


The Neuropharmacogenomical Perspectives of Bipolar Disorders

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ABSTRACT

Bipolar disorder (BD), also known as manic-depressive illness, is a brain disorder causing unusual shifts in mood, energy, activity levels, and the ability to carry out daily tasks, caused by multifactorial and enigmatic etiologies. The main objective of this overview is to review recent findings and critically evaluate BD based on neurogenomics and pharmacogenomics perspectives, through searching appropriate online database sources and relevant bibliographies. Recent studies and references explain genome-wide significant loci for bipolar disorder (polygenetics), potential biomarkers (apoptosis and neurotrophic factors, immuno-inflammatory factors, neurotrophins, BDNF, IGF-1, VEGF, etc.), dysregulation of immuno-inflammatory mechanisms, the role of neuroplasticity in the pathophysiology and treatment of BD, genetic effect of lithium response in BD. Stem cells, omics technologies, and optogenetics is considered to be effective strategies to overcome BD.

Keywords: Biomarkers, bipolar disorder (BD), neurogenomics, neuropharmacogenomics, neuroplasticity, optogenetics, pharmacogenomics.

ABSTRAK

Bipolar disorder (BD), dikenal pula sebagai *manic-depressive illness*, adalah gangguan otak dengan etiologi enigmatik dan multifaktorial yang menyebabkan perubahan *mood*, energi, tingkat aktivitas, serta kemampuan untuk melakukan tugas sehari-hari. *Review* ini menelusuri penemuan-penelitian terkini dan mengevaluasi BD secara kritis berdasarkan perspektif *neurogenomics* dan *pharmacogenomics*, melalui pencarian database *online* dan bibliografi yang relevan. Pelbagai riset-referensi termutakhir menjelaskan *genome-wide significant loci* (poligenetik), *biomarker* potensial (faktor apoptosis dan neurotrofik, faktor imun-inflamasi, neurotrofin, BDNF, IGF-1, VEGF, dll), disregulasi mekanisme imunoinflamatori, peran neuroplastisitas, efek genetik respon lithium pada BD. Teknologi sel punca, teknologi berbasis *–omics*, dan *optogenetics* yang mengungkap aspek-aspek neurofarmakogenomik berdasarkan riset berkesinambungan dipertimbangkan menjadi strategi efektif untuk mengatasi BD. **Dito Anurogo. Perspektif Neurofarmakogenomik Kelainan Bipolar.**

Kata kunci: Biomarkers, bipolar disorder (BD), neurogenomics, neuropharmacogenomics, neuroplasticity, optogenetics, pharmacogenomics.

INTRODUCTION

Bipolar Disorder (BD) is a complex neuropsychiatric disorder affecting 1-4% of the population worldwide, with a lifetime prevalence of 2.8 to 6.5% and a genetic diversity (heritability) of 59-93%. It is characterized by a cycle of recurrent depressive episodes, manic-hypomanic episodes, and interspersed with intervals of remission.1,2,3 Lithium (Li) is the mainstay in BD management. Even so, only about 30% BD patients indicate a good response in long-term cohort studies.4 Multifactorial causes and uncertainty in research findings have made BD unable to be resolved until now.

OBJECTIVE AND METHODS

The main objective of this scientific review was to find out various researches and new approaches in the management of BD, based on neurogenomics and pharmacogenomics perspectives. Literature for this overview was identified by searching database sources (PubMed, Medline, PsycINFO, Web of Knowledge Content, Medscape, etc.), Cochrane Libraries, and recent bibliographies.

Pharmacogenomics Perspective

Pharmacogenomic approach focuses on identifying genetic predictors of treatment response to Li and mood stabilizers. Candidate-gene approaches have so far focused on genes codifying for elements of biological pathways shown to be target of lithium, such as proteins of the intracellular second messenger cascade mediated by inositol, Wnt and neurotrophins pathways and the GSK-3β protein.5,6

Li response in BD can be determined using GRANITE (Genetic Regulatory Analysis of Networks Investigational Tool Environment), a genomic tool that provides visualization of complex data sets and produces interactive networks. By measuring a large data set of mRNAs and miRNAs, the tools finds that the Let-7 miRNA family is consistently and preferentially downregulated by Li in the BD responder group. The dynamic networks created by GRANITE will lead to a more effective and reliable tool for clinical use in predicting BD patients' response to medications.[7]

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Neurogenomics Perspective

Neurogenomics is the study of the genes of the nervous system. In a broad scope, neurogenomics is defined as the study of how the genome serves as a whole, which contributes to the evolution, development, structure, and function of the nervous system. Neurogenomics has applications in basic research, in pharmaceutical industry and in the management of neurological disorders.8

Brain abnormalities found in BD patients include enlargement of the lateral ventricles and abnormal white substance, particularly in prefrontal cortex. Structural imaging studies have also found volume deficits in the hippocampus in child and adolescent BD patients and larger volumes of amygdala in adults. N-acetylaspartate level as a marker of neuronal integrity decreased in the dorsolateral prefrontal cortex, anterior cingulate, and hippocampus in BD patients.[9,10]

Preliminary studies of PET (positron emission tomography) reported a reduction in 5-hydroxytryptamine (5-HT1A) receptor binding potential in raphe and hippocampus-amygdala in the depressives, especially in bipolar depressives and unipolar depressives with bipolar relatives. One of the factors that contribute to the reduction of 5-HT1A receptor binding in depression is the increased cortisol secretion, since the expression of postsynaptic 5-HT1A receptor mRNA is under tonic inhibition by corticosteroid receptor stimulation in several brain regions.[11]

Recent GWAS (genome-wide association studies) on BD populations have identified a number of genes with strong statistical association to susceptibility to BD. One of them is ankyrin 3 (ANK3), a gene that encodes multiple isoforms of ankyrin G protein, and alpha 1C subunit of L-type voltage-gated calcium channel (CACNA1C). XBP1 genes also play a role in the pathogenesis of BD.[12-14] GWAS have identified new genome-wide significant risk loci in the chromosome 4 gene (NDST3). The examination of SNP, rs11098403, showed a consistent effect regardless of diagnosis (schizophrenia or BD).[15,16] To determine the genome-wide significant loci, then please refer to **table**.[17]

Table. The genome-wide significant loci in BD.16

Locus	Implicated Gene(s) and Symbol(s)
Genome-wide significant in bipolar disorder	
10q21.2	Ankyrin 3 (ANK3)
12p13.3	Calcium channel, voltage-dependent, L-type, alpha 1C subunit (CACNA1C)
11q14.1	Teneurin transmembrane protein 4 (TENM4, formerly known as ODZ4)
19p12	Neurocan (NCAN)
6q25.2	Spectrin repeat containing, nuclear envelope 1 (SYNE1)
3p22.2	Tetratricopeptide repeat and ankyrin repeat containing 1 (TRANK1)
5p15.31	Adenylate cyclase 2 (ADCY2)
6q16.1	MicroRNA 2113 (MIR2113); POU class 3 homeobox 2 (POU3F2; formerly known as OTF 7)
10q24.33	Arsenite methyltransferase (AS3MT)
Genome-wide significant in bipolar disorder + schizophrenia (combined)	
2q32.1	Zinc finger protein 804A (ZNF804A)
3p21.1	Inter-alpha-trypsin inhibitor heavy chain 3 (ITIH3); Inter-alpha-trypsin inhibitor heavy chain 4 (ITIH4);
16p11.2	Mitogen-activated protein kinase 3 (MAPK3)
Genome-wide significant in bipolar disorder + unipolar depression (combined)	
3p21	Polybromo 1 (PBRM1)

Calcium Signaling Abnormalities

Ca^+ channel signaling genes have a role in BD. Ca^+ channel controls the movement of calcium between cells. There are certain genetic changes that increase the flow of Ca leading to the brain, thus producing excitement.[18] Calcium ions serve an important role in regulating the synthesis and the release of neurotransmitters, neuronal excitability, and long-term neuroplasticity. Numerous studies have successfully demonstrated the presence of intracellular Ca^{2+} in peripheral cells of BD patients.[19]

Inflammatory Hypothesis

Numerous studies have confirmed dysregulation of immuno-inflammatory mechanism in BD. Autoimmune thyroiditis was often found to be associated with BD.[20] The role of praecox stressors has been postulated to explain the dysfunction of brain prefrontal-subcortical region in BD.[21] Neurodevelopmental model of BD has revealed that immune system changes due to multifactorial causes, such as decreased vitamin D, hypoferremia and iron deficiency, contribute to brain development abnormalities.[22]

The relationship between M2 receptor, inflammation, and cognition can lead to an understanding that a change in inflammatory pathways may cause cognitive deficits associated with BD.[23]

Biomarker Panel

In BD patients, biomarker panel is found to be unique and distinctive such as the presence of endothelial inflammation. In the first year of BD, the oxidant status rises. In patients with chronic BD, the potentiated antioxidant system also increases.24

Abnormalities in neurotrophins and other trophic factors have important implications in the etiology of BD. The role of neurotrophins is important to be understood as the basis for the development of new therapies.[25,26] Recent studies also reveal that the involvement of brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), vascular endothelial growth factor (VEGF), etc. shows typical patterns in various different stages of BD. In the manic episode of BD, the serum levels of fibroblast growth factor-2 (FGF-2), NGF and IGF-1 are found to be increased, while in the mixed episode of BD, the plasma levels of BDNF are found to be decreased. BDNF serum potentially serves as a BD biomarker. BDNF-encoding genes are located on the short arm of chromosome 11 in the region where some BD linkage studies have found evidence of gene susceptibility. This clearly indicates the potential of various biomarkers for identifying BD subgroups and developing effective management.[27-30]

Inositol hexaphosphate (IP6, inositol hexakisphosphate, phytic acid) is a naturally-occuring derivative of phosphorylated myo-inositol. Myo-inositol has been proven to be able to control mood symptoms and have a good tolerability for BD. The efficacy and tolerability of IP6 as adjunctive lithium therapy is being studied.[31,32]

The Roles of Cytokines

The dysregulation of cytokines also serves as one of the neurodegenerative aspects, especially in patients with long-term BD.[33] BD is closely related to genetic polymorphisms of cytokines.[34] Cytokine level varies according to clinical symptoms. The presence of elevated level of interleukin 6 (IL-6) is a result of the activation of monocytes. Interestingly, the IL-6 alleles have different distributions among


adults with BD, control, and offspring (with and without mood disorders).[35] IL-1, one of cytokines, and its receptors are an example of immunological marker whose levels significantly increase in BD. IL-1 is found in postmortem frontal cortex.[36] Cytokines can act as a mediator between immune abnormalities and central nervous system development.[37] In fact, cytokines play a significant role in all stages of neurodevelopment process. Cytokines managed to become a "bridge" between altered immune system, neurotransmission dysfunction, and impaired neurodevelopment. All these aspects contribute to the onset of BD.[38]

The levels of monocytes and monocyte chemoattractant protein 1 (MCP-1) are also increased. MCP-1 is a cytokine that plays a role in innate immunity process, also known as CCL2. The increased level of serum CCL2 supports the hypothesis of Th1 hyperactivation.[49] In manic phase, the level of CCL11 rises. Moreover, the level of cortisol in patients with bipolar depression is found to be elevated. Decrease in PUFA (polyunsaturated fatty acids) in brain membranes is a result of hyperactivation of arachidonic acid cascade. The level of plasma cortisol decreases in mania.[39,40]

Neuroplasticity

The manifestation of neuroplasticity in mature central nervous system is characterized by changes in the function of dendrites, synaptic remodeling, long-term potentiation (LTP), axonal sprouting, neurite extension, synaptogenesis and neurogenesis.[41,42] The sustainability of neuroplasticity is determined by multifactorial causes. Protein Kinase C (PKC) plays an important role in the regulation of synaptic plasticity and various forms of learning and memory. GSK-3 plays an important role in regulating neuroplasticity and cellular resilience. The effects of Lithium and VPA on GSK-3 have an important role in the regulation of various processes, such as synaptic plasticity, cell survival in the mature central nervous system (mature CNS). BDNF serves as a mediator of various neuroplastic changes during mood episode.

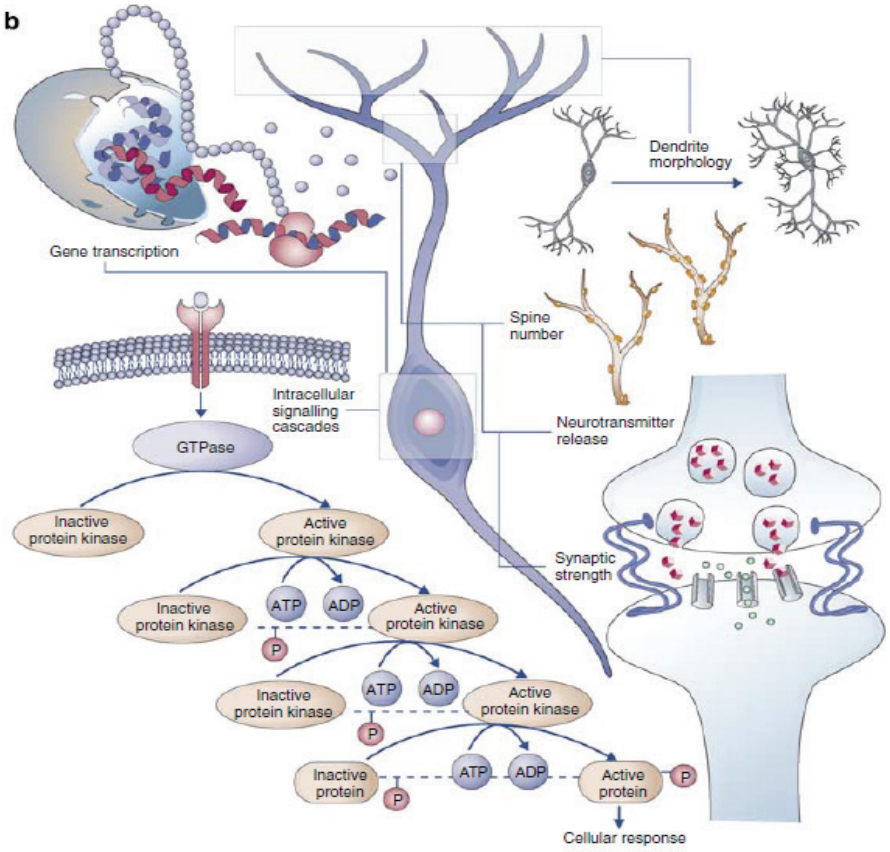

Figure. Biological mechanisms underlying neuroplasticity.45

Glia function abnormalities are clearly proven to impair the structural plasticity and overall pathophysiology of mood disorders. Abnormalities in the regulation of signal transduction cascades and neuroplasticity may underlie the pathophysiology of BD. It is clear that all these processes are involved in the pathophysiology and management of BD.[43-45]

Stem Cells

Along with the technological advancement, iPSC (induced pluripotent stem cells) studies are introduced to address various problems of BD. iPSCs and cell-derived neuronal-related studies are useful in understanding the actions of drugs and pathophysiology of BD.[46]

In the future, approaches based on gene therapy, stem cells, omics technologies, optogenetics[47,48] to analyze and reveal various aspects of BD are predicted to generate effective strategies in dealing with BD.[47-49]

SUMMARY

Bipolar Disorder (BD), also known as manic-depressive illness, is a complex neuropsychiatric disorder affecting 1-4% of the population worldwide, with a lifetime prevalence of 2.8 to 6.5% and 59-93% genetic diversity (heritability). Recent researches on neuropharmacogenomical perspectives of bipolar disorders has been discussed. The future and continuing studies to conquer bipolar disorders should be done based on comprehensive and multidisciplinary paradigm.

ACKNOWLEDGEMENT:

1. Adjunct Prof. Dr. Taruna Ikrar, M.D., M.Pharm.,Ph.D. from Department of Anatomy and Neurobiology, University of California, Irvine, USA and Brain Circulation Institute of Indonesia (BCII), Surya University, Indonesia for helpful and critical proof-reading and revising this manuscript.
2. Vicente Rey-Valenzuela, Ph.D., plant pathologist at Cenibanano – Augura, Colombia for supporting me with relevant references.

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