A Comprehensive Review on the Role of Non-coding RNAs in the Pathophysiology of Bipolar Disorder

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Abstract: Aim: Bipolar disorder is a multifactorial disorder being linked with dysregulation of several genes. Among the recently acknowledged factors in the pathophysiology of bipolar disorder are non-coding RNAs (ncRNAs). Methods: We searched PubMed and Google Scholar databases to find studies that assessed the expression profile of miRNAs, IncRNAs and circRNAs in bipolar disorder. Results: Dysregulated ncRNAs in bipolar patients have been enriched in several neuron-related pathways such as GABAergic and glutamatergic synapses, morphine addiction pathway and redox modulation. Conclusion: Altered expression of these transcripts in bipolar disorder provides clues for identification of the pathogenesis of this disorder and design of targeted therapies for the treatment of patients.

Keywords: bipolar disorder; circRNA; miRNA; lncRNA

1. Introduction

Bipolar disorder (BD) is a multifactorial disorder characterized by the occurrence of severe mood impairment episodes, neuropsychological complications, immunological alterations, and perturbation in personal/social functions [1]. As one of the main sources of disability all over the world [2], BD is associated with premature death from the co-existence of other medical conditions as well as suicide attempts [3,4]. Several genetic and environmental parameters have been recognized to modulate the risk of BD, yet most of them being liked with a number of other mental disorders as well. The causal link between a few of these risk factors and BD has been established [5]. Among the recently acknowledged factors in the pathophysiology of BD are non-coding RNAs (ncRNAs) [6]. These transcripts participate in the epigenetic marking of several genes through modulating chromatin configuration and RNA editing. Their binding with complementary sequences in the genome might alter methylation or RNA sites. Moreover, long ncRNAs (lncRNAs) are implicated in the complicated regulatory systems that control the expression of target sequences.
genes [7]. Transcript profiling in autopsy samples of medial frontal gyrus from bipolar patients and non-psychiatric controls have shown differential expression of ten lncRNA transcripts and a global higher number of alternative spliced variants in these patients [6]. Other types of ncRNAs such as microRNAs (miRNAs) and circular RNAs (circRNAs) have also been dysregulated in brain tissues or peripheral blood of patients with BD [6,8]. We performed a comprehensive search in PubMed and Google Scholar databases to find studies that assessed expression profile of miRNAs, lncRNAs and circRNAs in BD. This study is study is a narrative review and studies have been selected and discussed based on preference/choices from the authors. We included studies that reported dysregulation of ncRNAs between BD patients and normal controls. We also included data regarding the expression profile of targets of ncRNAs whenever this data was provided in the original articles.

2. CircRNAs and BD

CircRNAs have a circular secondary structure. This structure is formed by the rear-splicing of a single-stranded linear RNA and the creation of a covalent link. These procedures lead to the formation of an encircled non-polyadenylated RNA structure. Compared with linear RNAs, circRNAs have higher stability resulting from a lack of accessible ends for exoribonucleases. They are about 0.1–10% of linear transcripts in eukaryotes [9]. CircRNAs participate in brain development and integrity of neurons [10,11]. A number of studies have demonstrated the release of brain-specific circRNAs into the peripheral blood in the course of neurological disease, potentiating these transcripts as biomarkers for showing disease progression or response to therapies [9]. Few studies have assessed the expression of circRNAs in brain samples of patients with BD obtained through autopsy. Luykx et al. have shown up-regulation of two circRNAs in brain tissues of bipolar patients. These transcripts were originated from the NEBL and EPHA3 loci, respectively [6]. The latter locus is involved in the development of CNS. Eph receptors of the protein-tyrosine kinase family participate in the production of neurotransmitters, construction of dendritic spines, and synaptic and postsynaptic events [12]. Moreover, they contribute to memory-associated functions [13] and modulation of anxiety [14], two functions that are disturbed in bipolar patients. Authors have suggested circRNA molecules as possible markers for the diagnostic assessment of patients with BD [6]. Zimmerman et al. have recently shown expression of circHomer1a, a neuron-associated circRNA in the frontal cortex. Notably, expression of this circRNA was decreased in both the prefrontal cortex (PFC) and induced pluripotent stem cell–originated neurons of patients with BD. CircHomer1a has been shown to regulate the expression of several splicing variants of genes participating in synaptic plasticity and psychiatric disorders. Thus, circHomer1a modulates synaptic gene activity and intellectual flexibility [15]. Tables 1 and 2 summarize the results of studies that assessed the expression of circRNAs in BD.

| circRNA | Number of Clinical Samples | Type of Study | False Discovery Rate | Function | Ref |
|---------|---------------------------|---------------|----------------------|----------|----|
| cNEBL   | postmortem human medial frontal gyrus tissues from BPD cases (n = 4) and normal subjects (n = 4) | High throughput analysis | FDR < 0.05 | - | [6] |
| cEPHA3  | High throughput analysis | FDR < 0.1 | EPHA3 participates in the neuro-development. | |
Table 2. Summary of function of down-regulated circRNAs in BD (BD: bipolar disorder, SZ: schizophrenia).

| circRNA      | Number of Clinical Samples | Targets/Regulators                  | p Value | Function                                                                 | Ref  |
|--------------|-----------------------------|-------------------------------------|---------|--------------------------------------------------------------------------|------|
| circHomer1a  | Human OFC post-mortem brain tissues of BD patients (n = 32) and healthy controls (n = 34) | RNA-binding protein HuD              | p < 0.01 | circHomer1a is originated from HOMER1, a gene regulating neuronal excitability and synaptic plasticity. This gene is down-regulated in the OFC and stem cells-originated neurons of BD patients. | [15] |

3. LncRNAs and BD

Dysregulation of numerous lncRNAs has been described in peripheral blood and brain tissues of patients with BD. Hu et al. have profiled transcriptome in post-mortem brain tissues of patients with schizophrenia and BDs as well as healthy subjects. They reported differential expression of several long intergenic RNAs in various brain regions of bipolar patients. They showed that these lncRNAs have brain region-specific signatures and are mostly enriched in some pathways including immune system development and oligodendrocyte differentiation. Altered expression of these lncRNAs in patients was explained by modification of DNA methylation alteration [16]. Ji et al. have reported up-regulation of the XIST gene, the principal regulator of X chromosome inactivation (XCI) in the lymphoblastoid cells and brain tissues of female subjects with either BD or major depressive disorder. This up-regulation was accompanied by over-expression of the XCI escapee gene KDM5C. Authors have suggested that up-regulation of XIST might cause or result from delicate changes in XCI [17]. Table 3 summarizes the studies which reported up-regulation of lncRNAs in bipolar patients.
Table 3. Summary of function of up-regulated lncRNAs in BD (BD: bipolar disorder, SZ: schizophrenia).

| lncRNA | Number of Clinical Samples | Assessed Cell Line | Targets/Regulators | p Value       | Type of Study | Function                                                                 | Ref |
|--------|----------------------------|--------------------|--------------------|---------------|---------------|--------------------------------------------------------------------------|-----|
| PTCSC3 | Whole blood sample of BD patients with manic episode (n = 13) | -                  | -                  | $p = 2.39 \times 10^{-4}$ | High throughput analysis | PTCSC3 gene is reported to be associated with thyroid cancer. | [18] |
| CCAT2  | Peripheral blood specimens BD patients (n = 50) and healthy subjects (n = 50) | -                  | -                  | $p = 0.006$    | Candidate molecule analysis | CCAT2 is an oncogenic lncRNA in numerous neoplasms that enhances cell proliferation and suppresses apoptosis. | [19] |
| TUG1   | Peripheral blood mononuclear cells (PBMCs) of BD patients (n = 50) and controls (n = 50) | -                  | hsa-miR-92a-2-5p, hsa-miR363-5p, hsa-miR-1285-3p and hsa-miR-1268a | $p < 0.001$    | Candidate molecule analysis | TUG2 is an oncogenic lncRNA in numerous neoplasms that enhances cell proliferation and suppresses apoptosis. | [19] |
| PANDA  | Lymphoblastoid cells were from healthy females (n = 36) and female patients with either BD or recurrent major depression (n = 60) | -                  | -                  | $p = 0.004$    | Candidate molecule analysis | PANDA is an oncogenic lncRNA in numerous neoplasms that enhances cell proliferation and suppresses apoptosis. | [19] |
| DISC2  | Peripheral blood mononuclear cells (PBMCs) of BD patients (n = 50) and controls (n = 50) | -                  | hsa-miR-92a-2-5p, hsa-miR363-5p, hsa-miR-1285-3p and hsa-miR-1268a | $p = 0.0015$   | Candidate molecule analysis | DISC2 may regulate DISC1 expression. | [20] |
| XIST   | Lymphoblastoid cell lines | TSIX, FTX, JPX | -                  | $p = 1 \times 10^{-7}$ | Candidate molecule analysis | XIST is the master gene for XCI. | [17] |
| FTX    | Lymphoblastoid cell lines | XIST | -                  | $p < 0.1$      | Candidate molecule analysis | FTX is a positive regulator of XIST expression. | [17] |
Ghafelehbashi et al. have assessed the expression of IFNG-AS1 lncRNA, and IFNG and IL-1B mRNAs in peripheral blood of BD patients compared with healthy subjects. They reported down-regulation of IFNG-AS1 in patients and its correlation with IFNG expression. Moreover, expression of IL-1B was decreased in patients compared with controls. Thus, inflammatory lncRNAs might participate in the pathogenesis of BD [21]. Hu et al. have reported down-regulation of ENSG00000228794 in patients with BD. This lncRNA resides in a genomic region that is linked with BD. ENSG00000228794 is possibly implicated in calcium ion transport, thus it can modulate synaptic plasticity [16]. Table 4 summarizes the results of studies that reported down-regulation of lncRNAs in BD.
Table 4. Summary of function of down-regulated IncRNAs in BD (BD: bipolar disorder, SZ: schizophrenia).

| IncRNA         | Number of Clinical Samples | Assessed Cell Line | Targets/Regulators | Signaling Pathways | p Value | Type of Study                     | Function                                                                 | Ref   |
|----------------|----------------------------|--------------------|--------------------|-------------------|---------|-----------------------------------|--------------------------------------------------------------------------|-------|
| OIP5-AS1       | Peripheral blood samples of BD patients ($n = 50$) and healthy controls ($n = 50$) | -                   | -                  | -                 | $p = 0.001$ | Candidate genes analysis          | OIP5-AS1 is as an oncogene that enhances cell proliferation and suppresses of apoptosis. | [19]  |
| IFNG-AS1       | Blood samples of BD patients ($n = 30$) and healthy control individuals ($n = 32$) | -                   | IFNG               | -                 | $p < 0.0001$ | High throughput analysis          | IFNG-AS1 facilitates IFN-γ expression through association with the WDR methyltransferases and subsequent increase in H3K4 methylation at the IFNG locus. | [21]  |
| ENSG00000228794 | Post-mortem brain samples of patients with SZ and BD and control subjects ($n = 82$) | -                   | -                  | Calcium signaling | $p < 0.05$ | High throughput analysis          | ENSG00000228794 is located in a genomic region linked with BD and partakes in calcium ion transport. | [16]  |
| TSIX           | Lymphoblastoid cells were from healthy females ($n = 36$) and female patients with either BD or recurrent major depression ($n = 60$) | Lymphoblastoid cell lines | XIST               | -                 | $p < 0.01$ | Candidate genes analysis          | TSIX is a negative regulator of XIST expression. | [17]  |
| MALAT1         | Peripheral blood samples of BD patients ($n = 50$) and healthy controls ($n = 50$) | PBMCs              | hsa-miR-17-5p, hsa-miR-106a-5p, hsa-miR-30c-5p, hsa-miR-20b-5p, hsa-miR-92b-3p, hsa-miR-1224-3p | -                 | $p < 0.0001$ | Candidate molecule analysis       | MALAT1 takes part in the regulation of genes involved in synaptogenesis. | [22]  |
4. miRNAs and BD

The expression profile of miRNAs has been vastly assessed in different biological sources of patients with BD including whole blood, lymphoblastoid cell lines, brain tissues or extracellular vesicles. Squassina et al. have assessed miRNAs signature in lymphoblastoid cell lines from bipolar patients who deceased by suicide and those with low risk of suicide. They reported higher miR-4286 levels while lower miR-186-5p in lymphoblastoid cell lines obtained from suicide attempters compared with the low-risk group and healthy controls. Conversely, expression of miR-4286 was reduced in postmortem brains of bipolar patients who attempted suicide compared with controls, yet it could not yield the level of significance. Exposure of human neural progenitor cells with lithium down-regulates expression of miR-4286 [23]. Lee et al. have reported abnormal expression of a number of miRNAs in the serum samples of bipolar patients. Among dysregulated miRNAs has been miR-7-5p which was up-regulated in bipolar patients [8]. Notably, miR-7 has been previously shown to suppress the healing of damaged peripheral nerves by altering the migration and proliferation of neural stem cells [8]. Moreover, this miRNA has been over-expressed in the neocortex of superior temporal lobes of patients with Alzheimer’s disease [24]. Choi et al. have extracted extracellular vesicles (EVs) from the anterior cingulate cortex. They reported over-expression of miR-149 in bipolar patients compared to controls. They also validated dysregulation of both miRNAs in EVs extracted from brains of an animal model of depressive-like manners [25]. Figure 1 shows the molecular mechanisms of participation of miR-34a in the pathogenesis of BD.

**Figure 1.** Expression of miR-34a is increased in BD. This miRNA binds with 3’ UTR of SHAK3 to decrease its expression. Expression of this protein is correlated with CYLD levels [26,27]. CYLD is a deubiquitinase that targets PSD-95. The latter protein participates in the maturation and function of synapses [28].

Table 5 summarizes the studies which reported up-regulation of miRNAs in BD.
Table 5. Summary of function of up-regulated miRNAs in BD (BD: bipolar disorder, SZ: schizophrenia).

| microRNA   | Number of Clinical Samples | Assessed Cell Line | Targets/Regulators | Signaling Pathways                                                                 | \( p \) Value | Type of Study       | Function                                                                                           | Ref |
|------------|---------------------------|--------------------|--------------------|-----------------------------------------------------------------------------------|-------------|-------------------|---------------------------------------------------------------------------------------------------|-----|
| miR-7-5p   |                          |                    |                    | BDNF                                                                              | \( p < 0.001 \) | High throughput analysis | miR-7 has a role in inhibition of the repair of peripheral nerve damage by affecting the migration and proliferation of neural stem cells. | [8] |
| miR-142-3p | Whole blood samples of BD-II patients (n = 102) and controls (n = 118) |                    | TNF-\( \alpha \)    | GABAergic and glutamatergic synapses and TGF-beta, Hippo, and FoxO signaling       | \( p < 0.0001 \) | High throughput analysis | miR-142-3p may modulate the BMAL1 gene and regulate circadian functions.                          | [8] |
| miR-221-5p |                          |                    |                    |                                                                                  | \( p < 0.0001 \) | High throughput analysis | miR-221 is potentially involved in atherosclerosis.                                                   | [8] |
| miR-370-3p |                          |                    |                    |                                                                                  | \( p < 0.0001 \) | High throughput analysis | miR-370 is reduced in brain tissue of depressed animals.                                                | [8] |
| miR-23b-3p |                          |                    |                    |                                                                                  | \( p = 0.006 \)  | High throughput analysis | miR-23b may have an anti-inflammatory role in central nervous system inflammation.                   | [8] |
| miR-4286   | Lymphoblastoid cell line cultures from patients with BD who died by | Lymphoblastoid cell lines (LCLs) | PRKAB2, PTPRF, PIK3R3, CREB1, PPARGC1B, PIK3R1, CREB3L2, | Insulin resistance signaling pathway                                             | \( p = 0.000043 \) | High throughput analysis | miR-4286 might be a specific biomarker of suicide.                                                 | [23]|
| miRNA   | Expression in Samples | miR-330-3p | p < 0.05 | High throughput analysis | miR-193a-3p was upregulated in both BD and SZ. |
|---------|-----------------------|------------|----------|--------------------------|-----------------------------------------------|
| miR-193b-3p | -                     | -          | p < 0.05 | High throughput analysis | miR-330-3p has been over-expressed in the blood of subjects with BD and monopolar depression. |
| miR-330-3p | -                     | -          | p < 0.05 | High throughput analysis |                                               |
| miR-223 | -                     | GRIN2B, GRIA2 | p < 0.001 | High throughput analysis | miR-223 regulates glutamate receptors. miR-223 expression is negatively correlated with levels of its targets GRIN2B and GRIA2. |
| hsa-miR-155-3p | Lymphoblastoid cell line cultures from BD patients excellent responders (ER, n = 12) and non-responders (NR, n = 12) to lithium | Lymphoblastoid cell lines | SP4 | p = 0.0003 | High throughput analysis | hsa-miR-155-3p was up-regulated in ER. It partakes in inflammatory response and modulates differentiation and activation of innate and adaptive immune systems. |
| miR-193a-3p | -                     | -          | p < 0.001 | High throughput analysis |                                               | [30] |
| miR-330-3p | -                     | -          | p < 0.05 | High throughput analysis |                                               | [30] |
| miR-193b-3p | -                     | -          | p < 0.05 | High throughput analysis |                                               | [30] |
| miR-223 | -                     | GRIN2B, GRIA2 | p < 0.001 | High throughput analysis | miR-223 regulates glutamate receptors. miR-223 expression is negatively correlated with levels of its targets GRIN2B and GRIA2. | [30] |
| hsa-miR-155-3p | Lymphoblastoid cell line cultures from BD patients excellent responders (ER, n = 12) and non-responders (NR, n = 12) to lithium | Lymphoblastoid cell lines | SP4 | p = 0.0003 | High throughput analysis | hsa-miR-155-3p was up-regulated in ER. It partakes in inflammatory response and modulates differentiation and activation of innate and adaptive immune systems. | [29] |
| miR-193a-3p | -                     | -          | p < 0.001 | High throughput analysis |                                               | [30] |
| miR-330-3p | -                     | -          | p < 0.05 | High throughput analysis |                                               | [30] |
| miR-193b-3p | -                     | -          | p < 0.05 | High throughput analysis |                                               | [30] |
| miR-223 | -                     | GRIN2B, GRIA2 | p < 0.001 | High throughput analysis | miR-223 regulates glutamate receptors. miR-223 expression is negatively correlated with levels of its targets GRIN2B and GRIA2. | [30] |
| miR-28a-3p | - | - | - | - | 0.05 < p < 0.10 | High throughput analysis | miR-28a-3p is in the same family as miR-708, a miRNA that is associated with risk of BD. [30] |
| miR-1260 | - | - | - | - | p < 0.05 | High throughput analysis | - | [30] |
| miR-185-5p | Plasma samples of patients with BD type I (n = 69; 15 depressed, 27 manic, 27 euthymic) and healthy controls (n = 41) | - | Tyrosine kinase receptor type 2 | PI3K-Akt | p = 0.001 | High throughput analysis | miR-185-5p is a target miRNA for depression. [31] |
| miR-29a-3p, miR125a-3p | - | - | - | PI3K-Akt, TGF-beta | p = 0.035 | Candidate analysis | - | [32] |
| miR-106b-5p | Peripheral blood of BD I patients (n = 58, 19 manic, 39 euthymic) and healthy controls (n = 51) | - | IL-10 | PI3K-Akt, TGF-beta | p = 0.014 | Candidate analysis | miR-106 might be involved in immunomodulatory aspects of BD. [32] |
| miR-107 | - | GRIN2A, SLC1A4 | PI3K-Akt, TGF-beta | p = 0.011 | Candidate analysis | miR-107 is up-regulated in manic and euthymic patients. [32] |
| hsa-miR-150-5p, hsa-miR-25-3p, hsa-miR-451a, hsa-miR-144-3p | Plasma samples from drug-free psychotic bipolar patients (n = 15) and HC (n = 9) | - | - | - | p < 0.01 | High throughput analysis | These miRNAs were upregulated in patients. [33] |
| miRNA          | Condition                                                                 | p-value | Method                  | Description                                                                                                           | Literature |
|---------------|---------------------------------------------------------------------------|---------|-------------------------|-----------------------------------------------------------------------------------------------------------------------|------------|
| hsa-miR-4516, hsa-miR-6808-5p, hsa-miR-7977, hsa-miR-1185-2-3p, hsa-miR-6791-5p, hsa-miR-3194-5p, hsa-miR-6090, hsa-miR-3135b | -       | -                       | p < 0.05 High throughput data mining | These miRNAs are related to neuron development.                                                                 | [34]       |
| hsa-miR-29c-3p | Peripheral blood EV of BD patients (n = 20) and age- and sex-matched normal controls (n = 21) | -       | -                       | p = 0.010514 High throughput data mining | Increased levels of miR-29c have been detected in EVs isolated from post-mortem prefrontal cortex (BA9) of patients. | [34]       |
| hsa-miR-7975  | -                                                                         | -       | p = 0.048192 High throughput data mining | hsa-miR-7975 is associated with the brain. | The increased levels of miR-22 in EVs are supported by findings of up-regulation of these miRNAs in the prefrontal cortex of patients with BD. | [34]       |
| hsa-miR-21-5p | NTN1, NTNG1,                                                              | -       | p = 0.028475 High throughput data mining |                                                                                                                      | [34]       |
| miRNA          | Target Genes            | p-value       | High throughput data mining                                                                 |
|----------------|-------------------------|---------------|---------------------------------------------------------------------------------------------|
| hsa-miR-142-3p | NTN3, NTNG1, NTNG2     | p = 0.019266  | NTN3, NTNG1, NTNG2 are targeted by hsa-miR-142-3p.                                           |
| hsa-miR-22-3p, hsa-miR-92a-3p | NTN3, NTNG1, NTNG2 | p < 0.05     | NTN3, NTNG4, NTNG1, NTNG2 are targeted by hsa-miR-22-3p, hsa-miR-92a-3p.                  |
| hsa-miR-198   | GPX4                    | p < 0.05      | High throughput data mining                                                                 |
| hsa-miR-601   | ATP2B4                  | p < 0.05      | High throughput data mining                                                                 |
| hsa-miR-659   | SOD2, ATP5A1            | p < 0.05      | High throughput data mining                                                                 |
| hsa-miR-192   | TXN2, UQCR2C, ATP5L, PXDN, TXNIP, COX5A, TXN2 | p < 0.05 | High throughput data mining                                                                 |
| hsa-miR-346   | NDUFA1, COX5A           | p < 0.05      | High throughput data mining                                                                 |
| hsa-miR-9*    | ATP5F1                  | p < 0.05      | High throughput data mining                                                                 |
|               | ATP5B, COX10, TXNIP, BCL2L11, NDFUA7, TXNRD3, COX7A2, OXA1L, MGST1, PXDN, SOD2, COX5B, NDUFA5, UQCRQ | p < 0.05      | High throughput data mining                                                                 |

**Redox modulation pathways**

These are the top 10th percentile of up-regulated miRNAs that target redox modulators ranked for their ability to discriminate between BD and controls in Vladimirov dataset.
| miRNA           | Targets                                                                 | p Value | Notes                                      |
|-----------------|-------------------------------------------------------------------------|---------|--------------------------------------------|
| hsa-miR-199a-3p | ATP5B, UQCR12, COX10, TXNIP, BCL2L11, PTGS2, GLRX2, NDUFA2, NDUFA2,    | p < 0.05| High throughput data mining [35]           |
|                 | NDUFA2, NDUFA12                                                          |         |                                            |
| hsa-miR-34a     | TXNIP, NDUFS1, SOD2, PRDX3, NDUVF1                                       | p < 0.05| High throughput data mining [35]           |
| hsa-miR-145     | NDUFS1, NDUFA4                                                           | p < 0.05| High throughput data mining [35]           |
|                 | PPA1, TXNIP, ATP2B4, ATP5SL, PRDX1, PRDX4, FOXO3, NDUFA8, CAT, PXDN,   |         |                                            |
|                 | SOD1, FOXO1, NDUFA2, GSTO1, ATP5G3, NDUVF1, NDUFS2, NDUFS4, NDUVF1,    |         |                                            |
|                 | PRDX3, PPA1, GLRX5                                                       |         |                                            |
| hsa-miR-27a     | BCS1L, NDUFS1, SDHB, OXA1L                                               | p < 0.05| High throughput data mining [35]           |
|                 | MGST1, TXN2, NDUFS8, ATP5B, PRDX4, ATP5A1, OXA1L, NDUFS2, NOS3, COX5A,|         |                                            |
|                 | TXNRD3                                                                  |         |                                            |
| hsa-miR-92a-1*  | BCS1L, NDUFS1, SDHB, OXA1L                                               | p < 0.05| High throughput data mining [35]           |
| hsa-miR-103     | MGST1, TXN2, NDUFS8, ATP5B, PRDX4, ATP5A1, OXA1L, NDUFS2, NOS3, COX5A,| p < 0.05| High throughput data mining [35]           |
|                 | TXNRD3                                                                  |         |                                            |
| miR   | Targets                                                                 | p-value | Notes                                      |
|-------|-------------------------------------------------------------------------|---------|--------------------------------------------|
| hsa-miR-196b | ATP5G3, MT-ATP6, BCL2L2, BCL2L12, ATP2B4, GLRX3, NDUFC2, OXA1L, NDUVF3 | <0.05  | High throughput data mining [35]          |
| hsa-miR-449a | ATP5H, TXNIP, FOXO1, BCL2L11, ATP6V0A2, NDUFS1 | <0.05  | High throughput data mining [35]          |
| hsa-miR-196a | GPX1, ATP5G3, UQCRCC2, TXR1, MTATP8, MT-ATP6, BCL2L12, ATP2B4, GLRX3, FOXO1, OXA1L, NDUVF3, NDUFC2, GSTK1 | <0.05  | High throughput data mining [35]          |
| hsa-miR-675 | SOD2, PXDN                                                              | <0.05  | High throughput data mining [35]          |
| hsa-miR-184 | BCL2A1                                                                 | <0.05  | High throughput data mining [35]          |
| hsa-miR-200c | MT-ATP6, MGST1                                                          | <0.05  | High throughput data mining [35]          |
| hsa-miR-200b | BCL2, GLRX5                                                             | <0.05  | High throughput data mining [35]          |

**Extracellular vesicles (EVs) extracted from Human Postmortem Anterior Cingulate Cortices (BA24) Diagnosed With BD (n = 4)**

| miR-149 | Targets                                                                 | p-value | Notes                                      |
|---------|-------------------------------------------------------------------------|---------|--------------------------------------------|

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| miR-30d-5p | - | - | - | $p = 0.028$ | High throughput analysis | The blood expression of miR-30d-5p was increased also in MD patients after AD treatment. [36] |
| miR40-3p | - | - | - | $p = 0.027$ | High throughput analysis | The blood expression of miR40-3p was increased also in MD patients after AD treatment. [36] |
| miR330-5p | Blood samples of MD patients ($n = 20$) and BD patients ($n = 20$, 10 type I and 10 type II) and healthy controls ($n = 20$, 15 females, 5 males) | - | HTR2C, MAOA, DRD1, CAMKK2, NTRK3, CLOCK, CREB1, GABRA2, CNR1, MTHFR | - | $p = 0.030$ | High throughput analysis | miR-330-5p regulates many targets participating in neuronal plasticity and neurodevelopment. [36] |
| miR21-3p | - | - | - | $p = 0.043$ | High throughput analysis | miR-21-3p is decreased in MD fibroblast cultures. [36] |
| miR378a-5p | - | - | - | $p = 0.042$ | High throughput analysis | miR-378a-5p is mainly involved in lipid and metabolism homeostasis. [36] |
| hsa-miR-345-5p | - | HTR2C, MAOA, DRD1, CAMKK2, NTRK3, CLOCK, CREB1, GABRA2, CNR1, MTHFR | - | $p = 0.010$ | High throughput analysis | miR-345-5p is predicted to regulate several target genes with a putative role in the shared pathogenic mechanisms. [36] |
| miR-15b | Blood of uninfected individuals at higher genetic risk of developing a mood disorder (n = 34) and control subjects (n = 46) | - | - | PI3K/Akt, PTEN | p = 0.0166 | Candidate gene analysis (20 miRNAs) | miR-15b was overexpressed in the high-risk persons. It is involved in metabolism, angiogenesis, stress response, cancer, cardiovascular disease and neurodegenerative conditions. [37] |
| miR-132 | - | - | PI3K/Akt | p = 0.0249 | Candidate gene analysis (20 miRNAs) | miR-132 was overexpressed in the high-risk persons. miR-132 is transcribed from a cluster of miRNAs that partake in neuronal development and function. [37] |
| miR-652 | - | GABARB2, GABARB3, 5-HT1D, DISC1 | - | p = 0.01076 | Candidate gene analysis (20 miRNAs) | miR-652 was upregulated in the high-risk individuals. miR-652 plays a central role in myeloid development. [37] |
| miR-34a | Postmortem human brain samples from the cerebellum | - | ANK3, CACNB3, DDN, SHANK3 | WNT, cadherin | p < 0.01 | Candidate analysis | miR-34a expression is inversely [38] [27] |
miR-17-5p  | Human prefrontal cortex (Brodman area 10) of 15 SZ, 15 MDD, 15 BD, and 15 controls |  
| miR-29c-3p |  
| miR-106b-5p |  
| miR-579 |  

**miR-29c**  
Postmortem Human Prefrontal Cortex (Brodman area 9, BA9) 8 SZ, 9 BD, and 13 controls  
-  
-  
Wnt  
p = 0.0237  
High throughput analysis  
-  
[39]  

**hsa-miR-188-5p, hsa-miR-196b, hsa-miR-32*, hsa-miR-187, hsa-miR-383, hsa-miR-297, hsa-miR-876-3p, hsa-miR-490-5p, hsa-miR-499b, hsa-miR-513-5p**  
Dorsolateral prefrontal cortex tissue of control (n = 34), bipolar (n = 31), and schizophrenic (SZ, n = 35) subjects  
-  
-  
-  
p < 0.05  
High throughput analysis  
-  
[41]  

**hsa-miR-504**  
**hsa-miR-145**  
**hsa-miR-22***  
**hsa-miR-145**  
**hsa-miR-133b**  
**hsa-miR-154***  
**hsa-miR-889**  
**miR-34a**  
Postmortem DLPFC sections from 35 cases with schizophrenia 35 cases with BD  
-  
-  
-  
p = 0.00003  
p = 0.00080  
p = 0.00106  
p = 0.00177  
p = 0.00190  
p = 0.00195  
p = 0.00321  
p = 0.023917  
High throughput analysis  
-  
[42]  

**associated with expression of ANK3 and CACNB3.**
| miR-152 | 20 LCLs derived from bipolar disorder (BPI) family members with and without LiCl treatment in culture | AP2A1, AP2S1, CD2AP, EIF1, and VCL | p = 0.000405 | miR-34a, miR-152, miR-155, and miR-221 were consistently up-regulated at treatment time point day 4 and day 16. |
| miR-155 | | | p = 0.012045 | |
| miR-221 | | | p = 0.000073 | |

| miR-195-5p, miR-382-5p, miR-128-3p, miR-138-2-3p, miR-487b-3p, miR-744-3p | AXIN2, BDNF, CACNA1E, MIB1, NLGN1 and RELN, SYT4 | Axon guidance, Mapk, Ras, Hippo, Neurotrophin and Wnt signaling pathway | p < 0.05 | Candidate molecule analysis (58 miRNAs) - [44] |
Pisanu et al. have assessed miRNA profile in lymphoblastoid cell lines from BD patients who responded to lithium versus non-responders. They described differential expression of 31 miRNAs between these groups, among them were miR-320a and miR-155-3p. Expression of hsa-miR-320a was significantly lower in responders. Notably, targets of this miRNA participate in neuronal survival and differentiation, apoptosis, and plasticity of synapses [29]. Zhang et al. have demonstrated deceased circulating levels of miR-134 in bipolar patients as well as patients with schizophrenia or major depressive disorder compared with normal controls. Yet, the most significant downregulation of this miRNA has been described in major depressive disorder [45]. Table 6 summarizes the list of down-regulated miRNAs in BD.
Table 6. Summary of function of down-regulated miRNAs in BD (BP: bipolar disorder, SZ: schizophrenia).

| microRNA     | Number of Clinical Samples | Assessed Cell Line | Targets/Regulators | Signaling Pathways | p Value   | Type of Study | Function                                                                 | Ref  |
|--------------|----------------------------|--------------------|--------------------|--------------------|-----------|---------------|---------------------------------------------------------------------------|------|
| miR-320a     | BD patients (excellent responders, n = 12; non-responders, n = 12) to lithium | Lymphoblastoid cell lines | CAPNS1             | -                  | p < 0.0001 | High throughput analysis | Participates in response to lithium                                        | [29] |
| miR-134      | Whole blood samples of BD (n = 50) and controls (n = 50) | -                   | cAMP response element-binding protein (CREB) | -                  | p = 2.25 × 10⁻⁵ | Candidate molecule analysis | miR-134 regulates dendritic spine development and plasticity.               | [45] |
| miR-186–5p   | LCLs from patients with BD who deceased by suicide (SC, n = 7) and with low risk of suicide (LR, n = 11) and 12, non-suicidal controls | Lymphoblastoid cell lines (LCLs) | -                  | -                  | p = 0.032  | High throughput analysis | miR-186–5p was lower in lithium-treated LCLs from SC compared to controls. | [23] |
| miR-484      | Plasma samples of patients with BD type I and healthy controls (n = 41) | -                   | -                  | PI3K-Akt           | p < 0.001  | High throughput analysis | miR-484 is linked with neurogenesis, mitochondrial network and redox modulations | [31] |
| miR-142-3p   | Plasma samples from drug-free psychotic BD cases (n = 15) and HC (n = 9) | -                   | -                  | PI3K-Akt           | p = 0.001  | High throughput analysis | miR-142-3p regulates signaling pathways during embryonic development and homeostasis. | [31] |
| miR-652-3p   | Plasma samples from drug-free psychotic BD cases (n = 15) and HC (n = 9) | -                   | -                  | PI3K-Akt           | p < 0.001  | High throughput analysis | miR-652 is linked with immune system and oxidative stress.                 | [31] |
| hsa-miR-363-3p, hsa-miR-4454 + has-miR-7975, hsa-miR-873-3p, hsa-miR-548al, hsa-miR-598-3p, hsa-miR-4443, hsa-miR-551a, hsa-miR-6721-5p | Plasma samples from drug-free psychotic BD cases (n = 15) and HC (n = 9) | -                   | -                  | p < 0.01   | High throughput analysis | These miRNAs were downregulated in patients.                          | [33] |
hsa-miR-1281, hsa-miR-6068, hsa-miR-8060, hsa-miR-4433a-5p, hsa-miR-1268b, hsa-miR-1238-3p, hsa-miR-188-5p, hsa-miR-6775-5p, hsa-miR-6800-3p, hsa-miR-3620-5p, hsa-miR-1227-5p, hsa-miR-7108-5p, hsa-miR-671-5p, hsa-miR-6727-5p, hsa-miR-6125, hsa-miR-6821-5p

Peripheral blood EVs from BD patients (n = 20) and age- and sex matched normal subjects (n = 21)

- - - Axon guidance mediated by netrin, endothelin signaling, 5HT2 type receptor-mediated signaling, beta1 and beta2 adrenergic receptor pathways, and the androgen receptor signaling pathway

p < 0.05 High throughput analysis

These miRNAs were nominally downregulated between patients and controls. Pathway analyses identified some brain-relevant mechanisms enriched in these miRNAs, including axon guidance by netrin and the serotonin receptor pathway.

[34]

hsa-miR-5739

Peripheral blood EVs from BD type I (n = 20) and age- and sex matched healthy controls (n = 21)

- NTN1, NTN3, NTNG1, NTNG2 -

p = 0.024667 High throughput analysis

miR-5739 is suggested to be highly associated with the brain.

[34]

hsa-miR-133a-3p

and age- and sex matched healthy controls (n = 21)

- - -

p < 0.05 High throughput data mining

[35]

hsa-miR-299-5p

- SOD2, GPX4

p < 0.05 High throughput data mining

[35]

hsa-miR-197

- SOD1, GCLC, TXN, COX8A, ATP2B4

p < 0.05 High throughput data mining

[35]

hsa-miR-23a

3 frontal cortex miRNA expression datasets

- NDUFA2, PPA1, GCLM, PTGS1, SOD2, PRDX4, PXDN, TTN, UQCRQ, NDUFV1, PRDX3, NDUFA3, TXNIP, ATP50, TXNRD1

Redox modulation pathways

p < 0.05 High throughput data mining

These are the top 10th percentile of decreased miRNAs that target redox modulators ranked for their ability to discriminate between BD and controls in Miller dataset.

[35]

hsa-miR-450a

- GCLC, NDUFA10, ATP5C1

p < 0.05 High throughput data mining

[35]
| miRNA          | Targets                                                                 | p-value | Techniques                                       |
|----------------|-------------------------------------------------------------------------|---------|-------------------------------------------------|
| hsa-miR-17     | ATP5B, TXN, NDUFA10, TXNIP, MTATP6, BCL2L11, NDUFS1, OXA1L, ATP2B4, BCL2L13, TXN2, SOD2, SDHB, PXDN, FOXO1, BCL2, UQCRFS1, RXNRD2, GPX2, TXNRD2 | p < 0.05 | High throughput data mining                      |
| hsa-miR-944    | - FOXO1                                                                 | p < 0.05 | High throughput data mining                      |
| hsa-miR-19b    | GCLC, ATP2B4, NDUFB2, COX6A1, FOXO3, PXDN, NDUFS3, COX10, NDUFB2        | p < 0.05 | High throughput data mining                      |
| hsa-miR-503    | COX10, NDUFS1, PXDN                                                     | p < 0.05 | High throughput data mining                      |
| hsa-miR-7      | NDUFA4, SDHC, ATP5S, FOXO6, NDUFS1, GCLM, COX4I1, ATP2B4, TXN2, GSR, ATP5F1, SDHB, NDUFC2, PPA1, PRDX1 | p < 0.05 | High throughput data mining                      |
| hsa-miR-199a-5p| NDUFA13, MGST2                                                           | p < 0.05 | High throughput data mining                      |
| hsa-miR-484    | NOS3, PRDX1, COX7A2L, UQCRQ, GSTO1, UQCRFS1, ATP5J, BCL2L1, COX8A, PRDX1, MTATP6, PRDX4, COX5A, UQCRQ | p < 0.05 | High throughput data mining                      |
| hsa-miR-424    | NDUFS1, COX7A2L, BCL2L11, UQCRH                                         | p < 0.05 | High throughput data mining                      |
| miR-499 | Peripheral blood of adult women only, 17 UP (age: 50 ± 17) and 15 BP (age: 33 ± 13) patients | - | - | - | $p = 0.008$ | Candidate molecule analysis | miR-499 is down-regulated in depression episodes of the BD patients compared with remission phase. [46] |
|---------|------------------------------------------------------------------------------------------|---|---|---|-------------|-----------------------------|----------------------------------------------------------------------------------|
| miR-708 | Up (age: 50 ± 17) and 15 BP (age: 33 ± 13) patients                                        | - | - | - | $p = 0.02$  | Candidate molecule analysis | miR-708 is down-regulated in depression episodes of the BD patients compared with remission phase. [46] |
| miR-1908| - KLC2                                                                                     | - | - | - | $p = 0.004$ | Candidate molecule analysis | miR-1908 is down-regulated in depression episodes of the BD patients compared with remission phase. It is involved in lipid metabolism. Overexpression of miR-1908 in multipotent adipose-derived stem cells suppressed adipogenic differentiation and increased cell proliferation. [46] |
| miR-1908-5p | Two human NPC lines derived from dermal fibroblasts of either a control or a BD subject, treated with vehicle or 1 mM lithium or valproate for a week | Human neural progenitor cells (NPCs) | DLGAP4, GRIN1, STX1A, CLSTN1, GRM4 | NF-kappaB | $p < 0.05$ | Candidate molecule analysis | miR-1908 is an intronic miRNA of the fatty acid desaturase 1 (FADS1) gene. [47] |
| miR-132 | -                                                                                         | - | - | - | $p < 0.05$ | Candidate molecule analysis (29 miRNAs) | -                                                                                     [48] |
| miR-133a | Human post-mortem anterior cingulate cortex (AnCg) tissue. ($n = 8$, BP; $n = 15$, MDD; $n = 14$, Control) | - | - | - | $p < 0.05$ | Candidate molecule analysis (29 miRNAs) | While miR-133b levels did not change, miR-133a was differentially expressed in the AnCg of cohort of BP patients. [48] |
| miR-212 | -                                                                                         | - | - | - | $p < 0.05$ | Candidate molecule analysis (29 miRNAs) | miR-132 and miR-212 have been previously identified as differentially expressed in the DLPFC of SZ patients. [48] |
| miR-34a | - NCOA1, PDE4B                                                                           | - | - | - | $p < 0.05$ | Candidate molecule analysis (29 miRNAs) | miR-34a expression is dysregulated in SZ and BP patients. miR-34a expression is dysregulated in SZ and BP patients. [48] |
| miR-145-5p | Human prefrontal cortex (Brodmann area 10) of 15 SZ, 15 MDD, 15 BD, and 15 controls | - | - | - | \( p = 0.0069 \) | High throughput | - | [39] |
| miR-485-5p | - | - | - | \( p = 0.036 \) | - | - | - |
| miR-370 | - | - | - | \( p = 0.041 \) | - | - | - |
| miR-500a-5p | - | - | - | \( p = 0.041 \) | - | - | - |
| miR-34a-5p | - | - | - | \( p = 0.048 \) | - | - | - |
| hsa-miR-454* | Postmortem DLPFC tissues of individuals with schizophrenia (SZ, \( n = 35 \)) and BD (\( n = 35 \)) | - | - | - | \( p = 0.00004 \) | High throughput | - | [42] |
| hsa-miR-29a | - | - | - | \( p = 0.00005 \) | - | - | - |
| hsa-miR-520c-3p | - | - | - | \( p = 0.00018 \) | - | - | - |
| hsa-miR-140-3p | - | - | - | \( p = 0.00181 \) | - | - | - |
| hsa-miR-767-5p | - | - | - | \( p = 0.00209 \) | - | - | - |
| hsa-miR-874 | - | - | - | \( p = 0.00227 \) | - | - | - |
| miR-134 | Plasma sample of drug-free bipolar 1 patients (14 men and 7 women) and controls (\( n = 21 \)) | - | Limk1 | - | \( p = 0.009 \) | Candidate molecule analysis | miR-134 regulates dendritic spine development though Limk1, that controls synaptic development, maturation and/or plasticity. | [49] |
| miR-346 | DLPFC samples of SZ patients (\( n = 35 \)), BD (\( n = 32 \)), normal subjects (\( n = 34 \)) | - | CSF2RA | - | \( p = 0.086 \) | Candidate molecule analysis | miR-346 gene lies in intron 2 of the GRID1 gene, which has been proposed to be important in SZ susceptibility. | [50] |
| miR-19b-3p | Blood plasma from 7 UD patients, 7 BD patients, and 6 controls | - | MAPK1, PTEN, and PRKAA1 | mTOR, FoxO, and the PI3-K/Akt signaling pathway | \( p = 0.0462 \) | Candidate molecule analysis | MiR-19b-3p is a member of the miR-17/92 cluster, which controls lymphocyte growth, activation and proliferation. | [51] |
| miR-10b-5p | Skin biopsies of 3 control and 3 BP patient Pluripotent Stem Cell-derived neurons | ANK3, BDNF, CAMK2G, DLGAP2, and NFASC | Axon guidance, Mapk, Ras, Hippo, Neurotrophin and Wnt signaling pathway | \( p < 0.05 \) | Candidate molecule analysis(58 miRNAs) | - | [44] |
Lim et al. have appraised the expression of miRNAs in peripheral blood of bipolar manic patients after 12 weeks of receiving asenapine or risperidone. They reported differential expression of several miRNAs [52]. Table 7 summarizes these miRNAs.
### Table 7. Altered expression of miRNAs following treatment with antipsychotic drugs.

| miRNAs           | Expression Pattern | Targets/Regulators | p Value       | Function/Comments                                                                 | Ref  |
|------------------|--------------------|--------------------|---------------|-----------------------------------------------------------------------------------|------|
| hsa-miR-18a-5p   |                    |                    | p = 0.010761  |                                                                                   |      |
| hsa-miR-27a-3p   |                    |                    | p = 0.000161  |                                                                                   |      |
| hsa-miR-148b-3p  |                    |                    | p = 0.005188  |                                                                                   |      |
| hsa-miR-17-3p    | Up                 |                    | p = 0.018034  | These miRNAs were up-regulated in the Asenapine Group in this study. These findings suggest that candidate miRNAs might participate in the mechanism of function of both antipsychotics in bipolar mania. | 52   |
| hsa-miR-106b-5p  |                    |                    | p = 0.00445   |                                                                                   |      |
| hsa-miR-106a-5p  |                    |                    | p = 0.006898  |                                                                                   |      |
| hsa-miR-20a-5p   |                    |                    | p = 0.002247  |                                                                                   |      |
| hsa-miR-17-5p    |                    |                    | p = 0.011219  |                                                                                   |      |
| hsa-miR-19b-3p   | Up                 |                    | p = 0.013057  | These miRNAs were up-regulated in the Asenapine Group. miR-19b, miR145, and miR-339, were formerly shown to be dysregulated in patients with autism spectrum disorder and with Alzheimer’s disease. | 52   |
| hsa-miR-145-5p   |                    |                    | p = 0.029543  |                                                                                   |      |
| hsa-miR-339-5p   |                    |                    | p = 0.002185  |                                                                                   |      |
| hsa-miR-15a-5p   | Up                 | BDNF               | p = 0.002422  | hsa-miR-15a-5p was up-regulated in the Asenapine Group. miR-15a is reported to be involved in an interaction with brain-derived neurotrophic factor. | 52   |
| hsa-miR-30b-5p   | Up                 |                    | p = 0.015608  | hsa-miR-30b-5p was up-regulated in the Asenapine Group. MiR-30b is associated with schizophrenia, a psychiatric disorder that has been shown to share common genetic roots with BD. | 52   |
| hsa-miR-210-3p   | Up                 |                    | p = 0.005157  | hsa-miR-210-3p was up-regulated in the Asenapine Group. Overexpression of miR-210 induces angiogenesis and neurogenesis. | 52   |
| hsa-miR-92b-5p   | Down               |                    | p = 0.04547   |                                                                                   |      |
| hsa-miR-1343-5p  |                    |                    | p = 0.019721  |                                                                                   |      |
| hsa-miR-664b-5p  | Down               |                    | p = 0.035348  | These miRNAs were down-regulated in the Asenapine Group in this study.             | 52   |
| hsa-miR-6778-5p  | Down               |                    | p = 0.047124  | These miRNAs were down-regulated in the Risperidone Group in this study.           | 52   |
| hsa-miR-146b-5p  | Down               | BDNF               | p = 0.005919  | hsa-miR-146b-5p was down-regulated in the Risperidone Group. miR-146b partakes in an interaction with brain-derived neurotrophic factor. | 52   |
5. Discussion

Several studies have reported aberrant expression of ncRNAs in bipolar patients. Moreover, the expression of ncRNAs is influenced by drugs used for these patients. For instance, a combination of drugs including lithium, valproate, lamotrigine and quetiapine has been shown to alter the expression of several genes including miRNAs in cultured human neurons. Among the differentially expressed genes have been miR-128 and miR-378 whose targets are enriched in neuron projection development and axonogenesis [53]. Thus, ncRNAs not only are involved in the pathogenesis of BD but also they might participate in the determination of response to prescribed drugs. NcRNA profiling has revealed specific alterations in certain IncRNAs and miRNAs in the manic state indicating a possible role of these transcripts in the determination of disease status [18]. Notably, IncRNAs have been the largest group of differentially expressed ncRNAs [18]. Such state-specific transcript signature potentiates ncRNAs as preferable biomarkers for early diagnosis of BD.

Next generation sequencing technique has facilitated the identification of putative biomarkers for discrimination of bipolar patients from healthy subjects. A representative of this kind of experiment is the study conducted by Lee et al. which identified over-expression of miR-7-5p, miR-23b-3p, miR-142-3p, miR-221-5p, and miR-370-3p in bipolar patients compared with healthy individuals. The diagnostic accuracy of this panel of miRNAs was estimated to be 0.907 [8].

Dysregulated ncRNAs in bipolar patients have been enriched in several neuron-related pathways such as GABAergic and glutamatergic synapses, morphine addiction pathway, redox modulation as well as TGF-β, Wnt, Akt/PI3K, Hippo and FoxO pathways. Significance of a number of these pathways such as GABAergic and glutamatergic synapses signaling and TGF-β, Hippo and FoxO pathways have been recognized in the pathogenesis of BD [54,55]. The relevance of other pathways with this disorder should be appraised in future studies. Another functional annotation analysis of the differentially expressed coding and non-coding genes between patients with BD and healthy controls has shown remarkable enrichments of cellular pathways associated with angiogenesis and vascular system evolution [6]. The largest GWAS conducted in BD has reported that the most significant loci have been related to ion channels, neurotransmitter transporters and synaptic components. Yet, this study has not reported any indication for involvement of angiogenesis or vascular related loci in BD [56]. Pathway analysis revealed nine significantly enriched gene sets, including regulation of insulin secretion, circadian rhythm, and endocannabinoid signaling [56]. Notably, insulin resistance signaling pathway and circadian rhythm have been among the related pathways with dysregulated miRNAs in BD [8,23]. Finally, top genes existing in these pathways have been shown to encode Ca2+ and K+ channel subunits, MAPK and GABA-A receptor subunits [56], the latter being recognized as one of the most important pathways enriched among dysregulated ncRNAs in BD [8].

However, different studies have indicated abnormal activity of various signaling pathways in BD including immune response pathways [57], neuroplasticity, circadian rhythms and GTPase binding [58] and G protein-receptor dysregulation [59]. Such a heterogeneous range of biological pathways involved in BD might be related to distinct brain areas assessed in these investigations. Imminent investigations integrating particularly large sample sizes of patients with BD and comparison of transcriptome of coding and ncRNAs in different parts of the brain are required to find the most relevant pathways.

Dysregulation of ncRNAs has been reported in other brain disorders as well. For instance, assessment of IncRNA signature using high-throughput sequencing has led to the recognition of aberrantly expressed IncRNAs in acute ischemic stroke. ENSG00000226482 has been among up-regulated IncRNAs. This IncRNA has a potential role in activation of the adipocytokine signaling [60]. Moreover, another experiment in the animal model of blast traumatic brain injury has shown elevation of plasma amounts of a brain-enriched
miRNA, namely miR-127. This study has concluded that levels of sphingolipids, miR-128, and the let-7 family can show the presence of could blast traumatic brain injury. Moreover, a number of other miRNAs have been shown to serve as markers for a global level of damage after blast injury [61]. Moreover, miRNAs have been shown to serve as diagnostic markers for cognitive impairment. Certain panels of miRNAs have high sensitivity and specificity values in this regard [62].

Notably, several dysregulated ncRNAs in BD, are also dysregulated in other neuropsychiatric conditions such as schizophrenia or Alzheimer’s disease. Although this observation supports their potential roles in synaptic plasticity or neurodevelopment, it complicates the design of disease-specific diagnostic panels for BD.

Among dysregulated miRNAs in peripheral blood of patients with BD have been miR-128, miR-133b, miR-29a, miR-370, miR-451, miR-874 and miR-9* which have been recognized as brain-enriched miRNAs [63].

Taken together, circRNAs, lncRNAs and miRNAs are regarded as potential contributors in the pathology of BD and putative biomarkers for diagnosis of this disorder. Their participation in the response of patients to the prescribed medications and their potential as therapeutic targets have been less studied. Thus, these research areas should be explored in future studies.

ncRNAs are superior to transcripts of standard genes in the field of biomarker study as they represent the final step of function of the gene. As transcripts of standard genes should be translated to proteins to exert their function, the transcript level might not reflect the final level of the functional molecule. Moreover, miRNAs represent important regulators of gene expression as they can target several transcripts.

Finally, studies reporting dysregulation of ncRNAs in BD have some limitations. For instance, they often suffer from various confounding factors. This is especially true for postmortem brain studies. Moreover, most of the studies reviewed in this manuscript may not have sufficient statistical power due to their small sample sizes. Analysis and interpretation of differences between data of postmortem brains and blood samples, differences between expression data on ncRNA and protein coding genes, and matching with GWAS-identified loci are other research fields that should be explored in future studies.

6. Conclusions

ncRNAs are potential markers for neurological disorders such as BD. Several ncRNAs have been found to be dysregulated in blood samples of bipolar patients. Molecular studies for identification of the mechanism of dysregulation of these transcripts in bipolar patients would facilitate the development of new therapeutic strategies.

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Institutional Review Board Statement: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants. The study protocol was approved by the ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.MSP.REC.1399.042, 12/09/2020). All methods were performed in accordance with the relevant guidelines and regulations.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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