

Biomarkers of Major Depressive Disorder and Applications to Diagnosis and Treatment

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Abstract

This paper reviews recent research into potential biomarkers for major depressive disorder. These potential biomarkers are classified into one of three groups, including growth factors, cytokines, and glial marker proteins. In order to determine the relative reliability of these potential biomarkers, I examine how effectively these substances, upon measurement, indicate presence of disease and response to treatment. The results demonstrate that some biomarkers are more reliable than others, but a larger point emerges—that a comprehensive MDD biomarker test should be developed and MDD subtypes should be defined, so that individualized treatments based on subtype can be developed and administered.

Introduction

Mental health illnesses are extremely prevalent in the United States, and they carry high costs to society with them. In a 2005 landmark epidemiological study of mental health in America, Kessler et al. found that *lifetime prevalence* of at least one mental health disorder was 46.4%. In other words, almost half of Americans, at some point in their lifetime, experience at least one mental health disturbance that the American Psychiatric Association defines as abnormal and deserving of treatment.

One of the most prevalent mental health illnesses that Americans battle is *major depressive disorder* (MDD). The same 2005 Kessler study found that lifetime prevalence of MDD in America is 16.6%. The symptoms that characterize MDD include depressed mood, *anhedonia* (loss of enjoyment or interest in usual activities), and impaired cognitive function. These symptoms often lead to significant disruptions in daily life—in work, school, family responsibilities, social activities, etc.—and therefore place great burdens upon the millions of Americans who have MDD or are close to someone with MDD.

Not only are mental health disorders (and major depressive disorder in particular) so prevalent and harmful to our country's collective well-being, but our methods of diagnosing and treating these illnesses are also quite primitive, especially in comparison to other fields of medicine. A broken bone can be confirmed with an X-ray, diabetes can be detected with a blood test, and a tumor can be examined for cancer after a biopsy—and any of these diagnoses would lead to a specialized treatment based on the findings. However, MDD and other mental health disorders are diagnosed via subjective assessments that rely upon the expertise of a practitioner to perceive a disturbance in a patient's mental health. What's more, since these diagnoses focus on symptoms instead of neurobiological causes, treatments cannot be prescribed in an individualized manner, and doctors are often forced to engage in a process of trial-and-error—with the health of their patients in the balance.

Therefore, one of the most pressing concerns in mental health research today is to discover and refine more objective and reliable methods of diagnosis and treatment. Thankfully, a considerable amount of time

and effort has already been dedicated to this goal, and a variety of *biomarkers* have been proposed across the spectrum of mental health disorders.

Generally, a biomarker is a measurable substance or characteristic in the body that indicates the presence or absence of a disease, or the response to treatment or lack thereof (Schmidt et al., 2011). If any of the proposed mental health biomarkers were proven to be reliable, they could be tested in a patient and would allow clinicians to objectively diagnose disorders and observe whether or not specific treatments were having a positive effect. They might also allow researchers to define subpopulations within a disorder. For instance, symptom A might be the result of low levels of biomarker 1 or high levels of biomarker 2. Accordingly, the subgroup with low levels of biomarker 1 would probably require a completely different treatment than the subgroup with high levels of biomarker 2.

This review focuses on potential biomarkers of major depressive disorder; attempts to determine the most reliable of these biomarkers; and calls for the creation of a comprehensive MDD biomarker test, the delineation of MDD subtypes based on these biomarkers, and the development of specific treatments based on these subtypes.

Brain-Derived Neurotrophic Factor (BDNF) and Vascular Endothelial Growth Factor (VEGF) as MDD Biomarkers

One biomarker for major depressive disorder that has repeatedly been pinpointed by clinical studies is *brain-derived neurotrophic factor*. BDNF is a *growth factor*, or a protein that contributes to the survival, development, and function of cells—and more specifically, a *neurotrophin*, which is a growth factor associated with neurons. BDNF has been linked to neuronal growth, differentiation, repair, and synaptic

connectivity; in other words, it is crucial to the development and healthy functioning of the nervous system (Lewin and Barde, 1996).

In relation to mood regulation (and the breakdown of mood regulation that leads to illnesses such as major depressive disorder), studies have shown that brain-derived neurotrophic factor is an important component. For example, supplemental BDNF has been shown to reduce depressive behavior in an animal model of depression (Hoshaw et al., 2005). It has also been suggested that physical or psychological stress causes significant underproduction of BDNF in the brain (particularly in the *hippocampus*, a region focused on memory and emotion) and that this lack of BDNF, if chronic, might contribute to the development of MDD (Nibuya et al., 1995).

In line with these findings, strong evidence suggests that depressed patients exhibit lower levels of brain-derived neurotrophic factor in the blood than healthy controls do. This result has been replicated many times and verified by multiple meta-analyses (Brunoni et al., 2008; Sen et al., 2008). The data from several of these studies have been compiled in Table 1. Furthermore, multiple studies have found that BDNF levels in depressed patients rise to healthy levels upon treatment with antidepressant medication that leads to symptom improvement (Huang et al., 2008; Gonul et al., 2005; Aydemir et al., 2005).

All of these studies suggest that brain-derived neurotrophic factor is a reliable biomarker in both senses of the term; it can be measured to indicate the presence or absence of MDD, and it can be measured to provide biological evidence for positive, null, or negative response to MDD treatment.

It would be important for normal, abnormal, and borderline BDNF ranges to be experimentally determined in order for this biomarker to have any clinical relevance. At least with the information already available

(and compiled in Table 1), it seems feasible to say that a BDNF level of 20 $\mu\text{g/mL}$ or below might indicate the presence of major depressive disorder.

Table 1. Results of studies that compared BDNF serum levels of depressed patients and healthy controls.

First-named author (year)	Depressed BDNF, mean (SD) in $\mu\text{g/mL}$	Control BDNF, mean (SD) in $\mu\text{g/mL}$
Aydemir (2005)	17.9 (9.1)	31.6 (8.6)
Aydemir (2006)	27.7 (13.7)	41.2 (15.1)
Gervasoni (2005)	22.6 (3.6)	26.4 (3.6)
Gonul (2005)	20.8 (6.7)	26.8 (9.3)
Huang (2008)	10.7 (7.3)	14.1 (7.0)
Monteleone (2008)	29.0 (15.9)	42.5 (12.5)
Piccinni (2008)	19.3 (8.8)	33.6 (8.6)
Shimizu (2003)	17.9 (9.6)	27.7 (11.4)
Yoshimura (2007)	9.1 (7.7)	23.4 (10.1)

However, factors like age, weight, gender, etc., must also be properly included in the calculation of these ranges in order to respect the many nuances of human homeostasis. For example, some sort of gender interaction seems to be present; the three studies that measured the highest BDNF levels across both depressed patients and healthy controls are also the three studies in which women were most represented in the samples (Aydemir et al., 2006; Monteleone et al., 2008; Piccinni et al., 2008). In other words, women appear to exhibit higher levels of BDNF whether or not they have MDD. Therefore, the critical threshold between considering a patient MDD-positive or MDD-negative should probably be higher for women than for men.

Once further research is done to determine these ranges, a clinician could more confidently diagnose a patient with MDD with the combination of self-reported depressive symptoms and a positive blood test for abnormally low BDNF levels.

It should also be mentioned that brain-derived neurotrophic factor is not the only growth factor that has been studied for its potential as an MDD biomarker. Another growth factor that has received attention is *vascular endothelial growth factor*, which is mainly known to stimulate blood vessel growth but has recently been associated with the promotion of some of the same neuronal processes as BDNF (Greenberg and Jin, 2004). It has also been shown that stress causes downregulation of hippocampal VEGF (Heine et al., 2005), representing another similarity with BDNF and another potential connection to MDD.

In two different clinical examinations of VEGF, depressed patients exhibited higher levels of the protein than healthy controls did (Iga et al., 2007; Kahl et al., 2009). This was a notable finding because it subverted expectations that VEGF would continue to mirror the attributes of BDNF; if that were the case, VEGF levels would have been lower in depressed patients than in healthy controls. One of the research teams hypothesized that, like other neurological diseases including Alzheimer's disease and ALS, major depressive disorder might involve neuronal hypoxia, which is a known stimulant of VEGF production (Iga et al., 2007). The other team hypothesized that their sample of depressed patients might have been complicated by smoking habits or unrelated diseases that could have led to VEGF overproduction, or that their sample size was too small (Kahl et al., 2009). I also thought that this second team's inclusion of MDD patients comorbid with borderline personality disorder might have tainted the results; borderline personality symptoms

could be caused by a completely different neural mechanism than the mechanisms that result in depressive symptoms—and thus might affect VEGF expression in a completely different way.

Beyond these two studies, a third study found no difference in VEGF levels between depressed patients and healthy controls (Ventriglia et al., 2009). In addition to the relative lack of research into VEGF in comparison with BDNF, the presence of unclear and conflicting results suggests that more work must be done before vascular endothelial growth factor can be considered a reliable biomarker of major depressive disorder. Specifically, more studies with larger sample sizes and more stringent exclusion criteria need to be completed. After this research, if the results still bear out that depressed patients exhibit higher levels of VEGF than healthy controls do (perhaps as a side effect of MDD-produced neuronal hypoxia, as Iga et al. proposed), VEGF could be utilized as a diagnostic biomarker for MDD.

Cytokines as MDD Biomarkers

Apart from growth factors, *cytokines* constitute a second class of compounds that have been examined as potential biomarkers of major depressive disorder. These signaling molecules are secreted by immune system cells and play an important role in *the inflammatory response*. This process is a protective measure against the invasion of foreign pathogens. When the body recognizes an invader, cytokines are spontaneously secreted in order to alert *phagocytes* and *lymphocytes*, which are cells that kill the unwanted microbes (Dantzer et al., 2008).

Although the underlying connection is still unclear, many different studies have found that overactivation of the inflammatory response is somehow involved in the

pathophysiology of MDD. For example, a meta-analysis that combined the work of 24 studies found significantly higher concentrations of the pro-inflammatory cytokines tumor necrosis factor (TNF)- α and interleukin (IL)-6 in the blood of depressed patients than in that of healthy controls (Dowlati et al., 2009). The authors (and many others before them) hypothesized that intense and/or repeated exacerbation of the inflammatory response due to environmental/internal stress or underlying disease might somehow contribute to the development of major depression. I believe that it should also be considered that this overactivation of the inflammatory response is not a direct contributor to MDD, but instead, a signpost for the the downregulation of BDNF and VEGF in the hippocampus that also results from stress. In any case, an investigation of the interplay between stress, growth factor downregulation, and inflammatory response overactivation would surely contribute to our understanding of major depressive disorder and its underlying causes.

But the purpose of this review is not to determine the most likely mechanisms of MDD; it is to determine the most reliable biomarkers of MDD, and the literature provides several forms of evidence that TNF- α and IL-6 could serve as both diagnostic and treatment-response biomarkers. In addition to Dowlati et al.'s meta-analysis proving TNF- α and IL-6's diagnostic reliability, studies have shown that levels of TNF- α (Tuglu et al., 2003) and IL-6 (Frommberger et al., 1997) in depressed patients decrease to levels that are statistically equivalent to healthy control levels upon treatment with antidepressant medication that leads to symptom improvement.

On the other hand, one inquiry found that TNF- α levels in depressed patients were the same as in healthy controls and IL-6 levels were lower in depressed patients than

in healthy controls (Levine et al., 1999). Another team found that successful antidepressant treatment had no lowering effect on IL-6 levels in depressed patients (Kubera et al., 1999). Neither of these studies are encouraging results for the reliability of these signaling molecules as biomarkers. Similar to the current state of vascular endothelial growth factor, it would probably be helpful to see more research that confirms the reliability of TNF- α and IL-6 before these cytokines can be used as MDD biomarkers.

Glial Marker Protein S100B as MDD Biomarker

Marker proteins of *glial cells* constitute a final type of compound that has been discussed as an MDD biomarker; specifically, investigations have been made into the glial marker protein S100B.

Glial cells are the most abundant type of cells in the nervous system. They support and insulate neurons and are therefore vital to neuronal function and communication. Damage to glial cells has already been implicated in many neurological diseases including multiple sclerosis, ALS, and Alzheimer's disease, and recent evidence seems to suggest that glial pathology also contributes to major depressive disorder (Rajkowska et al., 1999).

Furthermore, it appears that this effect can be visualized by measuring patient levels of marker proteins like S100B that reside in glial cell membranes. Schroeter et al. (2008) found that S100B levels in depressed patients were higher than levels in healthy controls and that successful antidepressant treatment led to a reduction of these levels, thus satisfying both biomarker requirements. These findings were confirmed in a meta-analysis performed by the same research team (Schroeter et al., 2011). It would be encouraging to see more work done by other research teams before S100B is

considered a highly reliable biomarker, but it has had a promising start.

A very recent study performed by Polyakova et al. (2015) that also focuses on S100B came to an interesting conclusion that provides support for my forthcoming recommendations on MDD biomarkers in general. The team found that S100B levels in depressed patients were only higher than healthy control levels for one subpopulation of patients—specifically, males who had minor depressive symptoms. They also found that this subpopulation's BDNF levels showed no difference from healthy control BDNF levels. These findings imply the presence of MDD subgroups, which will be discussed in the Conclusion section.

Conclusion

This review focused on potential biomarkers of major depressive disorder; attempted to determine the most reliable of these biomarkers; and will call for the creation of a comprehensive MDD biomarker test, the delineation of MDD subtypes based on these biomarkers, and the development of specific treatments based on these subtypes.

An overwhelming amount of research indicates that brain-derived neurotrophic factor would be a reliable MDD biomarker in both diagnostic and treatment-response situations. Vascular endothelial growth factor, cytokines, and glial marker proteins would still benefit from additional research to confirm reliability, which was described in more detail above, but they all show promise. All biomarkers mentioned (especially BDNF, given that its reliability has been confirmed) would benefit from statistical analysis of already-completed research in order to determine normal, abnormal, and borderline ranges for different ages, weights, and genders, so that these biomarkers could begin to be used in a clinical setting in order to

diagnose MDD and assess MDD treatment effectiveness.

The Polyakova et al. S100B study reveals the notion that specific biomarkers might be more reliable for specific MDD subpopulations. This notion rests on the more foundational idea that MDD might be caused by a variety of different mechanisms. For example, while many patients might suffer from an MDD subtype based on stress that results in abnormal BDNF and TNF- α levels, another patient might suffer from an MDD subtype based on glial pathology that results in abnormal levels of S100B—but does not affect the patient's levels of BDNF or TNF- α . Therefore, the only biomarker that would be effective in detecting this patient's disease or measuring her response to treatment would be S100B.

This line of logic makes it clear that we must, as the mental health research community, work towards developing a comprehensive MDD biomarker test. This way, we might be able to not only diagnose MDD or assess MDD treatment effectiveness, but also define separate MDD subtypes based on etiology. From there, we can eventually develop separate MDD treatments based on these subtypes, which would presumably improve MDD treatment effectiveness considerably. At least one research team has already begun to develop a comprehensive MDD biomarker test (Papakostas et al., 2013), but the mental health research community must make this idea a priority. Once a biomarker panel has been established for major depressive disorder, it will be easier to develop comprehensive tests for generalized anxiety disorder, bipolar disorder, and other mental health illnesses as well. The development of these panels, and the information they reveal about mental illness, will continue to usher in the era of personalized medicine, in which treatment is based upon individual biology

instead of generalized assumptions—and in which patients are healthier as a result.

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