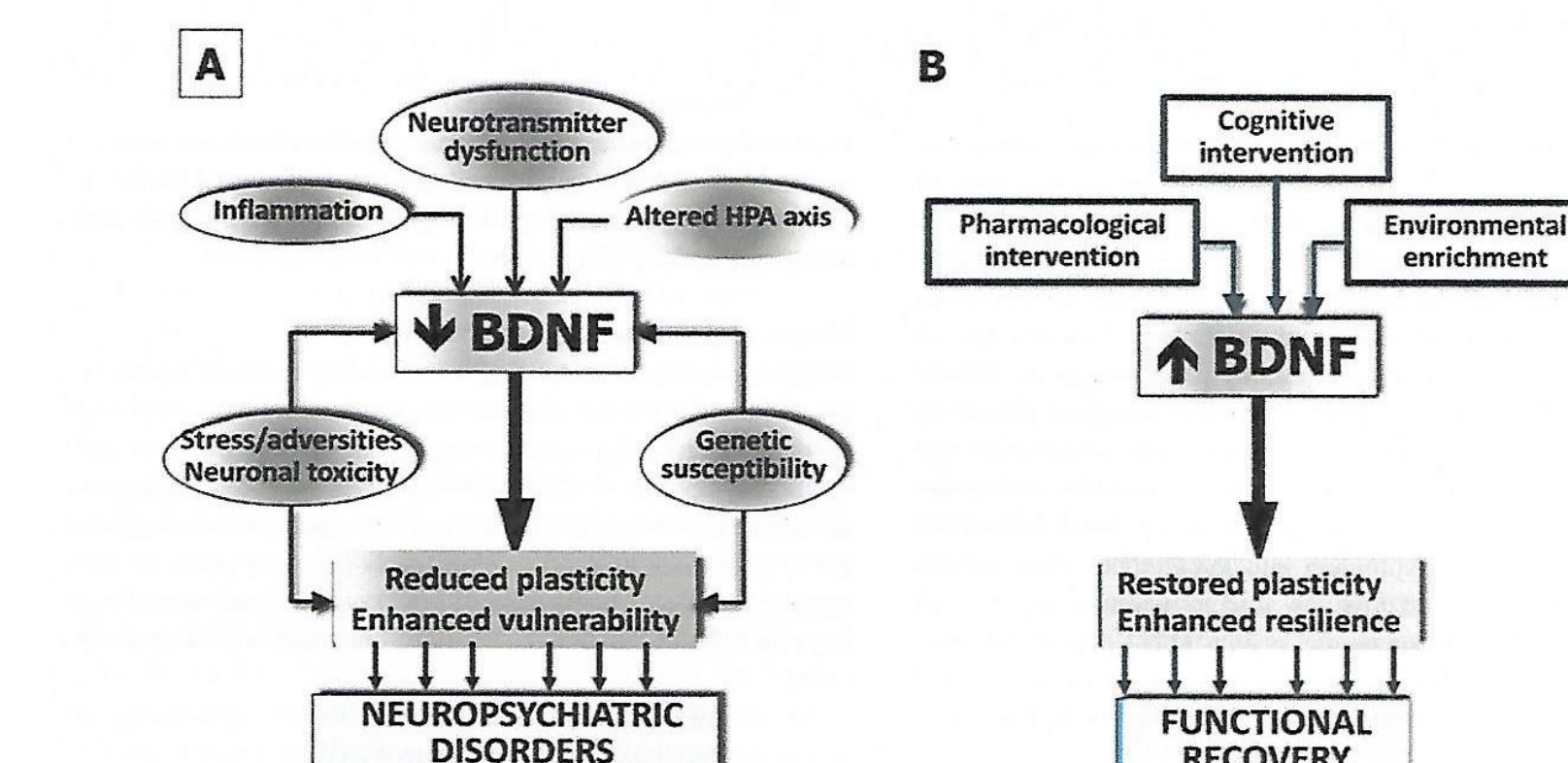


Figure 2: BDNF, a potential mediator of disease susceptibility in mental illness and a target for pharmacological intervention. (A) Reduced expression of BDNF may be one of the consequences of a genetic background of vulnerability, as well as of exposure to adverse environmental events. Furthermore, several factors, including inflammation, neurotransmitter dysfunction and altered HPA axis function, may affect BDNF function, leading to deficits in synaptic and neuronal identity and enhanced vulnerability to developing several neuropsychiatric disorders (see text). (B) Pharmacological and non-pharmacological strategies can increase BDNF expression and function which, in turn, may restore neuronal plasticity and improve resilience, thus leading to functional recovery (see text).