Bipolar disorder (BD) is a severe, recurrent mood disorder, associated with a significant morbidity and mortality, with high rates of suicides and medical comorbidities. There is a high risk of mood disorders among the first-degree relatives of patients with BD. In the current clinical practice, the diagnosis of BD is made by history taking, interview and behavioural observations, thereby lacking an objective, biological validation. This approach may result in underdiagnosis, misdiagnosis and eventually poorer outcomes. Due to the heterogeneity of BD, the possibility of developing a single, specific biomarker is still remote; however, there is a set of promising biomarkers which may serve as predictive, prognostic or treatment markers in the future. The review presents a critical appraisal and update on some of the most promising candidates for biomarkers, namely, neuroimaging markers, peripheral biomarkers and genetic markers, including a brief discussion on cognitive endophenotypes as indicative of genetic risk. The lessons learnt from other fields and specialties in medicine need to be applied to psychiatry to translate the knowledge from ‘bench to bedside’ by means of clinically useful biomarkers. Overall, the biomarkers may help in pushing the shift towards personalized medicine for psychiatric patients.

**Key words** Biomarkers - BDNF - bipolar disorder - cognitive endophenotypes - neuroimaging biomarkers

**Introduction**

Bipolar disorder (BD) is a severe, recurrent mood disorder, with episodes of hypomania/mania and depression interspersed with periods of euthymia. BD affects 1-2 per cent of the general population, with prevalence rates reaching as high as 4-5 per cent for the bipolar spectrum disorders\(^1\),\(^2\). Nearly seven per cent of the burden attributable to mental and behavioural disorders [as measured by disability-adjusted life years (DALY)] is contributed by BD\(^3\). It is associated with a significant mortality, with high rates of suicides and medical comorbidities (e.g. cardiovascular diseases). There is a high risk of developing mood disorders among the biological relatives of patients with BD, indicating a strong genetic component\(^1\),\(^2\).

The discovery of biological markers (or biomarkers) in medicine has led to a wide range of applications in various illnesses\(^4\), for example, troponin for myocardial infarction, \(BRCA\) gene for breast cancer, but there is no such biomarker for a psychiatric disorder which can be used routinely in clinical settings. The pathophysiology of BD is complex, poorly understood with possibly several molecular and morphological alterations. In the current clinical practice, the diagnosis of BD is made by history taking, interview and behavioural observations, thereby lacking an objective, biological
validation. This approach may result in underdiagnosis, misdiagnosis and eventually poorer outcomes. Due to the heterogeneity of BD and lack of understanding of pathophysiology, it is difficult to have a single, specific biomarker; however, there are some promising biomarkers which may serve as predictive, prognostic or treatment markers in the future.

Here we present a critical appraisal and selective review of some of the most promising candidates for biomarkers, namely, neuroimaging markers, peripheral biomarkers and genetic markers, including a brief discussion on the role of cognitive endophenotypes, which are indicative of genetic risk.

Potential biomarkers in bipolar disorder: A critical appraisal

Scope and applications of biomarkers

The Biomarkers Definition Working Group has defined a biomarker as ‘a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention’. These may be genes, proteins or other molecules, as well as morphological characteristics, associated with physiological or biological mechanisms.

How can the advent of biomarkers help in the context of psychiatric disorders? There are several clinical applications of biomarkers which may benefit patients and relatives. First, the discovery of disease markers can improve the diagnostic accuracy for BD and can supplement the clinical interviews and observations. The bipolar depression may be initially misconstrued as unipolar depression at times taking many years to receive an accurate diagnosis. Further, the biomarkers may also be state-specific especially for BD where disease may present itself in depressed, manic or mixed states (state marker). Second, these may also be used for staging of the illness, measuring the progression of the disease and/or prognosticate the mood disorder. Being able to predict the outcome at an early stage may guide treatment options. Third, biomarkers may have a role for primary prevention in at-risk individuals, with the emergence of potential ‘trait’ markers to identify the at-risk individuals. Fourth, the biomarkers may also be useful for early identification of illness relapse, perhaps even before clinical symptoms have started, helping in secondary prevention of BD. Fifth, the discovery of biomarkers carries a promise in terms of guiding further novel therapies to act on the potential targets.

Potential neuroimaging biomarkers

Structural neuroimaging: Cumulative evidence over the years has revealed the most common structural abnormalities in patients with BD as follows: (i) higher rates of white matter hyperintensities (WMH) as seen in T2-weighted magnetic resonance (MR) images, and (ii) increased lateral ventricular (and possibly, third ventricular) volume in morphometric studies. Both these findings, however, do not appear to be specific to BD as these are found in unipolar depression, schizophrenia and at times during ageing. In a meta-analytic study, the individuals with BD were 2.5 times as likely to have the WMHs as compared to healthy controls, and this finding was more prominent for children and adolescents with BD (odds ratio: 5.7). The deep WMHs as well as subcortical grey matter hyperintensities have been found to be associated with bipolar individuals. Evidence also indicates the presence of WMHs in the biological family members of patients with BD.

The increased volume of lateral and third ventricles has been found in several studies on patients with BD. In a meta-analysis of 98 studies on structural imaging, BD was associated with lateral ventricle enlargement with an effect size of 0.39. Some studies suggest that the abnormal ventricular volume may not be evident from the onset and found only after several mood episodes have occurred. For example, in a study by Strakowski et al., the lateral ventricles were 122 per cent larger after eight years of disease onset as compared to the time of the first episode. It could be a potential marker of disease progression for BD. Among the individuals with BD, the reductions were reported in whole brain and prefrontal lobe volume in addition to an increased volume of the globus pallidus and lateral ventricles. When compared to schizophrenia, BD appears to have smaller volume of lateral ventricles and enlarged amygdala.

Findings from the more recent structural studies implicate the emotion-processing as well as emotion-regulation neural circuitries. There is a significantly reduced grey and white matter associated with a decreased cortical thickness in certain areas (prefrontal, anterior temporal and insula cortices) among both the BD and at-risk individuals. There is a reduction in the subcortical regional volume, notably in amygdala and hippocampus. Amygdala was found to have a lower volume in a meta-analysis of studies on youth with BD but not necessarily in adults. The use of lithium treatment increases the grey
matter volume of prefrontal cortex\textsuperscript{17}, amygdala\textsuperscript{18} and hippocampus\textsuperscript{18,19}, which appears to be independent of mood states. Now, this increase in grey matter could be a potential marker of clinical response to lithium though it is only a speculation at this stage pending further exploration.

Diffusion tensor imaging studies have found microstructural abnormalities in the myelinated tracts of the prefrontal cortex in BD\textsuperscript{20,21}. Most consistent abnormalities are found in the anterior corpus callosum, anterior cingulum, uncinate fasciculus and superior longitudinal fasciculus. At-risk relatives of individuals with BD also were found to have findings similar to those in individuals with BD\textsuperscript{7,11}. Another study points to a decreased fractional anisotropy of the frontotemporal white matter, which may differentiate BD from the unipolar depressive disorder though it requires further replication\textsuperscript{22}.

Functional neuroimaging: The current neurobiological models for emotional dysregulation suggest the presence of abnormalities within fronto-limbic-subcortical structures in BD. These may be in the form of either an increased ‘bottom-up’ and/or decreased ‘top-down’ regulation of mood\textsuperscript{15,23}. This is supported by a meta-analysis of 13 functional magnetic resonance imaging (fMRI) studies related to emotional processing, which found a decreased activation in a cortical cognitive brain network and increased activation in ventral limbic brain regions among patients with BD\textsuperscript{24}. An interesting finding was that the degree of activation of amygdala observed in fMRI studies response to neutral faces and mildly sad faces might differentiate bipolar depression from the unipolar depression\textsuperscript{25}. Another meta-analysis has found that the abnormal limbic activation in BD is centred on the parahippocampal gyrus (may be extending to amygdala)\textsuperscript{26}. The fMRI studies of high risk individuals (using a working memory N-back task) reported a greater activation of a particular region of the brain (frontal polar cortex, BA10) with increased memory load\textsuperscript{27,28}.

Both common and distinct patterns are evident on comparing BD and major depressive disorder (MDD) to healthy participants as found in a systematic review of 20 fMRI studies using facial affect processing paradigms (168 BD, 189 MDD patients, 344 healthy controls). Decreased ventrolateral prefrontal cortical engagement was found in association with BD, whereas the hypoactivation of the sensorimotor cortices was associated with major depression, needing further exploration\textsuperscript{29}.

Using voxel-based quantitative meta-analytic methods (65 fMRI studies which compared a total of 1074 healthy volunteers and 1040 patients with BD)\textsuperscript{26}, the patients with BD showed an underactivation of the inferior frontal gyrus (IFG) and putamen in addition to an overactivation in the limbic areas, including medial temporal structures and basal ganglia. The IFG abnormalities were seen during processing of cognition and emotion, and increased limbic activation was seen during emotional processing. This has been one of the most consistent findings especially during manic episodes. The abnormalities pertaining to activity in IFG could be a biomarker. Future studies might explore whether this failure to activate IFG is specific to BD and whether it is predictive of treatment response\textsuperscript{7,26,30}. The relatively high cost and limited availability of expertise in fMRI remain a limiting factor. Our group has recently conducted a research on neurocognitive study and use of fMRI in patients having major depression and mania and studied neurocognition and fMRI in both the phases of the illness - mania and depression, and explored the relationship of fMRI findings to clinical parameters as well as neurocognition\textsuperscript{31,32}.

In contrast to fMRI studies, there are relatively less number of studies on positron emission tomography (PET) exploring the BD biomarkers. 18F-fluorodeoxyglucose (FDG)-PET studies of medication-free, BD-depressed patients have found decreased metabolic rates in dorsolateral/medial orbital/sub-genual prefrontal cortex and anterior cingulate when compared to healthy controls\textsuperscript{33-35}.

In the published literature, only very few systematic studies are available which have used proton MR spectroscopy (\textsuperscript{1}H-MRS) in at-risk populations for BD\textsuperscript{36,37}. \textsuperscript{1}H-MRS can detect alterations in the brain biochemistry for several metabolites of interest, including (i) N-acetyl-aspartate (NAA), which is a well-known marker of neuronal viability; (ii) glutamate (Glu); (iii) glutamine, the glial cell reservoir storage form of Glu; and (iv) myoinositol (MI), which is a part of the cellular phosphoinositol cycle second messenger system. The most consistent results across several studies are an increased or normal anterior cingulated cortex (ACC) Glu in bipolar depression in contrast to unipolar where it may be decreased or not different than healthy controls\textsuperscript{38}. The increased Glu levels may, therefore, differentiate between individuals with bipolar and unipolar depression. \textsuperscript{1}H-MRS appears to have the potential to find predictive biomarkers for treatment response. For example, treatment with
mood stabilizers with antidepressant properties has been associated with an increase in NAA levels in BD-currently depressed cases\textsuperscript{17,39}.

To summarize, the functional imaging studies support the proposed models of overactivation of limbic structures coupled with an underactivation of top-down cognitive control in BD. Available research is mostly performed on relatively smaller samples, different activation paradigms, with methodological or analytical heterogeneities, varying patient groups, due to which one cannot expect consistent findings across literature. Ideally, there is a need to plan longitudinal studies with assessments using the same neuroimaging paradigm over the course of multiple time points.

**Emerging themes in neuroimaging research**

Recent studies have begun to focus on the subgroups among BD to understand the findings which are similar and different across various subpopulations of BD and also across various major psychiatric disorders. More research is needed towards these relatively less explored areas\textsuperscript{40}, which need to be emphasized as follows: (i) neuroimaging studies in younger age groups with BD and/or who are at risk for BD; (ii) neuroimaging studies of different BD subtypes (e.g. BD type II, BD-not otherwise specified, psychotic BD, those with suicidal risk); and (iii) neuroimaging studies which compare the BD with psychotic disorders. Some of the emerging themes to gain more insights from the studies of neuroimaging biomarkers have been reviewed by Phillips and Swartz\textsuperscript{15} in more detail and only been briefly discussed here: (i) Integrated systems approach: Multimodal neuroimaging studies aim to dissect out the structure-function relationships in neural circuitries, and simultaneously, these studies have begun to look closely at the relationships between genetic variants and functioning. (ii) Dimensional approaches: Neuroimaging studies have also increasingly begun to take a dimensional approach to BD. For example, a study associated the patterns of function in the reward circuitry with information processing domains that followed the dimensions of BD as an illness and overlooked the diagnostic boundaries\textsuperscript{41}. (iii) Pattern recognition approaches: These involve development of algorithms to automatically learn and to recognize complex patterns from very large datasets\textsuperscript{15}. Although in relatively nascent stages at present, this approach holds a great promise in terms of risk identification and more ‘personalized’ choices.

**Peripheral biomarkers**

Much of the interest in early studies was directed at hypothalamic-pituitary-adrenal (HPA) axis and monoaminergic neurotransmitters and later platelet \textsuperscript{3}H-imipramine binding; however, the specific evidence has remained elusive in spite of some promising initial findings\textsuperscript{8}. In the subsequent years, there has been a rise in the number of studies looking at the peripheral biomarkers in BD\textsuperscript{7,30}. The potential advantages of this approach are its easy accessibility through venepuncture, low-cost and potential for wider availability and amenability to large-scale studies.

Of particular interest are these three areas, namely, (i) cell growth, survival and synaptic plasticity [inclusive of brain-derived neurotrophic factor (BDNF)]; (ii) pro- and anti-inflammatory cytokines; and (iii) markers for oxidative stress and mitochondrial function. Kapczinski et al\textsuperscript{42} proposed a ‘systemic toxicity index’ composed by the above three dimensions and attempted to arrive at ‘toxic indexes’ in patients with BD during various phases of illness in comparison to the healthy controls.

**Brain-derived neurotrophic factor (BDNF)**

One of the most replicated findings in the existing literature is the decreased peripheral levels of BDNF in BD\textsuperscript{43}. BDNF has a high expression in the brain areas involved in the regulation of cognition and emotion. A systematic review and meta-analysis (of 52 studies with 6481 patients with BD compared to controls) found that the peripheral BDNF levels were reduced both in the manic as well as depressive episodes and were comparable to controls during euthymia. Further, the severity of manic and depressive symptoms correlated negatively with the BDNF levels\textsuperscript{44}. There is evidence which supports that the peripheral BDNF may be inversely related to the age of patient and length of illness\textsuperscript{45}. Peripheral BDNF has been proposed as a staging biomarker which may give an idea about the neuroprogressive nature of BD. Those with long-standing BD (10 or more years in duration) have significantly decreased serum BDNF levels when compared to earlier stages (i.e. less than 3 years after disease onset)\textsuperscript{46}. The serum BDNF could differentiate the late from early stages with 100 per cent sensitivity and 89 per cent specificity and an overall accuracy of 0.95\textsuperscript{47}. However, it is to be noted that a significant limitation of this study was a significantly higher Hamilton depression scores in the patients in later stage.
Serum BDNF may also be of some assistance in differentiating between bipolar and unipolar depression accurately. Laboratory cut-off at 0.26 pg/ml may distinguish bipolar from unipolar depression with 88 per cent diagnostic accuracy. There was only a moderate discriminatory accuracy for mania. The change in the peripheral BDNF levels may precede the onset of mood symptoms, may concur along with the clinical symptoms or perhaps even change after the onset of an episode. In any of the scenarios, still, it could be of assistance by acting either as a predictive marker, marker of disease activity, or as a surrogate marker.

Another potential use of serum BDNF is as a predictor of treatment response. For example, it was found that the patients on lithium showing an excellent response had significantly high plasma BDNF compared to the non-responders. Till date, though in most of the BDNF research serum has been used, the plasma represents a different compartment altogether and may be more reflective of real-time changes in the central nervous compared to serum BDNF. Future studies on biomarkers may explore BDNF levels in plasma or a comparison of both serum and plasma.

In the Indian context, our group has evaluated the serum BDNF levels in a longitudinal manner (one-year, naturalistic follow up study) across various mood states and attempted to see its relationship to cognitive functions over time. To be able to respond to several unanswered questions, such longitudinal studies with frequent blood draws would be necessary to assess the relationship of BDNF with mood states.

To summarize, as per the available evidence, the peripheral BDNF might be a biomarker possibly for disease activity and may be associated with disease progression.

**Inflammatory markers**

Studies have shown consistently abnormalities in the peripheral inflammatory markers among patients with BD though it is not clear if the levels of these inflammatory markers are secondary to a change in mood state or are more inherent to the disease process itself. In a meta-analysis of case–control studies (761 cases and 919 healthy controls), patients with BD had a higher concentration of soluble interleukin (IL)-2 receptor (sIL-2R), sIL-6R, tumour necrosis factor-alpha (TNF-α), soluble TNF receptor-1 and IL-4. Of these cytokines, TNF-α has shown the most robust evidence base. Many of the studies did not consider the variations in the mood state as a possible factor to consider, frequently clubbing the patients together. The peripheral levels of pro-inflammatory cytokines were increased in the depressive and to a greater degree in the manic states. Proteomic analysis also supports the role of inflammation in BD. The study on lithium-treated BD patients has indicated lithium’s involvement in modulating inflammatory responses.

The mechanism of action of cytokines is not yet fully understood. Some of these have been found to disrupt the neurotransmitters (e.g. norepinephrine and dopamine signalling). Longitudinal studies shall help understand the precise role of inflammation in BD. The role of any underlying/co-occurring medical causes for inflammation is another tricky issue to deal with in studying the sample.

**Oxidative stress markers**

The evolving evidence has shown that mitochondrial dysfunction and oxidative stress may be influencing the pathophysiology of BD. The dysfunction of the mitochondrial electron transport chain has been consistently reported in BD and is associated with increased levels of reactive oxygen species (ROS) production. It is conceptualized that whenever there is more production of ROS at a level which overwhelms the antioxidant system, a state known as ‘oxidative stress’ may occur. There may be oxidative damage to macromolecules (proteins, lipids, DNA, etc.) as indicated by studies of post-mortem brain samples and peripheral blood cells.

A meta-analysis by Brown et al. included a total of 27 studies (with 971 patients of BD and 886 controls) exploring several markers for oxidative stress. Findings supported three of these markers, namely, lipid peroxidation, DNA/RNA damage and nitric oxide (NO). Notably, there was a high effect size for lipid peroxidation. The thiobarbituric acid reactive substances (TBARSs) are basically a pointer to lipid peroxidation. Both TBARS and NO were found to be increased in all phases of BD, with a large effect size and a moderate effect size for NO. It is possible that the mood stabilizers might produce the treatment effect through their action on oxidative stress pathways though it requires further study.

Together, it appears that the oxidative damage may be associated with certain alterations in brain which may impact the BD. Larger studies with repeated observations are needed to establish whether these have enough potential for translation to clinical application in future.
Genetic biomarkers

In genetic studies on patients with BD, a consistent association has been seen with BDNF, catechol-O-methyltransferase, and serotonin transporter (5-HTT) genes, however, the issue is that of specificity since these are also found in other psychiatric disorders\(^7\)\(^,\)\(^3\)\(^0\). The genome-wide association studies (GWASs) can compare the allele frequencies between cases and controls for thousands of single nucleotide polymorphisms; however, they require very large cohorts of individuals for statistical significance and to be interpreted meaningfully. Using these GWASs and whole-genome sequencing in BD, as found in meta-analysis, the calcium voltage-gated channel alpha 1C subunit (\(CACNA1C\)) and ankyrin 3 (\(ANK3\)) polymorphisms have the strongest evidence\(^6\)\(^4\)\(^,\)\(^6\)\(^5\). Moreover, \(CACNA1C\) has been found to cause disturbances in hippocampal, pregenual ACC and dorsolateral prefrontal cortex (DLPFC) functioning\(^3\)\(^0\). Through a meta-analysis, Nurnberger et al\(^6\)\(^6\) reported that there is a difference in gene expression levels in the DLPFC of patients with BD. These included \(CACNA1C\), \(DTNA\), \(ITPR2\), \(GNG2\), \(FOXP1\), \(LSAMP\), \(NCOA2\), \(NPAS3\) and \(NTRK3\).

The untreated manic patients presented downregulation of the micro RNA (miRNA) expression levels, which play a role in inflammation and gene expression\(^6\)\(^7\). These findings shed light on the pathophysiological aspects of BD and may open new avenues for treatment and to stop the illness progression. Studies that have used a combination of genetic and brain imaging are useful as these can pinpoint the neural pathways mediating the genetic risk\(^6\)\(^8\). For example, the presence of \(CACNA1C\) rs1006737 risk allele (G to A) has been shown to be related to distinct structural and functional neuroimaging findings.

Relatively, less research is available for the identification and role of genetic markers in paediatric BD in spite of possibly higher role of genetics in terms of an earlier onset\(^6\)\(^9\). In an Indian study which had BD-type I patients (\(n=311\)), schizophrenia patients (\(n=293\)) and age- and sex-matched normal controls (\(n=346\)), Per3 genotyping was done which revealed a five-repeat allele of Per3 as a possible risk factor\(^7\)\(^0\).

In summary, there is a need to further explore two potential biomarkers, particularly comprising \(CACNA1C\) and \(ANK3\) identified with use of GWAS. Imaging studies are now being employed to find out their functional correlates.

Endophenotypes as biomarkers for genetic risk and prevention

Important subtypes of biomarkers are the endophenotypes. Compared to other biomarkers, these have been defined in a restrictive manner. As outlined by Gottesman and Gould\(^1\), an endophenotype must (i) segregate with illness in the general population, (ii) be heritable, (iii) be state-independent, (iv) cosegregate with the disorder within families, (v) be present at a higher rate within affected families than in the general population, (vi) be measured reliably and be specific to the illness of interest. When these six criteria are met, the endophenotype is assumed to mark genetic risk of illness irrespective of the phenotypic expression of illness. As is evident from this definition, the ‘state-dependent’ biomarkers cannot qualify as endophenotype.

The endophenotypes may be explored further in the context of prevention of BD, as by definition, these can identify the high-risk individuals. The biomarkers have been identified for many disorders in various researches in psychiatry, but very few endophenotypes have been discovered. The continued search for endophenotypes is important for the discovery of aetiological mechanisms and heritable trait markers in BD.

Cognitive deficits in bipolar disorder (BD): A potential endophenotype?

The euthymic BD patients have certain demonstrable subtle, selective impairments rather than a global impairment\(^7\)\(^2\). In the available evidence base, the robust findings have been associated with impaired psychomotor processing, sustained attention, verbal learning and memory, response inhibition and set-shifting. For these deficits in euthymic patients, medium to large effect sizes were reported in meta-analyses\(^7\)\(^3\)\(^,\)\(^7\)\(^4\). For the first-degree relatives of BD, the effect sizes for response inhibition were medium while effect sizes were small for the rest of cognitive deficits, though significant compared to healthy individuals. Their presence in unaffected at-risk family members indicates that these measures may be quantitative endophenotypes for the disorder\(^7\)\(^3\)\(^,\)\(^7\)\(^4\). Furthermore, the cognitive functions are highly heritable.

The cognitive deficits, particularly in the executive functioning and verbal memory, merit a consideration as possible endophenotype of BD (though specificity of findings to mood disorders remains an issue)\(^7\)\(^2\)\(^-\)\(^7\)\(^5\).
It has been seen that the cognitive functioning in BD is inversely related to illness progression as indicated by the number of mood episodes, illness duration, hospitalizations, etc. Several Indian studies have evaluated the cognitive impairment in euthymic BD and/or at-risk first-degree relatives, and their findings have mostly supported their role as potential trait marker for BD. Future research should carefully try to differentiate the confounding factors, for example, medication, subthreshold symptoms, which have been the major limitations of studies so far. Longitudinal studies to know the long-term course and stability of cognitive deficits would be beneficial.

Most importantly, rather than carrying out isolated research, it would be more prudent to start integrating and linking the pattern of findings from cognitive studies in BD to those in other aspects such as neuroimaging and genetics.

Future directions

To make a translation from ‘bench to bedside’, a biomarker should be accurate, replicable, with adequate sensitivity and specificity and has patient acceptability. The clinically useful biomarkers for BD are still possibly not a reality as of now; however, the past decade has witnessed research which could culminate into discovery of biomarkers fulfilling the above criteria in the coming future.

To detect the biomarkers for progression of BD, longitudinal studies are needed over a period of time across various mood states. By assessing whether biomarkers of BD can help differentiate it from other major psychiatric illnesses would be clinically relevant. Further, it appears that a given biomarker may not be specific to BD; how to reconcile that information to the current psychiatric nosology is another question. There is a great dependence in current research on diagnostic category, however, historically; the psychiatric diagnosis and its sub-categories have kept on changing, still being in the process of evolution, thereby posing a problem for biomarker research. There is a need to include the candidate biomarkers into large cohorts and other trials to examine their clinical utility. Further, it is also important to find out how these markers are related to each other, for example, genetic markers in relation to structural and peripheral alterations in BD. Technological advancements in the various fields of medicine can also aid in the development of biomarkers for psychiatric disorders. There is a need to work in collaboration with other specialties, to benefit from the expertise and technical breakthroughs with potential applications for psychiatry.

As far as studies on inflammatory markers and BDNF are concerned, future studies need to have consistency for several methodological aspects to improve homogeneity and comparability. These include bigger samples, multiple points of assessments, in addition to incorporation of important covariates such as age, gender, stressors, and metabolic aspects.

There is a need for replication of current genetic findings in large, well-characterized samples, across various cultures and geographical areas, to determine their robustness and generalizability. To explore how the biological variation can influence the clinical phenotype, there is a need to plan phenotype–genotype studies across the entire mood–psychosis spectrum. Newer methodologies in genetic research can be expected to complement the existing approaches to facilitate progress. Emerging trends in genetics research include convergent functional genomic approach, polygenic exploration of BD, and transcriptomic approaches, which may reveal some new biological insights into BD.

Conclusion

Although the review emphasized the complexities associated with biomarkers for BD, yet it also discussed the possible ways and approaches to detect the disease activity, progression and perhaps guide the novel therapies on the target approaches. Some of the candidate biomarkers which have been discussed may not eventually turn out to clinically applicable, these may still, in the process of being tested and researched further, shed some light on the pathophysiological mechanisms and biological underpinnings of BD. The lessons learnt from other specialties and sub-specialties in medicine need to be applied to psychiatry in an effort to translate the knowledge from ‘bench to bedside’ by means of clinically useful biomarkers.

Conflicts of Interest: None.

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Reprint requests: Dr Rajesh Sagar, Department of Psychiatry, All India Institute of Medical Sciences, New Delhi 110 029, India e-mail: rsagar29@gmail.com