

Review Article

An Update on Biomarkers in Psychiatric Disorders - Are we aware, Do we use in our clinical practice?

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ABSTRACT

Psychiatric disorders exert a considerable toll on society in various ways. Approximately 450 million people suffer from such conditions, which places mental disorders among the leading causes of ill-health and disability worldwide. The core definition of a psychiatric disorder is based on subjective symptoms/manifestations and behavioral criteria, which are always assessed clinically. Compared with some non-psychiatric disorders, our understanding of the pathophysiology of most psychiatric disorders is limited. The symptoms of different psychiatric disorders always overlap, and false-positive clinical diagnoses are possible. There are many instances where patients are under- or over- diagnosed because there are no specific tests that can aid in diagnosis. As such, there is a lot

of curiosity to understand if molecular biomarkers can assist in making clearer diagnostic decisions. To label a biomarker for any disorder, it must be substantially detected in patients with the disorder and absent in healthy controls. Above all, it is very ambiguous to rely on such biomarkers especially in Psychiatry as to, even if they are not detected, still the patients must be treated based on the clinical presentation to alleviate their symptoms. To date, several biomarkers have been studied for various psychiatric disorders. However, further research is needed to define a comprehensive set of biomarkers to improve confirmatory diagnosis, early interventions for treatment, and the prognosis for disorders.

Introduction

Biomarker research has seen an extensive success in various medical fields so far. Nonetheless, using biomarkers to diagnose and predict treatment response for psychiatric disorders is a dream. At present, clinical application of biomarkers for psychiatric disorders is still in the very initial stages. Researchers have sought biomarkers of psychiatric illnesses for the past two decades. However, to use a biomarker clinically, it should be validated, feasible, easily reproducible, sensitive, and specific. Apart from diagnosing specific conditions, biomarkers can also be used to predict the clinical course of a disease, identify specific subgroups within the diagnostic syndromes [1]. It is very difficult to label a biomarker to aid in the diagnosis for any psychiatric disorder considering its heterogeneous expression. Coming up with a biomarker to predict treatment response to pharmacotherapy and psychotherapy for any disorder is

clinically more feasible and impactful. Almost all psychiatric disorders have implied underlying neuro-transmitter and neuro-inflammatory pathogenesis. Peripheral inflammation can cause inflammatory cells to cross the Blood-brain barrier eventually leading to brain inflammation and dysfunction. This is due to which some of the plasma inflammatory markers being studied to understand if they can be labeled as biomarkers for certain psychiatric disorders especially schizophrenia and other unspecified psychosis [2]. Research in biological psychiatry is gaining importance lately to understand the psychiatric disorders from their biological roots probably as it can affect the pathogenesis and thus improve clinical manifestations [3].

However, biomarkers in psychiatry cannot be restricted to molecular biology considering the complexity of psychiatric disorders. Recent advances in neuro-imaging have revolutionized the understanding of the bio-clinical substrata of

several psychiatric disorders [4,5]. Coupling molecular biology with neuroimaging and other qualitative brain studies is needed to understand brain dysfunction in light of structure, neuro-hemodynamics, alterations in neuro-transmitters and their connections to various manifestations of psychiatric disorders which might help determine clinically applicable biomarkers.

Methods

A review of the literature was performed from 1990 to 2016 through searches in the electronic databases PubMed, Institute for Scientific Information, Web of Knowledge, and EMBASE, using the following terms: biomarkers, psychiatric disorders, neuro-imaging, protein, genetics, miRNA, proteomics and inflammatory markers. Also, we have cited hand-searched articles, in case many publications could be missed from electronic research.

In this paper, we will review various studies to demonstrate the evidence for not only molecular biomarkers but also various other kinds of biomarkers for different psychiatric disorders. Then we could determine if these biomarkers could be used clinically to increase diagnostic certainty and improve prognosis. Later, we also discussed the clinical trials that are launched to predict the treatment outcomes in psychiatric disorders.

Biomarkers and Psychiatric Disorders

A biomarker is defined as 'a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathologic processes or biological responses to a therapeutic intervention' [6]. A biomarker can be a gene or a group of genes, proteins or other biomolecules [7].

In application, biomarkers technology can be used to understand the prediction, predisposition, diagnosis, progression, regression of disease or monitoring clinical response of an intervention [8]. (Predisposition biomarkers can reflect the causal mechanisms of diseases such as genetic and oxidative stress markers [9]. (McCgory 2014) Diagnostic biomarkers are used to confirm that a patient has a specific disease. For example, measuring α 1 anti-trypsin, Brain-derived neurotrophic factor levels to diagnose major depressive disorder. Phenotyping of (DISC1) gene for diagnosis of schizophrenia.

Prognostic biomarkers help indicate the natural course of a disease as Spermidine, N1-acetyltransferase1 for suicidality. Others may open the field for new therapeutic targets as N-acetylcysteine and omega-3 fatty acids for oxidative stress [10].

Various Biomarkers in Different Psychiatric Diagnosis – Sensitivity, Specificity, and Clinical Implications

Biomarkers for Psychiatry are a slow yet progressing research in recent times. Although the Diagnostic Statistical Manual of Mental Disorders proposes various psychiatric diagnoses based on clinical evaluation, it does not specifically correlate any phenotypic presentation to the underlying mechanism. Hypothetically, a biomarker should make it easier to conclude a psychiatric diagnosis. However, it is also possible

the specific biomarker being referred to is reflecting a subset of symptoms rather than the disorder. Henceforth, in Psychiatry the potential clinical uses for biomarkers are to measure them before intervention and predict drug response in various aspects of assessing prognosis, pharmacotoxicity and efficacy response [1]. A new research frame work has been developed recently, named Research Domain Criteria (RDoC) to help differentiate human behavior into normal and abnormal traits. This might help in diagnosis based on symptoms specific to the individual and come up with precise treatment. The goal is to integrate other medical branches like genetics to behavioral science to come up with more accurate diagnostic criteria and classify the psychiatric disorders [11].

Depression

Inflammatory markers: Depression is one of the most common and prevalent psychiatric illness worldwide. Studies have demonstrated the co-occurrence of depression particularly with atypical inflammatory markers (i.e., CRP, IL-6, TNF- α). However, analysis of the role of these markers is constrained because these markers are often present even before the first onset of depression. HsCRP has been reported as profoundly sensitive and specific in predicting the response to Infliximab in treatment--resistant depression (TRD) and discriminates the differential treatment response to escitalopram versus nortriptyline [12].

Protein: A blood test can determine the Major Depressive Disorder (MDD) score used to diagnose depression. The MDD score consists of nine biomarkers, namely α 1 antitrypsin, brain-derived neurotrophic factor (BDNF), apolipoprotein C3, epidermal growth factor, cortisol, resistin, prolactin, myeloperoxidase, and soluble tumor-necrosis factor α receptor type II [13]. It has also been found that brain-derived growth factors, cytokines, and insulin-derived growth factors not only serve as biomarkers for diagnosing depression, but they are also useful for predicting the response to treatment. Another neurotropic protein, the glial marker SB 100, is also considered a biomarker as it is elevated in patients with mood disorders, particularly in depression [14].

Electrophysiological markers: Depression affects the structural brain in certain regions and alters EEG findings in patients, although preliminary. The differences in the EEG alpha and theta frequency range during rest have been reported consistently, and both these measures have also been differentially associated with treatment outcome [15]. Another study showed decreased delta power values and increased beta activity in frontal brain regions in patients with depression [16]. The interpretation of these measures is unclear. **Other Biomarkers:** A study reported that in patients with depression plasma neopterin, malondialdehyde (MDA), and urinary isoprostranes are elevated. Apart from these, altered DNA methylation is also found in patients with depression. Methylation changes are found to occur in children if the mother is suffering from depression, exposed to smoking during pregnancy, or has a history of trauma. These methylation changes are found to cause a change in serotonin receptor which in turn causes depression in children [17].

Schizophrenia

Schizophrenia is another condition that needs careful assessment because of its complexity.

Inflammatory markers: Immune activation and inflammation are being implicated in the pathogenesis of schizophrenia since the past few decades. The consideration of plasma inflammatory markers to label as a biomarker and diagnose schizophrenia determine clinical prognosis has been proposed since a long time [18]. Evidence supports that pro-inflammatory markers are elevated in patients with schizophrenia compared to healthy controls, although it is preliminary [19].

Protein markers: In patients with suspected schizophrenia, upregulation of the miRNA assists in the diagnosis [20,21]. Another study revealed that a breath test for ammonia and ethylene can be used in patients with schizophrenia as it helps differentiate schizophrenia from other conditions with similar features and can thus be used as a confirmatory test [22]. In one study, samples from patients with schizophrenia and controls were read via multiplexed immunoassay. This 51-plex biomarkers test for schizophrenia had both sensitivity and specificity of 83% [23].

Electrophysiological markers: The symptoms of schizophrenia are due to affecting multiple brain structures thus causing alterations in EEG findings. Again, the EEG findings may vary accordingly to the positive and negative symptoms of the disorder. Evidence reports increased Beta activity in patients with schizophrenia. Increased theta activity is reported in upper temporal gyrus in patients with the positive symptoms [16].

Bipolar disorder: Bipolar disorder is another important psychiatric condition that needs careful evaluation. Recent meta-analyses confirm that Brain Derived Neurotrophic Factor is decreased and Pro-inflammatory markers are increased among adults with Bipolar disorder particularly during acute manic and depressive episodes. As the sample size is less in the study further, large prospective studies are required in future to replicate the preliminary evidence [24]. Another study demonstrated that six proteins expressed in the brain distinguish patients with mood disorder, especially bipolar I, from healthy controls [25]. The researchers concluded that these proteins are potential biomarkers for the diagnosis of bipolar disorder. Recent studies have also focused on understanding the neuroimaging markers for bipolar disorder, based on the activity in different regions of the brain [5].

Attention Deficit-Hyperactivity Disorder (ADHD): ADHD is a crucial diagnosis to be made in Psychiatry considering the treatment with stimulant medication which might have an abusive potential. Lately, few studies have proposed certain biomarkers for ADHD. Children with ADHD have low brain levels of iron which get normalized with stimulant medication [26]. A systemic review and meta-analysis concluded that five markers-- Norepinephrine [NE], monoamine oxidase [MAO], 3-Methoxy-4-hydroxyphenylethylene glycol [MHPG], cortisol, and zinc--are statistically significant and found in support for response to ADHD medications. All of these markers in

serum and urine and their alterations in pathogenesis and after treatment can be a potential biomarker profile for ADHD [27]. A new EEG- based diagnostic test (NEBA: Neuro-psychiatric EEG-based Assessment Aid) is considered a biomarker for diagnosing ADHD more accurately [28].

Post-Traumatic Stress Disorder (PTSD): PTSD is considered extremely difficult to diagnose accurately based on clinical evaluation. Accordingly, the need for biomarkers to diagnose PTSD is great. In PTSD, the startle response may be helpful for diagnosis, and increased startle response as assessed by the cortisol level when considered confirmatory [29]. Additionally, brain natriuretic peptide levels are low in patients who suffer chronically from PTSD [30]. Other studies have reported that increased levels of corticotrophin-releasing hormone (CRH) are found in the CSF of patients with PTSD [31] supporting the attenuation of the HPA axis in patients with PTSD without comorbid depression. Recently, evidence has been found that certain MRI findings are diagnostic for PTSD, particularly a small right-hippocampal volume in patients with PTSD compared to normal subjects [32].

Alzheimer's disease and other dementias

Dementias are the most concerning illness in the elderly. They are the foremost cause of disability in the elderly with the cognitive and behavioral sequel they cause in long-term. Biomarkers in dementias help us differentiate the various underlying pathologies and aid in staging the disease. Clinically for dementias, the major biomarker that is used widely is neuro-imaging, like structural brain imaging and functional imaging [33]. For example, in Alzheimer's disease (AD) complete atrophy of brain on structural MRI is a diagnosing criterion and is sensitive. Likewise, positive β -amyloid PET scan is specific for AD. Also, there are also CSF biomarkers like CSF- β amyloid, tau, and phospho-tau, when elevated are new diagnostic criteria for AD that can be more specific [34]. But unlike neuro-imaging markers, CSF biomarkers are still emerging in the clinical application for all the dementias [35]. Yet so far, no blood or urine biomarkers have been found with evidence for any dementias.

Suicidality: Suicide is a psychiatry emergency and leading cause of death. Currently, studies are going on to predict biomarkers to predict suicidality in patients. Four biomarkers were identified so far differentiating past and future hospitalizations due to suicidal ideations. Spermidine/spermine N1-acetyltransferase 1 (SAT 1) is identified as a primary biomarker in brains of suicide [17]. Few studies concluded few peripheral biomarkers to predict suicidal behavior, although larger prospective studies are needed in the future to replicate the same [36] (Table 1).

Genetic and proteomic biomarkers in psychiatric disorders

Recent genetic techniques have revolutionized the investigations of psychiatric illness. Genotyping of genetic pleomorphism is progressively helping detection of etiologically relevant mutations, disease diagnostics, screening techniques

Table 1: Various studies proposing different biomarkers for different Psychiatric diagnoses.

Name of the Study	Disorders Studied	Biomarkers Studied		Comments/Results
		Name of Biomarkers	Type of Biomarkers	
Young et.al, 2016 [7]	Depression	C-reactive protein, Interleukin-6, Tumor necrosis factor- α .	Inflammatory markers	Co-occurrence of these inflammatory markers with depression. But, the analysis is constrained as these markers are often present even before the first onset of depression.
Bilello et.al, 2015 [8]	Major Depressive Disorder	α 1 anti-trypsin, Brain-derived neurotrophic factor, Epo-lipo-protein C3, Epidermal growth factor, Cortisol, Resistin, Prolactin, Myeloperoxidase, Tumor necrosis factor- α receptor type II	Protein markers	The study concluded these biomarkers not only serve to diagnose depression, but also can predict treatment response.
Yang et.al, 2008 [9]	Mood disorders and Depression	S B100	Protein marker	S B100 is elevated in patients with mood disorders particularly depression.
Olbrich et.al, 2013 [10]	Depression	EEG α and θ	Electrophysiological markers	Differences in EEG α and θ frequency range during rest is reported consistently in patients with depression, and these measures are differentially associated with the treatment outcome as well.
Begic et.al, 2009 [11]	Depression	Variation in δ and β activity of EEG	Electrophysiological markers	Decreased δ power and increased β activity in frontal brain regions in patients with depression. But, the interpretations are not clear
	Schizophrenia	Variation in β and θ activity	Electrophysiological markers	Evidence reports increased β activity in all brain regions and increased θ activity in upper temporal gyrus in patients with positive symptoms.
Shi et.al, 2012 [13]				
Sun et.al, 2015 [14]	Schizophrenia	mRNA	Protein marker	Upregulation of mRNA can assist in diagnosis for patients with schizophrenia.
Popa et.al, 2015 [15]	Schizophrenia	Breath test for ammonia and ethylene	Protein marker	Study revealed this test can be used to differentiate schizophrenia from other conditions with similar clinical features.
Hope et. al, 2015 [17] Al-Hakeim et. al, 2015 [18]	Schizophrenia	Pro-inflammatory markers	Inflammatory markers	Studies concluded that inflammation is implicated in the pathogenesis of schizophrenia and certain pro-inflammatory markers can be labeled as biomarkers to diagnose schizophrenia.
Goldstein et.al, 2013 (19)	Bipolar disorder	Brain-derived neurotrophic factor and pro-inflammatory markers	Protein and Inflammatory markers	Brain derived neurotrophic factor is decreased, and pro-inflammatory markers are increased in acute manic and depressive episodes, but the sample sizes of the studies in the meta-analysis are low.
Frye et.al, 2015 [20]	Bipolar disorder	Growth differentiation factor-15, Hemopexin, Hepsin, Matrix metalloproteinase-7, Retinol binding protein-4, Trans thyretin.	Protein markers	Study demonstrated that six proteins expressed in the brain distinguish patients with mood disorder especially bipolar I vs. healthy controls.

Adisetiyo et.al, 2014 [21]	ADHD	Iron	Other	Study demonstrated low brain levels of iron which get normalized with stimulant medication.
Scassellati et.al, 2012 [22]	ADHD	Norepinephrine, 3-methoxy-4-hydroxyphenyl ethyleneglycol, Monoamine oxidase, Zinc, Cortisol	Other	These biomarkers are found in support of the response to ADHD medications. These markers in serum and urine and their alterations in pathogenesis and after treatment can be a potential biomarker profile for ADHD.
Butler et.al, 1990 [24]	PTSD	Cortisol	Protein marker	Study demonstrated that increased startle response as assessed by cortisol level might be helpful for diagnosis.
Berger et.al, 2010 [25]	PTSD	Brain natriuretic peptide	Protein marker	Brain natriuretic peptide levels are low in patients with chronic PTSD
Baker et.al, 1999 [26]	PTSD	Corticotrophin-releasing hormone	CSF protein marker	Increased levels of the corticotrophin-releasing hormone found in CSF of patients with PTSD supporting the attenuation of HPA axis in pathogenesis.
Douglas et.al, 1995 [27]	PTSD	MRI findings	Neuroimaging marker	MRI findings suggest small right hippocampal volume in patients with PTSD compared to normal subjects is diagnostic.
Risacher et. al, 2013 [28]	Alzheimer's Disease	MRI findings	Neuroimaging marker	Complete atrophy of brain on structural MRI is diagnostic for Alzheimer's disease.
Ahmed et.al, 2014 [29]	Alzheimer's Disease	B-amyloid, tau, and phospho-tau	CSF protein markers	Elevated CSF β -amyloid, tau, and phospho-tau are new diagnostic criteria for Alzheimer's disease that can be more specific.
Kalia et.al, 2015 [12]	Suicidality	Spermidine, N1-acetyltransferase I	Protein marker	These are identified as primary biomarkers in the brains of suicide. Further, larger studies are required to replicate the same.

and prognosis of special forms of disease. For example, SNP genotyping and miRNA techniques. SNP genotyping identifies pathogenic mutations and biomarkers as in schizophrenia. Nearly 70% of known miRNAs- small non-coding RNAs- are expressed in the brain [37]. MiRNAs can be used as predisposition biomarkers as patients with DiGeorge 22q11.2 deletion have a deficiency in DGCR8 (a key miRNA-processing gene) expression, leading to decreased miR biosynthesis, imposing a 30-fold increased risk of schizophrenia [38]. In bipolar disorder, miRNAs are considered as therapeutic target and diagnostic biomarker. miR-134 levels in bipolar patients are inversely proportional to severity of manic symptoms, and their levels increase after treatment [39]. In depression, miR-16 acts as a central regulator of SERT expression. It also mediates of the adaptive response of serotonergic and noradrenergic neurons to fluoxetine treatment [40].

Proteomics is the science that studies every protein and post translational modification produced by a cell type or subcellular structure [41,42]. Proteomic technologies include MS platforms, liquid chromatography (LC), and 2D gel electrophoresis (2DE). They can be used on biofluids including CSF, saliva, serum or

urine which are more easily available. Proteomics can identify etiologic factors, diagnostics and prognostics of psychiatric disorders. For example, 2D-DIGE analysis of brain from subjects suffering from schizophrenia and bipolar disorder implicated cytoskeletal abnormalities. Apo A-1 protein level is decreased in the serum of patients with bipolar disorder. Oxidized proteins forms of fibrinogen γ -chain prec, transferrin, homopexin, α -1-antitrypsin proteins can be identified by 2D-PAGE, MALDI-TOF/MS techniques in plasma of Alzheimer's patients. In patients with major depressive disorder, bipolar disorder or schizophrenia, altered levels of GFAP, albumin, ubiquinol-cytochrome c reductase complex core is found [42] (Table 2).

Imaging biomarkers in psychiatric disorders

National Institute of Mental Health (NIMH) proposed a scheme that might help in developing neuroimaging biomarkers for psychiatric disorders. Neuroimaging methods like Positron Emission Tomography scan (PET scan), Single Positron Emission Tomography scan (SPECT scan), Magnetic ((Resonance Spectroscopy (MRS), Magnetic Resonance Imaging (MRI), Functional)) Magnetic Resonance Imaging (fMRI), and Diffuse

Table 2: Various studies proposing genetic and proteomic biomarkers for different Psychiatric diagnoses.

Name of the Study	Disorders Studied	Biomarkers Studied		Comments/Results
		Name of Biomarkers	Type of Biomarkers	
Roberts RC et. Al, 2008 [43]	Schizophrenia	(DISC1) gene	Genetic marker	DISC1 is associated with multiple cognitive functions that are impaired in schizophrenia. The study provided evidence of implicated mutant DISC1 in the pathophysiology of schizophrenia and other mental illnesses.
Ou ML et.al, 2016 [44]	Schizophrenia	rs1625579 miR-137	Genetic MiRNA marker	The rs1625579 miR-137 genetic variant significantly increases schizophrenia risk.
Mads Engel Hauberg et.al, 2016 [45]	Schizophrenia	miR-9-5p	Genetic MiRNA marker	The study provides evidence for the miR-9-5p in the etiology of schizophrenia.
Wan C. et.al, 2007 [46]	schizophrenia	Abnormal changes of plasma acute phase proteins. Hp alpha1/ Hp alpha2 (Hp 1/2) polymorphism, rs2070937 and rs5473	Proteomic and genetic markers	The results from proteomic and genomic aspects both indicate that acute phase reaction is likely to be an etiological agent in the pathophysiology of schizophrenia, but not just an accompanying symptom.
Jaros JA. et.al, 2012 [47]	Schizophrenia	Protein phosphorylation patterns	Proteomic marker	This study provided evidence that schizophrenia patients feature serum abnormalities in phosphorylation of proteins involved in acute phase response and coagulation pathways.
Sarkar K. et. al, 2011 [48]	ADHD	SNAP25 gene	Genetic marker	The study indicated that rs3746544 'T' allele may have some role in the disease etiology in the studied Indian population.
Pazvantoglu O et. al, 2013 [49]	ADHD	SNAP-25 gene	Genetic marker	The 5-HT2A (rs6311) A allele appears to be a risk factor for ADHD. The SNAP-25 (rs3746544) T allele is associated with a genetic load for ADHD. A combination of the NET1 gene and SNAP-25 gene appears to increase the risk of ADHD.
Herken H et. al, 2014 [50]	ADHD	SNAP-25 Gene Ddel and MnlI Polymorphisms	Genetic marker	The study provided significant association of the MnlI polymorphism in their ADHD sample. The study also revealed that SNAP-25 MnlI polymorphism was also associated with symptom severity of ADHD.
Galvez JM et. al, 2014 [51]	ADHD	SNAP25 gene	Genetic marker	The study found evidence of the association of SNAP25 and ADHD in the Latin American population.
Liu LJ. et.al, 2016 [52]	Depression	PTEN gene	Genetic marker	The study provided evidence that rs701848, rs2735343 and rs112025902 polymorphisms in the PTEN gene may be correlated with the risk of depression and depressive symptoms in the Chinese population.
Cui X. et.al, 2016 [53]	Major depressive disorder	Long non-coding RNAs (lncRNAs)	Genetic marker	Results suggest that the combined expression of six lncRNAs in PBMCs may serve as a potential biomarker for diagnosis and therapy response of MDD in the clinical setting.
Stelzhammer. V. et.al, 2014 [54]	Antidepressant drug-naïve major depression patients.	Angiotensin-converting enzyme, acute phase proteins, brain-derived neurotrophic factor, complement component C4-B, cortisol, cytokines, extracellular newly identified receptor for advanced glycosylation end products-binding protein, growth hormone and superoxide dismutase-1.	Proteomic markers	This study provides evidence of an increased pro-inflammatory and oxidative stress response, followed by a hyperactivation of the HPA-axis in the acute stages of first onset MDD, as well as a dysregulation in growth factor pathways.

Tensor Imaging (DTI) are currently used to find biomarker for mental illness. Research Domain Criteria approach is mainly implemented to find a neuroimaging biomarker [43-54]. When using radioactive tracers, establishing anatomical changes in the brain, detecting the change in blood flow, measuring oxygen level, cognitive functions can be used by neuroimaging techniques to find a biomarker in patients with mental illness. However, before using these imaging modalities, creating a data base and setting up normal criteria should be helpful to differentiate normal population from patients with psychiatric illness. The use of these neuroimaging biomarkers might be limited because of validity as that parameter should be sensitive, specific and easy to implement clinically as a use of these imaging modalities might be available at all health care facilities and may not be affordable by all the patient population [55].

Clinical trials to predict treatment outcomes

It is very unlikely that a single biomarker can be labeled for diagnosing and predicting the outcomes, considering there are different markers for each disorder with varied sensitivity and specificity. It would be better to have a combination of multiple specific biomarkers to improve the predictive outcome [56]. Therefore, National Institute of Mental Health (NIMH) proposed various clinical trials like Establishing Moderators and bio-signatures of Anti-depressant response in clinical care (EMBARC) and The International Study to predict Optimized Treatment for Depression and ADHD (iSPOT D and iSPOT A).

EMBARC is a randomized placebo-controlled trial of sertraline in patients with Major Depressive Disorder (MDD) who are assessed with a comprehensive array of clinical and biological markers for outcome leading to personalized treatment. As part of this clinical trial various moderators like blood moderators, neuro-imaging moderators, clinical moderators and electrophysiological moderators studied thoroughly in congruence. EMBARC helps in identifying qualitative and quantitative markers in specific subsets of the population, which helps towards developing precise medicine. It also provides more insight as how the studies can be done in the future [56].

iSPOT-D: It is a clinical trial where in, multicenter, prospective and randomized longitudinal studies are done in patients with depression. According to Brain resource iSPOT-D trial summary (<http://www.brainresource.com/research/ispot/ispotd>) is over 165 clinical, ((cognitive, functional, structural and genomic brain and body)) markers are being studied to understand if they can predict the treatment response and non-response. This helps to personalize treatment in patients with depression.

iSPOT-A: It is a clinical trial, which consists of cognitive testing in children with ADHD, 6 weeks before starting treatment and who have and don't have responses to methylphenidate medication. This trial of cognitive testing in patients with ADHD has preliminary evidence to be a cost-effective tool for diagnosis. This trial is in very preliminary stage and needs further comprehension for clinical application [57].

Discussion

Determining biomarkers that can be used for diagnosing psychiatric disorders and predicting prognosis following interventions is simultaneously crucial and intricate. As previously mentioned, most psychiatric disorders share symptoms and molecular pathways. Although some biomarkers have been shown to be highly associated with a psychiatric disorder with high sensitivity, the specificity of the biomarkers for the disorder can be controversial. In the past decade, many studies have focused on highlighting the biomarkers for psychiatric disorders, especially PTSD, MDD, bipolar disorders, and schizophrenia. However, no studies have conclusively related a specific biomarker to one disorder. The most important factor confounding the utility of the many potential biomarkers is that they are altered in many psychiatric and neurologic disorders. Some markers are also readily influenced by environmental and lifestyle factors such as diet, stress, activity levels, and substance abuse, and by co-morbidities. Additionally, the confounding effects of psychotropic medications on biomarker findings remain an ongoing issue.

Given the lack of specificity due to an involvement of multiple molecular pathways in the pathogenesis of psychiatric disorders and the very intrinsic essence of these disorders to be multifactorial in etiology and heterogeneous in expression, it is very unrealistic that one biomarker will greatly impact the diagnosis and treatment. In future, more trials should be focused on consolidating a range of biomarkers that might be associated with a psychiatric disorder like EMBARC, iSPOT-A, iSPOT-D. Taking such an approach will likely be beneficial to the field of psychiatry, but large studies are needed to analyze biomarker data in psychiatric disorders to define patient subgroups and test whether these markers predict at-risk patients before the advent of clinical symptoms, as well as predict treatment response in clinically diagnosed patients. If biomarkers suggest an early response to drug treatment, the efficacy of medication can be assessed sooner, and continued use of unsuccessful treatments can be minimized. A further issue is determining whether this approach is practical and economical in clinical practice. To make this determination, plausible differences in diagnosis and treatment response must be first characterized for a manageable set of biomarkers before a more comprehensive set is considered. Also, there should be a protocol for standardization of biomarker use in clinical settings. Integrating a range of biomarkers sensitive and specific for a disorder that are feasible to use in clinical settings will likely provide improved outcomes compared to current clinical diagnosis methods.

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