Chapter 7
The Role of Biomarkers in Psychiatry

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Abstract Psychiatric illnesses are cognitive and behavioral disorders of the brain. At present, psychiatric diagnosis is based on DSM-5 criteria. Even if endophenotype specificity for psychiatric disorders is discussed, it is difficult to study and identify psychiatric biomarkers to support diagnosis, prognosis, or clinical response to treatment. This chapter investigates the innovative biomarkers of psychiatric diseases for diagnosis and personalized treatment, in particular post-genomic data and proteomic analyses.

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P. C. Guest (ed.), *Reviews on Biomarker Studies in Psychiatric and Neurodegenerative Disorders*, Advances in Experimental Medicine and Biology 1118,
https://doi.org/10.1007/978-3-030-05542-4_7

Keywords Proteomics · Biomarker · Post-genomic diagnostics · Psychiatric disease · Epigenetics · Microbiota · Lifestyle · Depressive disorder · Schizophrenia · Bipolar disorder

7.1 Introduction

7.1.1 The Significance of "Biomarker"

One of the most important goals of psychiatry research is to find appropriate biomarkers for mental illnesses [1]. According to the National Institute of Health Biomarkers Definitions Working Group, a "biomarker" is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" [2]. Another definition of biomarker made by the International Program on Chemical Safety is "any substance, structure, or process that can be measured in the body (or its products) and their influence or prediction about the incidence of outcome or disease" [3]. Based on these ideas, a biomarker can be used to identify the presence or progression of a disease or the effectiveness of a given treatment from a clinical viewpoint [4].

The use of biomarkers in medicine is a common and valuable approach in several clinical fields [5], and biomarker analyses are growing in number and providing potential targets for several medical conditions, such as diabetes and cancer. However, clinical applications of biomarkers for neuropsychiatric illnesses and possible use for clinical diagnosis and prognosis have not consistently led to better quantifiable outcomes [6]. In the present chapter, we discuss the innovative biomarkers of psychiatric diseases for diagnosis and personalized treatment, with a focus on post-genomic data and proteomics analyses.

7.1.2 Biomarker Potential Role in Psychiatric Setting

Certainly, finding consistent biomarkers for early discovery of psychiatric illnesses has been an attractive topic for researchers, in particular with the study of the brain (postmortem, neuroimaging, and neurophysiological studies), of cerebrospinal fluid (CSF), and of serum and plasma biomarkers (cytokines, neurotrophins, neurotransmitters, and genes).

The goals of biomarker applications in psychiatry are diagnosis, prognosis (risk), prediction and assessment of responses to treatment (therapeutic failures), prevention of adverse drug reactions, classification within diagnostic categories, and prediction of intervention effects [7, 8]. Biomarkers could also define the staging of psychiatric illnesses, risk vulnerability across stages, syndrome progression, and epiphenomena [9]. Network neuroscience pursues new ways to model, analyze, map, and record the elements and interactions of neurobiological systems,

considering the multi-scale nature of brain networks [10]. In this regard, a primary focus is the neuropsychological construct and the analysis of cognitive functions (attention, working memory, processing speed, learning and memory, executive functions, and global intellectual functions, including social cognition) as endophenotypes for psychiatric illnesses [11, 12]. From recent evidences, social dysfunction and its most evident clinical expression (i.e., social withdrawal) may represent an innovative transdiagnostic domain, with the potential of being an independent entity in terms of biological roots, with the prospect of targeted interventions not only in psychiatric but also in neurodegenerative disorders [13, 14].

Actually, the need to categorize and validate biomarkers has grown to enable clinicians to match specific individual patient treatments to increase the probability of an optimal, personalized outcome. Thanks to genotyping, it could be possible to assess factors that predict antidepressant or antipsychotic drug response [15, 16]. There is a need for characterizing patient variability, for example, to guide pharmacological dosing according to specific phenotypes [17, 18]. The goal of personalized medicine is important in the case of psychiatric diseases to reduce side effects of inappropriate medication or to enable detection of an efficacy signal quickly without potential toxicity [19].

The success of disease-specific biomarkers or endophenotypes is still fragmentary, based on neuroimaging, neuropsychological, biological, biochemical, and genetic aspects. The interest for the psychiatric setting is to go beyond this, to ensure a consistent value of their actual contribution in disease, also through application of post-genomics techniques [20]. One of the most important advances in psychiatry has been the sequencing of human genome in the 1990s [21], but genomic methods cannot differentiate splice variants or proteins with posttranslational modifications (PTMs). Moreover, gene expression is regulated at the posttranscriptional level by microRNAs (miRNAs), small noncoding RNAs. The most important targets of epigenetic regulation in psychiatric processes are synapse development, plasticity, neurogenesis, dendritic extension, and dendritic spine formation [22]. Furthermore, brain imaging, neurotrophic and electrophysiological factors, neurotransmitters, epigenetics, epigenomics, pharmacogenomics, and proteomics are complementary to yield a more complete understanding of the biological basis and appropriate treatments of psychiatric disorders (Figs. 7.1, 7.2, 7.3 and 7.4) [23–27].

7.2 Brain Imaging Biomarkers

Neuroimaging techniques have the power to capture the structure and function of the brain in health and disease. This has revolutionized the study of the organization of the human brain and how its structure and function are changed in psychiatric illnesses. Advances in neuroimaging techniques have made it possible to more clearly elucidate the neural basis of psychiatric disorders. In the past few decades, neuroimaging analyses have served as the main tools for exploring the

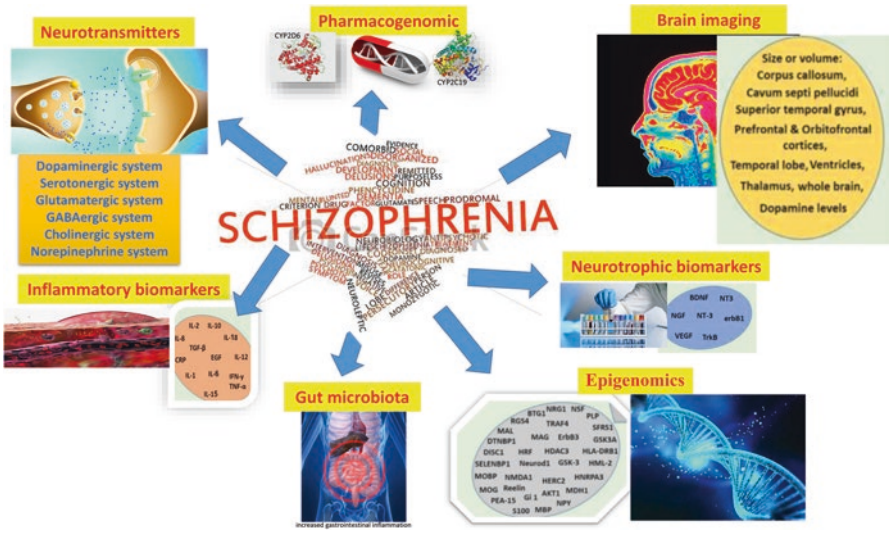

Fig. 7.1 Innovative biomarkers in schizophrenia

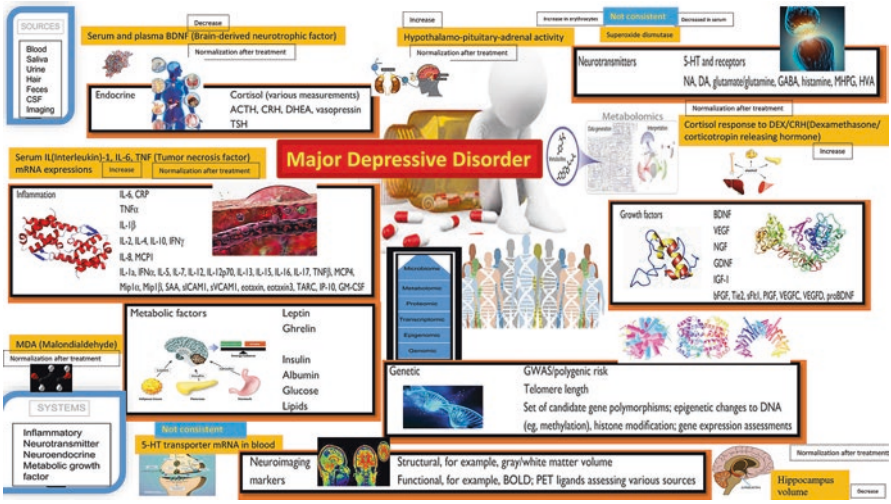

Fig. 7.2 Innovative biomarkers in major depressive disorders

neurobiological etiology of psychiatric disorders [28]. The most important brain imaging techniques are magnetic resonance imaging (MRI), computed tomography (CT), diffusion tensor imaging (DTI), functional magnetic resonance imaging (fMRI), positron-emission tomography (PET), and single photon emission computed tomography (SPECT) [29–33].

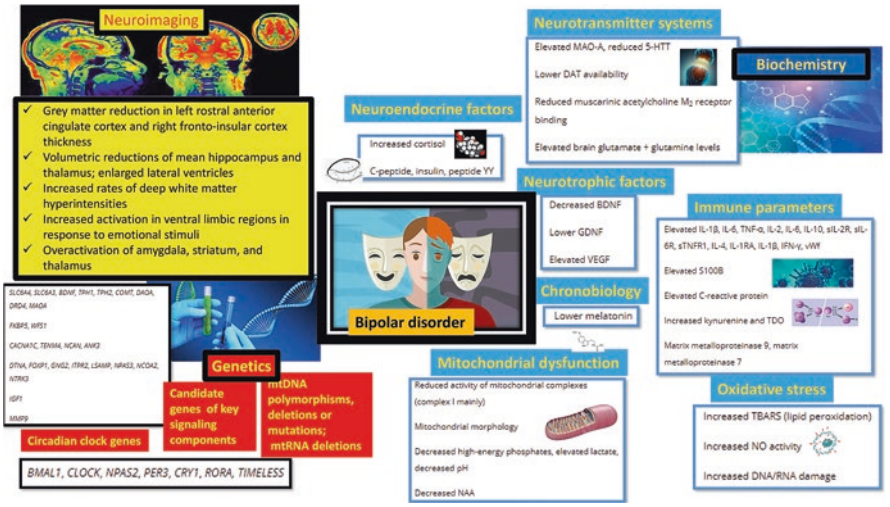

Fig. 7.3 Innovative biomarkers in bipolar disorders

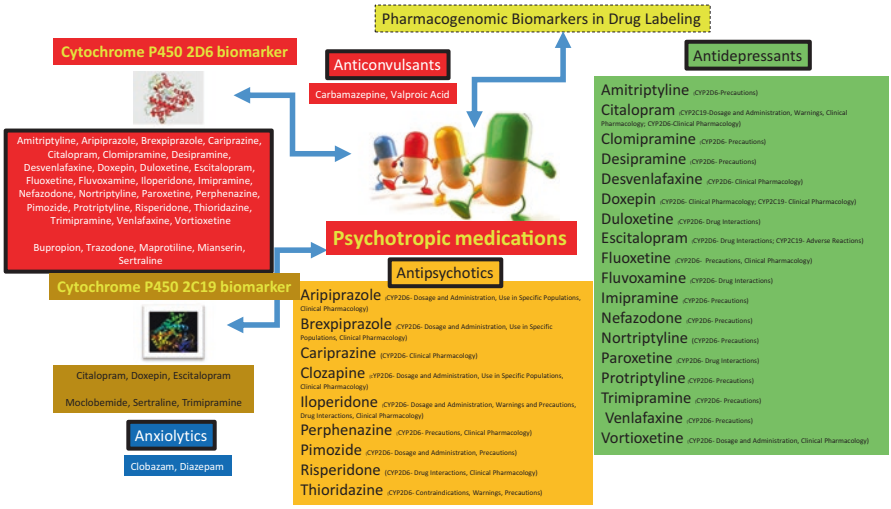

Fig. 7.4 Psychotropic medications: pharmacogenomic biomarkers in drug labeling

7.2.1 Schizophrenia

Patients with schizophrenia (SCZ) have differences in brain structure, brain volume, glucose metabolism, and blood flow at rest and during the performance of cognitive tasks [34] (Fig. 7.1). In SCZ, there are reduced activation in the dorsolateral prefrontal cortex (DLPFC) and the right temporal and ventral prefrontal cortices during the performance of working memory tasks [35] and abnormalities

in the DLPFC, medial temporal lobe, hippocampus, parahippocampal gyrus, anterior cingulate, medial frontal and posterior parietal cortex, striatum, thalamus, and cerebellum [36].

The findings indicate a greater randomization of large-scale brain networks in SCZ relative to healthy controls as well as alterations in the modularity of both static and time-varying networks. Notably, approaches aiming to characterize patients with SCZ relative to healthy controls based on network organization indices (clustering coefficient) show promising levels of classification accuracy [37, 38], suggesting that network neuroscience indices may have future clinical utility as SCZ biomarkers [10]. Recent studies show that small-world brain networks are significantly reduced in SCZ compared to healthy controls across rest and task states [39], and the extent of this reduction may be associated with the length of illness [40]. Hence, SCZ is characterized by differences in the small-world architecture of functional brain organization, marked by a subtle randomization of network topology [41], even in the absence of significant findings for structural networks. Moreover, SCZ patients have significant reductions in connectivity [37, 41]. Large-scale organization features (small-world organization) seem to be less impacted in major depressive disorder (MDD) compared to SCZ. Instead MDD is characterized by disconnectivity across both static and dynamic measures of connectivity, and this is a potential future clinical utility factor [42].

Several brain abnormalities have been reported in SCZ by neuroimaging studies concerning the corpus callosum, thalamus, medial temporal lobe (hippocampal formation, subiculum, and parahippocampal gyrus), superior temporal gyrus (particularly on the left side), frontal lobe (particularly prefrontal and orbitofrontal regions), amygdala-hippocampal complex, cortical size, and size of the whole brain [43–47]. Conversely, there are a higher ventricle-to-brain ratio, greater absolute ventricular volume, and increased size of the cavum septi pellucidi [46].

SCZ patients usually have greater absolute volumes of all ventricular subdivisions, total ventricular volume, and relative volumes of basal ganglia structures (the left and right caudate, putamen, and globus pallidus) as well as reduced cerebral volume, relative volumes of the thalamus, and medial temporal lobe structures including the amygdala, the hippocampus/amygdala ratio, the hippocampus and parahippocampus, and the relative volume of the left anterior superior temporal gyrus [47].

Duration of untreated psychosis (DUP) has been associated with poor outcome in SCZ [48]. Recently, a naturalistic longitudinal study with matched healthy controls highlighted the function of hippocampal volume loss as a biomarker of DUP [49]. This leads to the idea that early hippocampal volume loss may play a role in mediating the association between DUP and poor outcomes in SCZ. Therefore, accelerated hippocampal volume loss could be associated to DUP and poor response in SCZ. Finally, in SCZ, there is also white matter disorganization in prefrontal and temporal white matter, corpus callosum, and uncinate fasciculus [50].

7.2.2 Major Depressive Disorders

Structural imaging works show anatomical and neuropathological abnormalities concerning the disruptions to cortico-striatal-limbic circuits in patients with MDD [51]. MDD patients have reduced metabolism or hypoactivity with "hypofrontality" of the DLPFC, in the left central executive network, along with increased activity in the subcallosal cingulate cortex and limbic regions, such as the amygdala and the insula. The increased inter-functional connectivity between the salience network and right executive network, and the decreased inter-functional connectivity between the anterior default mode network and right central executive network, could be considered as biomarkers of MDD (Fig. 7.2) [52, 53]. Yang et al. suggested a paradigm using a multiple classifier evaluation with external validation by diffusion MRI, to evaluate orientation and diffusion characteristics of white matter and, by inference, white matter microstructure. Although four features (mean fractional anisotropy in the right cuneus and left insula, asymmetry in the volume of the pars triangularis and cerebellum) were implicated across all analyses, low classification and prediction accuracy using these features indicated that they cannot represent the entire pathophysiology of MDD. However, they may be relevant for future investigations of MDD neurobiology in conjunction with other methods [54]. MDD patients show volumetric reductions in the hippocampus, basal ganglia, subcallosal cingulate cortex, and orbitofrontal cortex in patients with more severe or chronic forms of disease [55]. A neuroimaging meta-analysis highlighted reduced volumes of the right hippocampus and reduced gray matter volumes in the left DLPFC as structural imaging predictors of nonresponse to treatment [56].

7.2.3 Bipolar Disorders

The International Society for Bipolar Disorders Biomarkers Network Task Force has described the results of neuroimaging biomarker studies in bipolar disorder (BD) patients as loss of gray matter in cortical-cognitive brain network, as well as increased activation in ventral limbic regions in response to emotional stimuli [24]. Specifically as shown by morphometric measures, BD patients have amplification of the lateral and third ventricles after several manic episodes (Fig. 7.3) [57]; progressive decline in hippocampal, fusiform, and cerebellar gray matter density after frequent episodes; subregion-specific gray matter volume reductions in the prefrontal cortex; and increased rates of deep white matter hyperintensities [58]. BD patients have gray matter reductions in the left rostral anterior cingulate cortex and right fronto-insular cortex thickness, above all in anterior limbic regions (executive control and emotional processing abnormalities) [59], volumetric reductions in hippocampus and thalamus, and enlarged lateral ventricles [60]. Although gray/white matter changes appear early in BD development, the brain volume may be altered by environmental factors such as drugs [61].

Studies of fMRI point out excessive activation in numerous corticolimbic pathways, including overactivation of the amygdala, striatum, and thalamus [24, 62, 63]. Decreased activity in prefrontal cortical areas shown by imaging data underscores an insufficient modulation of limbic/subcortical regions, related to depressed mood and poor cognitive coping in BD [62, 63]. Recently, Li et al. [64] studied cortical thickness and subcortical volume alterations in euthymic BD type I patients treated with lithium and valproate. In particular, patients treated with lithium had increased cortical thickness of the left rostral middle frontal cortex and right superior frontal cortex compared with valproate, while cortical thickness was not different between BD patients on lithium treatment compared to healthy controls in the bilateral rostral middle frontal cortex. Moreover, there were no differences observed in subcortical volume. These data indicate that lithium and valproate have different effects on cortical thinning of the prefrontal cortex in BD but an analogous effect on subcortical volumes [64]. However, neuroimaging could be used as a potential biomarker for lithium response prediction in BD [65, 66]. In MRI studies, patients exposed to lithium treatment showed a bigger volume of gray matter mainly in the hippocampus as a direct consequence of the drug (neurotrophic and neuroprotective influence) or secondary to better symptomatic outcome [67, 68].

7.3 Inflammatory Biomarkers

There is increasing evidence on the involvement of inflammatory pathways in the pathophysiology of major psychiatric disorders including MDD, SCZ, and BD. Elevated levels of cytokines and C-reactive protein and alterations in serum molecules involved in pro-inflammatory and oxidative stress response and immune molecules, including hyperactivation of the hypothalamic-pituitary-adrenal (HPA) axis, have been demonstrated in these major psychiatric illnesses (Figs. 7.1, 7.2 and 7.3) [69, 70]. According to the recent scientific literature, anomalies in the immune system (blood or CSF levels of certain cytokines) are involved in the pathogenesis of SCZ, MDD, and BD and may be useful as biomarkers for diagnosis and treatment monitoring. Studies have also shown increased levels of peripheral pro-inflammatory markers related to the genes involved in regulation of the immune system in both SCZ and MDD [71–75].

In particular, increased levels of C-reactive protein (CRP) [23, 76] and increased levels of IL-1β, IL-6, IL-8, IL-10, IL-12, IL-15, IL18, endogenous IL-1 receptor antagonist (IL-1RA), and soluble IL-2 receptor (sIL-2R) in the blood, CSF, and serum have been found in SCZ patients [69, 77, 78] (Fig. 7.1). It should be noted that the potential of IL-2 has been a matter of controversy as it was found to be elevated in some studies and diminished in others [79, 80]. Other cytokines [tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), and interferon γ] have been shown to be altered in SCZ, while epidermal growth factor (EGF) has been associated with an increased risk of developing SCZ [81].

More generally, according to recent meta-analysis, all patients with severe mental disorders have increased CSF levels of interleukin 1β (IL-1β), IL-6, and IL-8 [82]. Moreover, autoimmune dysregulation has been found to occur in BD II and MDD as underlined by proteomic analysis based on two-dimensional electrophoresis coupled with matrix-assisted laser desorption/ionization time-of-flight/time-of-flight tandem mass spectrometry analysis of plasma samples [83]. An area of particular attention in mental disorders is immunology linked to infections and autoimmune diseases with a larger risk identified for SCZ and affective disorders [84, 85].

The CSF/serum albumin ratio was known to be increased in SCZ, and affective disorders and total CSF protein levels were elevated, indicating increased blood-brain barrier (BBB) permeability [86]. Furthermore, the IgG ratio, IL-6 levels, and IL-8 levels are increased in the CSF of SCZ but not in the case of affective disorders [87–90]. A correlation of the levels of inflammation markers and symptoms has been found and also between albumin and IgG levels and the Scale for the Assessment of Negative Symptoms [91] and between IL-8 levels and the Montgomery-Asberg Depression Rating Scale [92]. Furthermore, altered chemokine levels were found in the CSF and plasma of suicide attempters [93].

A number of studies have found that HPA axis activation in MDD may be linked to the severity of illness. Moreover, MDD patients are at specific risk for cardiovascular syndromes, because of higher levels of inflammatory biomarkers such as the high sensitivity C-reactive protein and pro-inflammatory acute phase cytokines interleukin-1β and interleukin-6. For this reason, cytokines could be considered as biomarkers of depression severity [94]. The heat shock proteins CPN10, CPN60, and CPN70 might have potential as biomarkers for BD, and CPN60 blood level might distinguish patients with abnormal and normal HPA axis activities [95]. Among other biomarkers in BD, increased pro-inflammatory cytokines could be considered markers of mitochondrial dysfunction and oxidative stress (Fig. 7.3) [96].

7.4 Neurotrophic Biomarkers

The etiology of major psychiatric disorders has often been linked to altered intracellular signaling, synaptogenesis, and neuroplasticity. Over the last years, the role of brain-derived neurotrophic factor (BDNF) in cognitive impairments in psychiatric patients has become a focus of interest. BDNF is the most common neurotrophin in the human brain and is involved in the synthesis, differentiation, maintenance, and survival of neurons, both in the central and in the peripheral nervous systems [97]. According to some genomic studies, there is a correlation between the BDNF gene polymorphism (Val66Met) and SCZ as found by whole-blood polymerase chain reaction (PCR) studies [98], and this association was correlated with cognition [99, 100]. Additionally, BDNF Met alleles are associated with age of onset and with phenotype of aggressive behavior in SCZ [25, 101] (Fig. 7.1).

Postmortem studies have shown that the mRNA levels of BDNF and TrkB and BDNF protein levels are decreased in the hippocampus and prefrontal cortex of SCZ and major psychiatric disorders [102, 103]. Also, the levels of other neurotrophins such as nerve growth factor (NGF) and NGF receptor, vascular endothelial growth factor (VEGF), and neurotrophin-3 (NT-3) have been found to be reduced [25, 104–110]. Moreover, serum levels of BDNF can be influenced by pharmacotherapy. Generally, BDNF levels were found to be decreased in treated SCZ [111–115].

Recently, the differential levels of neuregulin-1 (NRG1), its receptor ErbB4, BDNF, DNA methyltransferases 1 (DNMT1), and ten-eleven translocation 1 (TET1) proteins in peripheral blood have exhibited promising efficiency for diagnosis of first episode psychosis [116].

7.5 Neurotransmitters Biomarkers

Considering the classical monoamine hypothesis of MDD, several studies conducted on CSF biomarkers for affective disorders have focused on the levels of 5-hydroxytryptamine (serotonin), dopamine, and noradrenaline and on the respective enzymes monoamine oxidases and catechol-*O*-methyltransferase involved in their degradation to 5-hydroxyindoleacetic acid (5-HIAA), homovanillic acid (HVA), and 3-methoxy-4-hydroxyphenylglycol (MHPG) [117–122]. In addition, peripheral metabolic disturbances have been found in MDD, suggesting that characteristic metabolic alterations associated with the pathogenesis of MDD may generate a detectable molecular phenotype in the blood using metabonomic methods [123]. Previous studies have also shown that perturbations in central and peripheral neurotransmitters are a hallmark of MDD. In particular, MDD patients showed disturbances in several neurotransmitters in the periphery and brain, including dopamine, glutamate, γ-aminobutyric acid (GABA), and serotonin which were thought to be involved in the pathogenesis of the disorder [124]. In this regard, plasma metabolite biomarkers (GABA, dopamine, tyramine, kynurenine) could be used to distinguish MDD subjects from healthy controls and BD patients with high accuracy [123, 124].

7.5.1 Dopaminergic System

The levels of dopamine uptake have been investigated as a potential biomarker in SCZ [125]. In addition, tyrosine hydroxylase (TH), dopamine transporter (DAT) mRNA [126, 127], HVA (a major metabolite of dopamine), and the dopamine D3 receptor (DRD3) mRNAs were found to be increased and DRD4 mRNA levels decreased in SCZ [25, 128]. Also brain functional imaging conducted with SPECT in SCZ patients showed elevated synaptic dopamine levels [129], increased

numbers of postsynaptic dopamine receptors and signal transduction, and striatal amphetamine-induced dopamine release [130]. Regarding dopaminergic metabolites in MDD, a recent meta-analysis concluded that only CSF levels of HVA, and not those of 5-HIAA or MHPG, are reduced in MDD. Therefore, the potential utility of CSF HVA concentrations as a potential biomarker in MDD should be investigated further (Fig. 7.2) [131].

Another area of specific interest for neurotransmitter biomarkers is the association between neuroreceptor density and self-reported personality dimensions, to examine the neurobiology of the underlying behavioral phenotypes. As shown from recent molecular imaging studies, there are significant correlations between dopaminergic markers and specific behavioral traits. In particular, correlations were found between striatal D2R density and detachment, a measure of social avoidance and withdrawal [132–134]. Conversely, psychosis-related traits do not appear to be linked to D2R, but striatal amphetamine-induced dopamine release was found to be related to schizotypal personality traits [135]. Similarly an increase in dopamine release was reported in SCZ patients using the presynaptic marker [18F]DOPA [136].

7.5.2 Serotonergic System

Alterations in the cortical serotonergic system have been reported in SCZ patients [137], such as the findings of decreased levels of the 5-HTT receptors in the frontal cortex [138–140]. Altered levels of 5-HT1A and 5-HT1B and reduced 5HT2A receptors have been reported in prefrontal cortex and hippocampus of BD and MDD patients [141]. In addition, plasma serotonin levels have been found to be decreased, while platelet serotonin levels were found to be higher in SCZ [142].

The study of the biological underpinnings of personality traits with the use of molecular imaging techniques has several advantages for the early stages, evolution, and treatment of psychiatric diseases. In particular, these methods can be used to examine the relationship between serotonin receptor availability, social trust, and status as potential novel biomarkers in psychiatry. Molecular imaging studies of associations between serotonin receptors and transporters with personality traits, such as neuroticism, have not been clear. Although the association between the 5-HT1A receptor and neuroticism was found to have a strong negative correlation, there were no associations with the serotonin transporter [143].

7.5.3 Glutamate and Other Amino Acid Systems

SCZ patients show decreased levels of glutamate, glycine, and D-serine in the CSF and plasma, but increased homocysteine [144–146]. An important focus in SCZ is glutamatergic dysfunction, in particular *N*-methyl-D-aspartate (NMDA) receptor

hypofunction, as this can be informative about several SCZ symptoms linked to excitatory-to-inhibitory imbalance. In this way, administration of the NMDA receptor antagonist ketamine leads to SCZ-like positive, negative, and cognitive symptoms [147].

7.5.4 GABAergic System and Neurosteroids

SCZ patients have been found to display decreased plasma levels of GABA, with downregulation of the GABA-A receptor alpha 5 subunit in prefrontal regions and polymorphisms and haplotypes in the GABA-A receptor β2 subunit gene [148–150]. According to the specific role in modulating the GABA receptor, the deficiency of the biosynthesis of allopregnanolone, a positive allosteric modulator of GABA action at GABA-A receptors, was found in several neuropsychiatric disorders such as MDD, post-traumatic stress disorder (PTSD), epilepsy, postpartum depression, and anorexia nervosa, as well as in premenstrual syndrome and obesity [151–156]. The special focus on neurosteroids, inhibitors of NMDA-mediated tonic neurotransmission [157], was confirmed in women with post-traumatic stress disorder (PTSD) through an association with a block in conversion of progesterone to the GABAergic neurosteroids allopregnanolone and pregnanolone [158]. This is important for potential therapeutics in PTSD considering the role of the endocannabinoid system and associated neurosteroids in this condition [159].

7.5.5 Cholinergic System

A number of studies have demonstrated involvement of the cholinergic system in psychiatric disorders. For example, studies have shown that the nicotinic and muscarinic receptors are reduced in thalamus and frontal regions of SCZ [160–162]. Thus, studies of these systems may also lead to identification of novel biomarkers and drug targets in these diseases.

7.6 Epigenetics

Epigenetics or epigenomics is a modification of the genome expression without changes in the DNA sequence and can result in alterations of gene expression, allowing for differential expression of common genetic information [163]. New techniques such as genomics, epigenomics, transcriptomics, and proteomics guarantee a more global examination of stress-related dysregulation, allowing the discovery of novel biomarkers and targets for new therapies, compared to standard biochemical analyses. Many psychiatric patients have alterations in stress response

and stress reactivity levels, influenced by biological moderating factors such as the HPA axis and early life trauma [164]. Stress hormones (glucocorticoids) and immune mediators (cytokines) provide a connection between the peripheral and central pathways and have exemplified functional biomarkers of stress response, as found in PTSD [165]. The link is further demonstrated by the finding that affective and psychotic patients have elevated cortisol secretion and an enlarged pituitary gland volume, with hyperactivity of the HPA axis [166–168].

Recently, molecular examinations have discovered aberrant microRNA expression in different biological samples from psychiatric patients, including brain tissue, plasma, serum, and peripheral blood mononuclear cells. Such microRNA alterations may be useful biomarkers in studies of MDD, SCZ, or BD [169–171] as certain gene expression patterns are present in subgroups of patients [172–183]. A recent meta-analysis found that the utilization of blood-derived microRNAs, especially those from peripheral blood mononuclear cells isolated from patients, may lead to a useful set of biomarkers for SCZ diagnosis [184]. Also, the candidate gene targets of these microRNAs have been linked to increased risk for developing BD, including pathways such as circadian rhythm, neuronal development, and calcium metabolism [25].

MicroRNAs are ~22-nucleotide-long, noncoding RNA molecules, which are important regulators of posttranscriptional gene expression. They may lead to increased or decreased regulation of the translational stage of mRNA processing or render it stable or unstable [185].

MicroRNA-16 is a posttranscriptional repressor of the serotonin transporter (SERT) and acts as a central regulator of SERT expression. It provides a mechanism for adaptive changes in SERT expression in monoaminergic neurons, which can differentiate into either serotonergic (1C115-HT) or noradrenergic (1C11NE neuroectodermal cell line) neuronal cells [186]. MicroRNA-134 represses the translation of the Limk1 mRNA, a protein kinase that influences dendritic spine development. The miRNA-mediated repression of translation occurs via exogenous stimuli like BDNF, which has emerged as a key mediator for synaptic efficacy, neuronal connectivity, and neuroplasticity [187]. Interestingly, one study showed that microRNA-134 levels in BD were inversely correlated with severity of manic symptoms [187].

Chromosome 8p, which contains at least seven transcribed microRNAs, has been linked to neurodevelopmental disorders such as autism and SCZ. Patients with DiGeorge syndrome and 22q11.2 deletion have a deficiency in DGCR8 microprocessor complex subunit expression, resulting in decreased microRNA biosynthesis and leading to a 30-fold increased risk of SCZ [187, 188]. The functional targets of these microRNAs include a number of genes that have been implicated in SCZ, such as BDNF, the dopamine D1 receptor, the synaptic protein neuregulin-1 (NRG1), and the early growth response gene 3 (EGR3) [188]. Furthermore microRNA-219 has been found to negatively regulate the function of NMDA receptors, serving as an integral component of the NMDA receptor signaling cascade. MicroRNA-219 may directly modulate NMDA receptor signaling by regulating the expression of components in this cascade [188].

7.7 Pharmacogenomic Biomarkers

An important type of pharmacogenomic biomarker individuation in psychotropic drug classification relates to the cytochrome P450 enzyme family [12, 13, 189]. These enzymes play a critical role in drug metabolism and therefore may be important in efficacy- and toxicity-related issues. Interestingly, a majority of the commercially available pharmacogenomic testing resources assay for CYP2D6 and CYP2C19, considering that these enzymes are involved in metabolism of many commercial drugs and variants, exist which could affect their activities with respect to specific drugs. Pharmacogenomics could be useful in determining dosage and administration, warnings, precautions, or other areas listed on the package insert of commercially available drugs. This will be helpful in providing information at the personalized level to minimize adverse events, to provide genotype-specific dosing, and to identify polymorphic drug targets and genes [15, 27, 190] (Fig. 7.2).

7.8 Electrophysiological Biomarkers

The autonomous nervous system (ANS) and its imbalance is important in physiological and pathological disorders [191, 192], including stress. Accordingly, resting heart rate (RHR), heart rate variability (HRV), respiration rate (RR), skin temperature (ST), and skin conductance (SC) are common clinical methods to measure ANS activity, and HRV is the most established parameter to evaluate the sympatho-vagal balance [193–197]. Recent studies show that useful stress indexes may also be obtained from electroencephalogram (EEG)-based features [198].

Psychiatric patients have an ANS imbalance, especially in psychosis [199–201] and depression [202–204]. There are also sympatho-vagal alterations in patients affected by anxiety and phobic anxiety, social anxiety and somatoform disorders [205–207], alcohol dependence [208, 209], and cognitive impairment [210]. Considering intraindividual variability, electrophysiological parameters could be possible biomarkers in psychiatry, even if some parameters (RR, RHR, LF, and HF parameters of HRV) are more robust and stable over time than others (SC, ST, time domain parameters of HRV), and RHR and RR are easy to obtain in everyday clinical practice and can be used as measures of ANS dysregulation [211]. Certainly, two or more different parameters should be evaluated to moderate intraindividual variability [211].

Electrophysiological changes, including the components of sensory gating, mismatch negativity (MMN), and P300 of the evoked potentials are consistently reported to be abnormal in SCZ [212].

7.9 Gut Microbiota

The microbiota is composed of over 100 trillion of commensal bacteria in symbiosis with human body, in the distal gut and fecal metabolites, and can be examined with metabolomic analysis [nuclear magnetic resonance (NMR) spectroscopy] of fecal water [213].

The gut and the brain are strictly connected through bidirectional signaling pathways [214]. Bacteria can produce GABA, tryptophan, 5-HT, and several neurotransmitters and monoamines. Therefore, the gut microbiota could regulate many activities within the brain including hippocampal neurogenesis, myelin-related gene expression in the PFC (an important brain region involved in anxiety and social behavior), CNS serotonergic neurotransmission, and stress and antidepressant treatment response [215–217]. The gut microbiota could also control brain functional pathways through inflammasome signaling and could therefore be useful as both biomarkers and potential drug targets in psychiatry [218]. Moreover, in epigenetic studies of SCZ, the impact of microbiota should also be taken into consideration [219, 220] (Fig. 7.1).

MDD patients have an increase in gut microbiota alpha diversity, in the genera *Eggerthella*, *Holdemania*, *Gelria*, *Turicibacter*, *Paraprevotella*, and *Anaerofilm*, with overrepresentation of *Bacteroidales*, *Oscillibacter*, and *Alistipes*, reductions in *Prevotella* and *Dialister*, and lower numbers of *Bifidobacterium*, *Lachnospiraceae*, and *Lactobacillus* [221–223], with high levels of serum IgM and IgA against lipopolysaccharide of gram-negative gut commensals. This is coherent with the pathophysiology of psychiatric illnesses linked to bacterial translocation, through increased gut permeability [224]. Interestingly, diet and depression are strongly linked through the gut microbiota. Dietary fiber can modify the composition of the intestinal flora and affect brain and behavior [225]. Indeed, higher intake of dietary fiber (fruits and vegetables) leads to a lower prevalence of MDD [226]. Specifically, the Mediterranean diet could be protective, while the Western diet could increase risk of MDD through effects on the microbiota [227]. A probiotic combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 has been shown to have beneficial effects in human resilience to stress [228]. A recent systematic review on the fecal microbiota concluded that Archaeon *Methanobrevibacter smithii* is increased in anorexia nervosa patients [229]. *Methanobrevibacter smithii* may be a benchmark biomarker for future studies.

7.10 Conclusions

Psychiatry is in need of an objective, valid diagnostic classification that transcends the Diagnostic and Statistical Manual (DSM) model of symptom clusters. The US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) [230] has called for the inclusion of biological markers for either diagnosis or

treatment outcomes. However, there have been many criticisms, and, at present, there are no accepted specific biomarkers in psychiatry [230, 231].

A focal point of medicine is the search of biomarkers to aid correct diagnosis, risk prognosis, and prediction of response to treatment. In the case of psychiatric disorders, it is important to have clear criteria for distinguishing pathological behaviors and appropriate methods to categorize these diseases and facilitate earlier intervention for better outcomes. And one of the most important aims in psychiatric medicine is that of personalized treatment for prediction of response and therapeutic or adverse effects at the level of the individual [232]. In summary, we should view with optimism our capabilities to develop biomarkers that will ultimately lead to new interventions and personalized medicines and transform our ability to prevent illness onset and treat complex psychiatric disorders more effectively [232].

Considering the complex interactions among genotype, lifestyle, diet, pharmacological therapy, environmental exposure, and gut microflora, the most ambitious goals could be the discovery of novel pharmacological targets and to rationalize the utilization of known drugs. Finally, this chapter underlines important advices for future studies, to create a link between several types of biomarkers considering that psychiatric disorders are complex diseases. Thus, the use of a single biomarker is not advised, but rather a combination of diverse biomarker types. This could lead to improved treatment of psychiatric patients on a personalized level for the best possible outcomes.

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