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Review Article **Biochemistry**

Biomarkers for Depression: A Detailed View

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Abstract

A plethora of research has implicated hundreds of putative biomarkers for depression but has not yet fully elucidated their roles in depressive illness or established what is abnormal in which patients and how biologic information can be used to enhance diagnosis, treatment, and prognosis. This lack of progress is partially due to the nature and heterogeneity of depression, in conjunction with methodological heterogeneity within the research literature and the large array of biomarkers with potential, the expression of which often varies according to many factors. We review the available literature, which indicates that markers involved in inflammatory, neurotrophic, and metabolic processes, as well as neurotransmitter and neuroendocrine system components, represent highly promising candidates. These may be measured through genetic and epigenetic, transcriptomic and proteomic, metabolomic, and neuroimaging assessments. The use of novel approaches and systematic research programs is now required to determine whether, and which, biomarkers can be used to predict response to treatment, stratify patients to specific treatments, and develop targets for new interventions. We conclude that there is much promise for reducing the burden of depression through further developing and expanding these research avenues.

Keywords: mood disorder, major depressive disorder, inflammation, treatment response, stratification, personalized medicine.

INTRODUCTION

Taking a Challenge

Although psychiatry has a disease-related burden greater than any single other medical diagnostic category, a disparity of esteem is still apparent between physical and mental health across many domains including research funding and publication [3]. Among the difficulties that mental health faces is a lack of consensus surrounding classification, diagnosis, and treatment that stems from an incomplete understanding of the processes underlying these disorders. This is highly apparent in mood disorders, the category which comprises the single largest burden in mental health. The most prevalent mood disorder, major depressive disorder (MDD), is a complex, heterogeneous illness in which up to 60% of patients may experience some degree of treatment resistance that prolongs and worsens episodes. For mood disorders, and in the broader field of mental health, treatment outcomes would likely be improved by the discovery of robust, homogeneous subtypes within (and across) diagnostic categories, by which treatments could be stratified. In recognition of this, global initiatives to delineate functional subtypes are now in progress, such as the research domain criteria. It has been posited that biological markers are priority candidates for subtyping mental disorder [11].

Can be Improved?

Despite an extensive range of treatment options for major depression, only approximately a third of patients with MDD achieve remission even when receiving optimal antidepressant treatment according to consensus guidelines and using measurement-based care, and rates of treatment response appear to fall with each new treatment. Furthermore, treatment-resistant depression (TRD) is associated with increased functional impairment, mortality, morbidity and recurrent or chronic episodes in the long term12. Thus, obtaining improvements in treatment response at any clinical stage would afford wider benefits for overall outcomes in depression. Despite the substantial burden attributable to TRD, research in this area has been sparse. Definitions of TRD are not standardized, despite previous attempts: some criteria require only one treatment trial that fails to achieve a 50% symptom score reduction (from a validated measure of depression severity), while others require non-achievement of full remission or nonresponse to at least two adequately trialed

antidepressants of different classes within an episode to be considered TRD. To improve response to treatments, it is helpful to identify predictive risk factors of nonresponse. Some general predictors of TRD have been characterized, including a lack of full remission after previous episodes, comorbid anxiety, suicidality, and early onset of depression, as well as personality (particularly low extraversion, low reward dependence, and high neuroticism) and genetic factors. These findings are corroborated by reviews synthesizing the evidence separately for pharmacologic and psychological treatment for depression [13]. Antidepressants and cognitive-behavioral therapies show approximately comparable efficacy, to attain a full understanding of molecular pathways and their contribution to psychiatric disorders, it is now considered important to assess multiple biological "levels", in what is popularly referred to as an "omics" approach. Provides a depiction of the different biologic levels at which each of the five systems can be assessed, and the potential sources of markers on which these assessments can be undertaken. However, note that while each system can be inspected at each omics level, the optimal sources of measurement vary at each level.

Aims

As a deliberately broad review, this article seeks to determine the overall needs for biomarker research in depression and the extent to which biomarkers hold real translational potential for enhancing response to treatments. We begin by discussing the most important and exciting findings in this field and direct the reader to more specific reviews about relevant markers and comparisons [15]. We outline the current challenges faced in light of the evidence, in combination with the need to reduce the burden of depression. Finally, we look ahead to the important research pathways for meeting current challenges and their implications for clinical practice.

Recent Developments

The most commonly used treatments were conceived from the monoamine theory of depression; subsequently, neuroendocrine hypotheses gained much attention. In more recent years, the most prolific research has surrounded the inflammatory hypothesis of depression. However, a large number of relevant review articles have focused on all five systems; see below for a collection of recent insights across biomarker systems [16]. While measured at many levels, blood-derived proteins have been examined most widely and provide a source of biomarkers that is convenient, cost- effective, and maybe closer to translational potential than other sources; thus, more detail is given to biomarkers circulating in the blood. Those identified as potentially representing risk factors for nonresponse included inflammatory proteins: low interleukin (IL)-12p70, the ratio of lymphocyte to monocyte count; neuroendocrine markers (dexamethasone no suppression of cortisol, high circulating cortisol, reduced thyroid-stimulating hormone); neurotransmitter markers (low serotonin and noradrenaline); metabolic (low high-density lipoprotein cholesterol) and neurotrophic factors (reduced S100 calcium-binding protein B).

Inflammation in Depression

IL-6 (P<0.001 in all meta-analyses; 31 studies included) and CRP (P<0.001; 20 studies) appear frequently and reliably elevated in depression. Elevated tumor necrosis factor alpha (TNFα) was identified in early studies (P<0.001), but substantial heterogeneity rendered this inconclusive when accounting for more recent investigations (31 studies). IL-1β is even more inconclusively associated with depression, with meta-analyses suggesting higher levels of depression (P=0.03),[41] high levels only in European studies, or no differences from controls. Despite this, a recent article suggested particular translational implications for IL-1β, supported by an extremely significant effect of elevated IL-1β ribonucleic acid predicting a poor response to antidepressants; other findings above pertain to circulating blood-derived cytokines. The chemokine monocyte chemoattractant protein-1 has shown elevations in depressed participants in one meta-analysis. Interleukins IL-2, IL-4, IL-8, IL-10, and interferon-gamma were not significantly different between depressed patients and controls at a meta-analytic level, but have nonetheless demonstrated potential in terms of altering with treatment: IL-8 has been reported as elevated in those with severe depression prospectively and cross- sectionally, different patterns of change in IL-10 and interferon-gamma during treatment have occurred between early responders versus nonresponders [14], while IL-4 and IL-2 have decreased in line with symptom remission. In meta- analyses, small decreases alongside treatment have been demonstrated for IL-6, IL-1β, IL-10, and CRP. Additionally, TNFα may only reduce with treatment in responders, and a composite marker index may indicate increased inflammation in patients who subsequently do not respond to treatment.

Growth Factor

Brain-derived neurotrophic factor (BDNF) is the most frequently studied of these. Multiple meta-analyses demonstrate attenuations of the BDNF protein in serum, which appear to increase alongside antidepressant treatment. The most recent of these analyses suggests that these BDNF aberrations are more pronounced in the most severely depressed patients, but that antidepressants appear to increase the levels of this protein even in the absence of clinical remission. proBDNF has been less widely studied than the mature form of BDNF, but the two appear to differ functionally (in terms of their effects on tyrosine receptor kinase B receptors) and recent evidence suggests that while mature BDNF may be reduced in depression, proBDNF may be overproduced [1]. Nerve growth factor assessed peripherally has also been reported as lower in depression than in controls in a meta-analysis,

but may not be altered by antidepressant treatment despite being most attenuated in patients with more severe depression [7].

Metabolic Biomarkers

The main biomarkers associated with metabolic illness include leptin, adiponectin, ghrelin, triglycerides, high-density lipoprotein (HDL), glucose, insulin, and albumin [2]. The associations between many of these and depression have been reviewed: leptin and ghrelin appear lower in depression than controls in the periphery and may increase alongside antidepressant treatment or remission. Insulin resistance may be increased in depression, albeit by small amounts. Lipid profiles, including HDL-cholesterol, appear altered in many patients with depression, including those without comorbid physical illness, though this relationship is complex and requires further elucidation[3]. Additionally, hyperglycemia and hypoalbuminemia in depression have been reported in reviews.

Neurotransmitter Findings

Recent work points toward the serotonin (5-hydroxytryptamine) 1A receptor as potentially important for both diagnosis and prognosis of depression, pending new genetic and imaging techniques [4]. There are new potential treatments targeting 5-hydroxytryptamine; for example, using a slow-release administration of 5-hydroxytryptophan. Increased transmission of dopamine interacts with other neurotransmitters to improve cognitive outcomes such as decision-making and motivation. Similarly, the neurotransmitters glutamate, noradrenaline, histamine, and serotonin may interact and activate as part of a depression-related stress response; this might decrease 5- hydroxytryptamine production through "flooding". A recent review sets out this theory and suggests that in TRD, this could be reversed (and 5-HT restored) through multimodal treatment targeting multiple neurotransmitters [5]. Interestingly, increases in serotonin do not always occur conjunctively with therapeutic antidepressant benefits.

Oxidative Stress Markers

Levels of lipid peroxidation products such as malondialdehyde (MDA) have been reported to be generally elevated in depressed patients [6]. There are also studies reporting that MDA levels are higher in patients with recurrent depression than in those with a single episode. MDA levels have mostly been reported to decrease and return to normal with antidepressant therapy. Another parameter investigated as an oxidative stress marker in patients with MDD is superoxide dismutase (SOD) activity. The results of SOD studies are not as consistent as those in MDA studies. In depressed patients, several studies have reported that serum SOD is decreased or that erythrocyte SOD is increased [7].

Endocrine Biomarkers

In depressed patients, HPA axis findings including abnormal cortisol levels during awakening, abnormalities in the diurnal rhythm of cortisol release, and abnormal cortisol response to pharmacological suppression tests such as the dexamethasone suppression test (DST) or experimental stress have been reported [9]. HPA axis changes in depression are accepted as mostly state-dependent, that is, they improve with treatment [8]. It is suggested that the increased activity of the HPA axis in MDD is largely due to the reduced negative feedback of endogenous glucocorticoids. This is also partly related to the reduced GR expression in patients with depression. It has been suggested that elevated cortisol in some patients with depression develops to compensate for reduced GR expression and function. Indeed, postmortem human studies have shown a reduction in GR mRNA expression in the frontal and temporal regions of patients with MDD. Preclinical studies have shown that the use of antidepressants upregulates GR expression and function in the brain, thereby increasing the negative feedback of the HPA axis [9].

Tumor Necrosis Factor

A recent paper by Benedetti *et al*., evaluated the examination of peripheral levels of several pro-inflammatory cytokines, including the TNF, as a predictive method to assess the success of antidepressant therapy. TNF elevation at the baseline was associated with worse treatment outcomes. Das *et al*., evaluated the relationship between TNF serum levels and MDD [9]. They found that TNF was not only increased in MDD, but the levels were also directly proportional to its severity. Therefore, the peripheral levels of TNF might have a predictive value in clinical practice [In 2020, Bialek *et al*., were the first to study the SNPs in various cytokine-coding genes, including the *TNF* gene, namely c.-1211T > C—*TNF-* α (rs1799964) and c.-488G > A—*TNF-*α (rs1800629) and its relation to MDD development and treatment effectiveness [10]. The preliminary results showed that the C allele in the C/T genotype of rs179964 was associated with positive treatment outcomes and low serum levels of TNF. These results indicate that the molecular biological approach can provide additional information beneficial for a complex diagnostic assessment of MDD and its treatment prediction. Ng *et al*., published a systematic review and meta-analysis on the relationship between peripheral levels of TNF and four other cytokines in the elderly diagnosed with depression and AD [11]. The primary conclusion was that there was no difference in the TNF levels between study groups and controls in either of the reviewed disease entities. On the contrary, a meta-analysis by Dowlati *et al*., found the opposite. Those studies that met the inclusion criteria showed a significant rise in TNF serum levels compared to controls [12].

Noval Treatment Targets

There are a huge number of potential treatments that could be effective for depression, which have not been adequately examined, including novel or repurposed interventions from other medical disciplines.

Some of the most popular targets have been in anti-inflammatory medications such as celecoxib (and other cyclooxygenase-2 inhibitors), TNFα antagonists etanercept and infliximab, minocycline, or aspirin. These appear promising. Antiglucocorticoid compounds, including ketoconazole and metyrapone, have been investigated for depression, but both have drawbacks with their side effect profile and the clinical potential of metyrapone is uncertain. Mifepristone and the corticosteroids fludrocortisone and spironolactone, and dexamethasone and hydrocortisone may also be effective in treating depression in the short term. Targeting glutamate *N*-methyl-d-aspartate receptor antagonists, including ketamine, might represent efficacious treatments for depression [12]. Omega-3 polyunsaturated fatty acids influence inflammatory and metabolic activity and appear to demonstrate some effectiveness for depression. Statins may have antidepressant effects through relevant neurobiological pathways.

In this way, the biochemical effects of antidepressants (see the "Medication" section) have been utilized for clinical benefits in other disciplines: particularly gastroenterological, neurologic, and nonspecific symptom illnesses. The anti-inflammatory effects of antidepressants may represent part of the mechanism for these benefits. Lithium has also been suggested to reduce inflammation, critically through glycogen synthase kinase-3 pathways. A focus on these effects could prove informative for a depression biomarker signature and, in turn, biomarkers could represent surrogate markers for novel drug development.

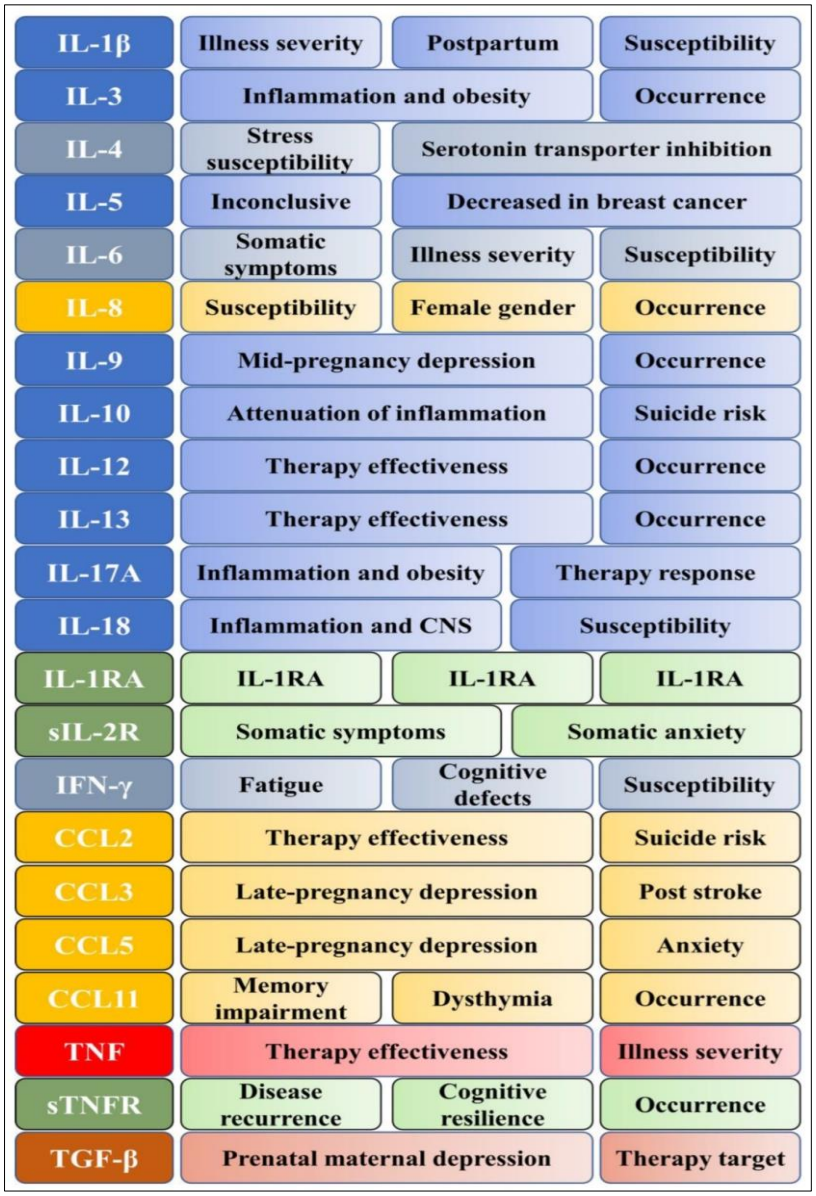

Figure 1: Cytokines and their main associations with depression. Blue—interleukins, gray—lymphokines, yellow—chemokines, green—soluble receptors, red—tumor necrosis factor, brown—transforming growth factor

Table 1: Overview of recent insights into biomarkers for depression

Biomarker system	Review topic/summary	References	Evidence strength*
Inflammation	Proinflammatory markers are higher in depression than controls		Strong
	Inflammation tends to decrease with antidepressant treatment		Haapakoski *et al*
	Inflammation seems more aberrant in treatment nonresponders	Strawbridge *et al*	Hiles *et al*
	Anti-inflammatory treatments reduce depression severity	Köhler *et al*	Strong
Neuroendocrine	HPA axis appears overactive in people with depression	Horowitz and Zunszain	Strong
	Atypical depression may show hypocortisolism	Juruena and Cleare	Medium
	High cortisol may predict a poorer response to psychological therapy and pharmacologic therapy	Fischer *et al*., Anacker *et al*.,	Medium
GF	Some neurotrophic factors are reduced in depression compared to controls (BDNF, NGF, GDNF)	Molendijk *et al*.,	Strong
	Some GFs may be overproduced in depression (VEGF, bFGF)	Tseng *et al*.,	Medium
	Neurotrophic factors appear to increase alongside treatment, regardless of response	Castrén and Kojima	Medium
Neurotransmitter	There is widespread increased 5-HT1A binding in people with depression that can be influenced by treatment	Kaufman *et al*.,	Strong
	Monoamines interact to influence cognitive function and responses to stress; may provide mechanisms of TRD	Coplan *et al*.,	Medium
Metabolic	Depression is associated with altered metabolic profiles	Pan *et al*.,	Medium
	The promise of metabolic markers for improving depression treatments is limited by the confounders BMI and severity	Carvalho *et al*.,	Medium
	Atypical depression linked with greater metabolic abnormalities	Lamers *et al*.,	Strong

Table 2: Biomarkers with potential translational use for depression

Source/system	Biomarker(s) with potential	References
Inflammation	IL-6, CRP	Haapakoski *et al*.,
	TNFα	Strawbridge *et al*.,
	IL-1β	Farooq *et al*.,
	IL-2, IL-4, IL-10, IFNγ	Dowlati *et al*.,
	IL-8, MCP1	Eyre *et al*.,
	IL-1a, IFNα, IL-5, IL-7, IL-12, IL-12p70, IL-13, IL-15, IL-16, IL-17, TNFβ, MCP4, Mip1α, Mip1β, SAA, sICAM1, sVCAM1, eotaxin, eotaxin3, TARC, IP-10, GM-CSF	Novel markers
Growth factors	BDNF	Molendijk *et al*.,
	VEGF	Carvalho *et al*.,
	NGF	Chen *et al*.,
	GDNF	Lin and Tseng
	IGF-1	Tu *et al*.,
	bFGF, Tie2, sFlt1, PlGF, VEGFC, VEGFD, proBDNF	Novel markers
Neurotransmitters	5-HT and receptors	Kaufman *et al*.,
	NA, DA, glutamate/glutamine, GABA, histamine, MHPG, HVA	Coplan *et al*., Yoshimura *et al*.,
Endocrine	Cortisol (various measurements)	Fischer *et al*.,
	ACTH, CRH, DHEA, vasopressin	Pierscionek *et al*.,
	TSH	Hage and Azar
Metabolic factors	Leptin	Lu
	Ghrelin	Wittekind and Kluge
	Insulin	Kan *et al*.,
	Albumin	Maes *et al*.,
	Glucose	Lustman *et al*.,
	Lipids	Liu *et al*.,
Neuroimaging markers	Structural, for example, gray/white matter volume	Wise *et al*.,

CONCLUSIONS

The literature indicates that approximately two-thirds of patients with depression do not achieve remission to an initial treatment and that the likelihood of nonresponse increases with the number of treatments trialed. Providing ineffective therapies has substantial consequences for individual and societal costs, including persistent distress and poor well-being, risk of suicide, loss of productivity, and wasted healthcare resources. The vast literature on depression indicates a huge number of biomarkers with the potential to improve treatment for people with depression. In addition to neurotransmitter and neuroendocrine markers which have been subject to widespread study for many decades, recent insights highlight the inflammatory response (and the immune system more generally), metabolic, and growth factors as important involved in depression. However, excessive contrasting evidence illustrates that several challenges need to be tackled before biomarker research can be applied to improve the management and care of people with depression. Due to the sheer complexity of biological systems, simultaneous examinations of a comprehensive range of markers in large samples are of considerable benefit in discovering interactions between biological and psychological states across individuals. Optimizing the measurement of both neurobiological parameters and clinical measures of depression is likely to facilitate greater understanding. This review also highlights the importance of examining potentially modifying factors (such as illness, age, cognition, and medication) in gleaning a coherent understanding of the biology of depression and mechanisms of treatment resistance. Some markers will likely show the most promise for predicting treatment response or resistance to specific treatments in a subgroup of patients, and the concurrent measurement of biological and psychological data may enhance the ability to prospectively identify those at risk for poor treatment outcomes. Establishing a biomarker panel has implications for boosting diagnostic accuracy and prognosis, as well as for individualizing treatments at the earliest practicable stage of depressive illness and developing effective novel treatment targets. These implications may be confined to subgroups of depressed patients. The pathways toward these possibilities complement recent research strategies to link clinical syndromes more closely to underlying neurobiological substrates. Apart from reducing heterogeneity, this may facilitate a shift toward parity of esteem between physical and mental health. It is clear that although much work is needed, the establishment of the relationship between relevant biomarkers and depressive disorders has substantial implications for reducing the burden of depression at an individual and societal level.

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