Neurosci. Bull. August, 2019, 35(4):608–612
https://doi.org/10.1007/s12264-019-00389-2

www.neurosci.cn
www.springer.com/12264

INSIGHT

Perspective on Etiology and Treatment of Bipolar Disorders in China: Clinical Implications and Future Directions

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Received: 6 September 2018 / Accepted: 16 February 2019 / Published online: 16 May 2019

Bipolar disorder (BD) is a chronic, recurrent, disabling disease, even when given currently-available pharmacological and psychological treatments. Currently, the etiology and pathogenesis of BD remain unclear. As a consequence, patients with BD are frequently unrecognized, misdiagnosed, and inappropriately treated, which often yields a low treatment response and poor outcome. In the last decade or so, researchers in the fields of neuroscience and clinical psychiatry in China have worked together to explore the clinical phenomenology, etiology and pathogenesis of BD, and to investigate strategies for the treatment and management of BD. These efforts have not only moved researches in BD forward, but also have changed the practice of treating BD in China.

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Etiology and Pathogenesis of BD

The available evidence supports the idea that the etiology of BD is multifactorial, including genetic loading, gene-gene, and gene-environment interactions [1]. The pathogenesis has been hypothesized as dysfunctions of neurons and circuitry, neurotransmitters, signal transmission, neuroendocrine regulation, immune pathways, and biological rhythms (Fig. 1) [1]. Current effective pharmacological treatments also support the multifactorial hypothesis of BD. Lithium is the gold-standard treatment for BD, but most of the medications approved for the treatment of BD are antipsychotics. The neuronal basis and pharmacological mechanisms of lithium and antipsychotics are quite different, suggesting that multiple neurotransmitters and pathways are involved in the pathogenesis.

Neurotransmitter Dysfunction

The involvement of the monoaminergic system in BD has been explored mostly with genetic association studies in China and the findings are consistent with the results from other researchers worldwide. A study team from Taiwan region stratified their study participants according to temperament (harm-avoidance *vs* no harm-avoidance), gender (men *vs* women), bipolar subtype (BD-I *vs* BD-II), and comorbidities (alcoholism *vs* no alcoholism or anxiety disorder *vs* no anxiety disorder). The team found that harm avoidance, BD-II, male gender, and comorbid alcoholism or anxiety disorder were associated with specific-genes. These genes included the serotonin transporter-linked polymorphic region gene, the dopamine D2 receptor gene (DRD2), and the monoamine oxidase-A gene [2–4].

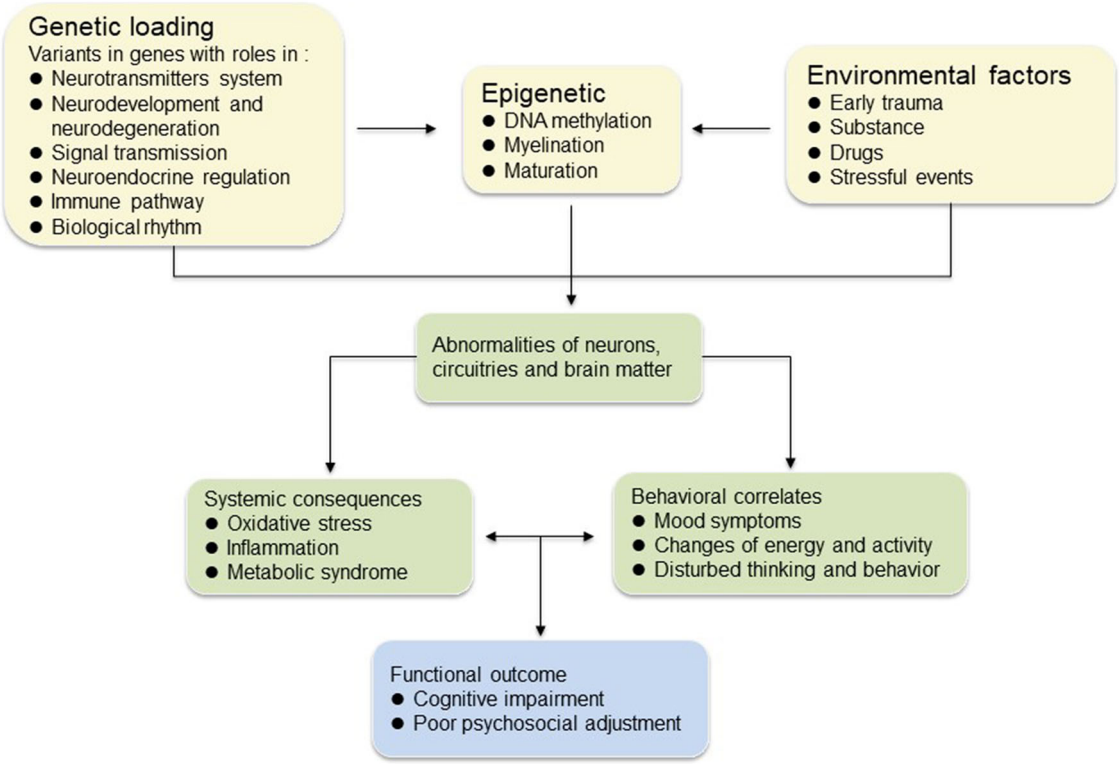

Fig. 1 Multifactorial model of etiology and pathogenesis for bipolar disorders.

Currently, there is increasing evidence supporting the hypothesis that an imbalance between glutamic acid and γ-aminobutyric acid (GABA) affects the occurrence of BD. The glutamate ionotropic receptor N-methyl D-aspartate receptor subtype 2B gene has been reported to be significantly associated with BD. Recently, Chung *et al.* explored whether or not the glutamic acid dehydrogenase 1 (GAD1) gene, the rate-limiting enzyme for synthesizing GABA, was associated with BD, and found a weak effect of the GAD1 gene on the susceptibility to BD [5].

Neurodevelopment Hypothesis

The available data across different populations support the proposal that both neurodevelopmental and neurodegenerative factors are involved in the etiology and pathogenesis of BD [1]. Researchers in China have also explored the possible role of these factors in BD, and found several risk genes associated with BD. These genes are related to brain-derived neurotrophic factor (BDNF) and its receptor neurotrophic tyrosine kinase receptor type 2 (NTRK2), and neuregulin 1, all of which are associated with neurodevelopment.

The association between BDNF (especially the Val66-Met variant) and the risk for BD is the most widely replicated, but the overall results are still inconclusive. A systematic meta-analysis showed that the Val66Met polymorphism was significantly associated with BD in Europeans but not in Asians [6]. Wang *et al.* first found that polymorphisms of BDNF and NTRK2 likely play essential but different roles in the treatment response to mood stabilizers for BD-I and BD-II patients [7, 8]. The inconsistent results of the association between BDNF pathways and the risk for BD might be due to multiple gene-to-gene, and gene-to-environment interactions, and differences among the populations studied and BD subtypes.

Intracellular Signal Transmission Dysfunction

Dysfunction of the signal transmission pathways, *i.e.* intracellular G-protein activity and Ca^{2+}-level abnormalities, has attracted increased attention to the etiology and pharmacology of BD. First, the regulator of G-protein signaling-4 gene has been reported to be a potential susceptibility gene in the Han Chinese population. Second, the associations of BD susceptibility with genetic variants encoding subunits of the Ca^{2+} voltage-gated channels CACNA1C and CACNB2, neurogranin encoding postsynaptic protein kinase substrate, cAMP responsive element binding protein 1, and ankyrin 3 (a protein-coding gene) have also been replicated in the Han Chinese population

[9–11]. Glycogen synthase kinase 3 (GSK3) is a central component of many signal transmission pathways and has been identified as one of the major candidate targets for the treatment of BD. One mechanism of action of lithium was believed to be inhibiting GSK3β, indicating that GSK3β may be as a new target for BD treatment.

Neuro-Immuno-Endocrine Network and Biological Rhythms

Available evidences have supported that disturbance of the neuro-immuno-endocrine networks was related to the etiology and pathogenesis of BD. Findings of dysfunctions of the hypothalamus-pituitary-adrenal and hypothalamus-pituitary-thyroid axes in BD patients have been replicated in the Han Chinese population. It is well known that the change in 24-h cortisol levels is one of the important indications of normal circadian rhythms. Lai *et al.* were the first to find a correlation between genes regulating the circadian rhythms (NR1D1, RORA, and RORB) and the susceptibility to BD in a Chinese population [12]. In addition, the involvement of some inflammatory markers in the pathophysiology and treatment of BD has also been replicated in the Han Chinese population, but further investigations are still needed for routine clinical practice.

Diagnostic Biomarkers for Identifying BD

Because of the heterogeneity of etiological mechanisms and clinical phenomena, it is necessary to find specific biomarkers for identifying BD subtypes and discriminating them from major depressive disorder (MDD). From this point of view, Li *et al.* followed up patients after the first episode of depression for three years, and found that a combination of the BDNF mRNA expression with its plasma concentration at baseline was the best model for predicting the occurrence of mania/hypomania during three years [13]. They also investigated the role of mature BDNF (mBDNF) and its precursor (proBDNF) in distinguishing BD from MDD during an acute depressive episode. The ratio of mBDNF to proBDNF (M/P) during a depressive episode may be saved as a potential differential diagnostic biomarker for patients with BD [14].

Researchers worldwide have also used neuroimaging technology to identify BD subtypes and to study differences between MDD and BD patients. In China, Fung *et al.* found that BD patients had significantly larger cortical surface areas and subcortical regions than MDD patients. Using these differences to discriminate BD from MDD had a sensitivity of 62.5% and a specificity of 84.2% [15]. Yang *et al.* found significant increases in regional homogeneity (ReHo) in the right medial superior frontal cortex, left inferior parietal cortex, and middle/inferior temporal cortex, and significant decreases in ReHo in the left postcentral cortex and cerebellum in MDD patients with hypomanic symptoms compared to those without hypomanic symptoms. The receiver operating characteristic curve showed good sensitivity and specificity for distinguishing these two subgroups of patients with MDD [16].

Treatment and Management of BD

The evidence-based data on the treatment and management of BD from China are scarce. Most of the data used in the Chinese guidelines for BD were from developed countries and the majority was supported by pharmaceutical companies [17]. There is no systematic study assessing the safety and tolerability of these medications in bipolar patients in China, although a few studies have been carried out in Chinese patients with acute mania or bipolar depression. As a result, the off-label use of psychotropics for the treatment of BD patients in China is the rule rather than the exception. In addition, patients with BD are often inappropriately treated in clinical practice. The National Bipolar Mania Pathway Survey in mainland China found that the rate of guideline-discordant treatments in patients with acute mania was 11.1%, 50.2% for bipolar depression, and 35.6% for remitted BD [18].

The first two double-blind, randomized, controlled studies (DB-RCTs) of BD in China were designed to assess the efficacy and tolerability of quetiapine and olanzapine in Chinese patients with acute bipolar mania. Since then, several studies have been published on the acute treatment of mania, including atypical antipsychotic monotherapy or adjunct therapy with a mood stabilizer. There are fewer studies of bipolar depression than that of mania. The first study of acute bipolar depression in China was part of an international multiple-center study of olanzapine *vs* placebo, although the majority of patients were from China [19]. A DB-RCT of the efficacy and safety of quetiapine extended-release (XR) monotherapy *vs* placebo in the acute treatment of bipolar depression was the first study of bipolar depression in Chinese patients designed and conducted solely by Chinese researchers [20]. To date, there have been no high-quality DB-RCTs investigating the efficacy and safety of any pharmacological maintenance treatment in Chinese BD patients. Thus, it is an urgent unmet need for Chinese researchers to explore the polarity indexes of the drugs used for the maintenance treatment of Chinese patients with BD.

Conclusions and Future Perspectives

Due to the lack of specific markers for diagnosing of BD, an early and accurate diagnosis will continue to be a challenge for clinicians. Before objective diagnostic measures become available, clinical skills to uncover manic/hypomanic symptoms are essential. These skills include how to ask questions about mania/hypomania and how to form a trustful relationship with patients who are commonly reluctant to share manic/hypomanic experiences because they may fear to be labeled as "bipolar." These skills can be developed through systematic training in different settings.

For Chinese bipolar researchers, more studies are needed on the clinical presentations of manic/hypomanic symptoms, comorbidity, and other clinical factors in both patients with MDD and those with BD. These phenomenological data may not only help to differentiate BD from MDD, but also to more accurately define the subtypes of BD. The subtype data on BD and clinical differences between MDD and BD are critical to finding biomarker(s) for the diagnosis and treatment of BD, regardless of the methodology and technology used.

For the treatment of BD in China, randomized efficacy and effectiveness trials should be conducted to determine the efficacy and safety of the medications commonly used for BD to provide evidence-based data for Chinese patients. Collaboration of researchers with pharmaceutical companies, basic science researchers, and psychologists should be carried out to develop new pharmacological and psychological treatments for BD. One example of new drug development is melatonin, which has been shown to have an antidepressant-like effect on an animal model [21]. Similarly, neuropsychological assessment and treatment research [22] and non-pharmacological treatments such as psychotherapy also deserve further studies in Chinese patients with BD. The successful completion of single-center and multi-center studies in the treatment of BD indicates that Chinese bipolar researchers can conduct high-quality clinical trials on BD.

One obstacle to developing new treatments for BD is a lack of animal models. Scientific advances have provided researchers with tools such as genetics, genomics, proteomics, and neuroimaging for directly understanding the etiology, pathogenesis, clinical presentations, and treatment responses in patients with BD. However, lack of replications from studies using these advanced technologies has hindered their application in clinical practice.

Two important factors for the replication of a study are homogeneity of the study sample and the study sample size. Since BD, like other psychiatric disorders, is a polygenetic and multifactorial disease, focusing on one or a few single-nucleotide polymorphisms, genes, or proteins is very unlikely to provide clinically-relevant information. Therefore, like international researchers, Chinese researchers must form networks to use the same standardized diagnostic tool(s) and procedures to collect biomaterials for large genetic, genomic, and proteomic studies, and to conduct large neuroimaging and traditional clinical trials. Undoubtedly, Chinese researchers have made progress in the diagnosis, treatment, etiology, and pathogenesis of BD. We are still far from evidence-based and personalized treatments for Chinese patients with BD. Implementation of the above-proposed strategies will narrow the gap between developed countries and China in the diagnosis and treatment of BD.

Acknowledgements This insight article was supported by the National Key Research and Development Program of China (2016YFC1307100 and 2016YFC1307105), the Shanghai Key Medicine Specialties Program (ZK2015A06), Projects of International Cooperation and Exchanges National Natural Science Foundation of China (81761128032), and the Sanming Project of Medicine in Shenzhen, China (SZSM201612006).

Conflict of interest The authors claim that there are no conflicts of interest.

References

1. Vieta E, Berk M, Schulze TG, Carvalho AF, Suppes T, Calabrese JR, *et al*. Bipolar disorders. Nat Rev Dis Primers 2018, 4: 18008.
2. Lu YA, Lee SY, Chen SL, Chen SH, Chu CH, Tzeng NS, *et al.* Gene-temperament interactions might distinguish between bipolar I and bipolar II disorders: a cross-sectional survey of Han Chinese in Taiwan. J Clin Psychiatry 2012, 73: 339–345.
3. Wang TY, Lee SY, Chen SL, Chang YH, Chen SH, Huang SY, *et al.* Gender-specific association of the SLC6A4 and DRD2 gene variants in bipolar disorder. Int J Neuropsychopharmacol 2014, 17: 211–222.
4. Hu MC, Lee SY, Wang TY, Chang YH, Chen SL, Chen SH, *et al.* Interaction of DRD2TaqI, COMT, and ALDH2 genes associated with bipolar II disorder comorbid with anxiety disorders in Han Chinese in Taiwan. Metab Brain Dis 2015, 30: 755–765.
5. Chung YE, Chen SC, Chuang LC, Shih WL, Chiu YH, Lu ML, *et al.* Evaluation of the interaction between genetic variants of GAD1 and miRNA in bipolar disorders. J Affect Disord 2017, 223: 1–7.
6. Li M, Chang H, Xiao X. BDNF Val66Met polymorphism and bipolar disorder in European populations: A risk association in case-control, family-based and GWAS studies. Neurosci Biobehav Rev 2016, 68: 218–233.
7. Wang Z, Li Z, Chen J, Huang J, Yuan C, Hong W, *et al.* Association of BDNF gene polymorphism with bipolar disorders in Han Chinese population. Genes Brain Behav 2012, 11: 524–528.
8. Wang Z, Fan J, Gao K, Li Z, Yi Z, Wang L, *et al.* Neurotrophic tyrosine kinase receptor type 2 (NTRK2) gene associated with treatment response to mood stabilizers in patients with bipolar I disorder. J Mol Neurosci 2013, 50: 305–310.
9. Jan WC, Yang SY, Chuang LC, Lu RB, Lu MK, Sun HS, *et al.* Exploring the associations between genetic variants in genes

encoding for subunits of calcium channel and subtypes of bipolar disorder. J Affect Disord 2014, 157: 80–86.
10. Li M, Luo XJ, Rietschel M, Lewis CM, Mattheisen M, Müller-Myhsok B, *et al*. Allelic differences between Europeans and Chinese for CREB1 SNPs and their implications in gene expression regulation, hippocampal structure and function, and bipolar disorder susceptibility. Mol Psychiatry 2014, 19: 452–461.
11. Wen Z, Chen J, Khan RA, Wang M, Song Z, Li Z, *et al*. Polymorphisms in NRGN are associated with schizophrenia, major depressive disorder and bipolar disorder in the Han Chinese population. J Affect Disord 2016, 194: 180–187.
12. Lai YC, Kao CF, Lu ML, Chen HC, Chen PY, Chen CH, *et al*. Investigation of associations between NR1D1, RORA and RORB genes and bipolar disorder. PLoS One 2015, 10: e0121245.
13. Li Z, Zhang C, Fan J, Yuan C, Huang J, Chen J, *et al*. Brain-derived neurotrophic factor levels and bipolar disorder in patients in their first depressive episode: 3-year prospective longitudinal study. Br J Psychiatry 2014, 205: 29–35.
14. Zhao G, Zhang C, Chen J, Su Y, Zhou R, Wang F, *et al*. Ratio of mBDNF to proBDNF for Differential Diagnosis of Major Depressive Disorder and Bipolar Depression. Mol Neurobiol 2017, 54: 5573–5582.
15. Fung G, Deng Y, Zhao Q, Li Z, Qu M, Li K, *et al*. Distinguishing bipolar and major depressive disorders by brain structural morphometry: a pilot study. BMC Psychiatry 2015, 15: 298.
16. Yang H, Li L, Peng H, Liu T, Young AH, Angst J, *et al*. Alterations in regional homogeneity of resting-state brain activity in patients with major depressive disorder screening positive on the 32-item hypomania checklist (HCL-32). J Affect Disord 2016, 203: 69–76.
17. Wang Z, Chen J, Yang H, Ma Y, Meron D, Liu T, *et al*. Assessment and management of bipolar disorder: Principal summary of updated Chinese guidelines. Bipolar Disord 2018, 20: 289–292.
18. Wang Z, Chen J, Zhang C, Gao K, Hong W, Xing M, *et al*. Guidelines concordance of maintenance treatment in euthymic patients with bipolar disorder: Data from the national bipolar mania pathway survey (BIPAS) in mainland China. J Affect Disord 2015, 182: 101–105.
19. Wang G, Cheng Y, Wang JN, Wu SH, Xue HB. Efficacy and safety of olanzapine for treatment of patients with bipolar depression: Chinese subpopulation analysis of a double-blind, randomized, placebo-controlled study. Neuropsychiatr Dis Treat 2016, 12: 2077–2087.
20. Li H, Gu N, Zhang H, Wang G, Tan Q, Yang F, et al. Efficacy and safety of quetiapine extended release monotherapy in bipolar depression: a multi-center, randomized, double-blind, placebo-controlled trial. Psychopharmacology (Berl) 2016, 233: 1289–1297.
21. Li K, Shen S, Ji YT, Li XY, Zhang LS, Wang XD. Melatonin augments the effects of fluoxetine on depression-Like behavior and hippocampal BDNF-TrkB signaling. Neurosci Bull 2018, 34: 303–311.
22. Liang S, Vega R, Kong X, Deng W, Wang Q, Ma X, et al. Neurocognitive graphs of first-episode schizophrenia and major depression based on cognitive features. Neurosci Bull 2018, 34: 312–320.