

Title:

Major Depression and Its Treatment: MicroRNAs as peripheral biomarkers of diagnosis and treatment response

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Abstract:

Purpose of Review: Major Depressive Disorder (MDD) is among the most prevalent and disabling medical conditions worldwide. Despite its considerable burden, our understanding of its pathophysiology remains rudimentary, and a validated biomarker has yet to be identified. Antidepressants (ADs) are the most common treatment for MDD, yet roughly one third of patients experience an inadequate response. Thus, there is a great need for not only identifying biomarkers of MDD but also those that can predict and/or monitor response to treatment.

Recent Findings: MicroRNAs (miRNAs) act as endogenous fine-tuners and on-off switches of gene expression. Several lines of evidence now suggest that miRNAs are involved in the pathogenesis of neuropsychiatric disorders. As such, miRNAs offer great hope as biomarkers of disease and response to treatment.

Summary: In this review, we discuss the growing field investigating peripheral miRNAs as potential biomarkers of major depression and treatment response. A non-invasive and validated biomarker of MDD or treatment response will help clinicians guide treatment selection. Ultimately, these findings provide important steps in the development of early diagnostic tools, preventive strategies, and effective pharmacological treatment for psychiatric disorders.

Keywords: MicroRNA, Biomarker, Major Depressive Disorder (MDD), Antidepressant Treatment

Key Points:

1. Major depressive disorder is among the most prevalent and disabling medical conditions worldwide.
2. Currently there is no validated biomarker for identification of major depressive disorder or that can predict or monitor treatment response.
3. MicroRNAs post-transcriptionally regulate specific mRNA transcripts and play a critical role in the pathogenesis of neuropsychiatric disorders.
4. Peripheral microRNAs have the potential to be used as biomarkers of major depression and treatment response.

1. Introduction

Major depressive disorder (MDD) is highly prevalent in the general population and is associated with grave consequences, including excessive mortality, disability, secondary morbidity and high socio-economic costs(1). Treatment of MDD includes a variety of biopsychosocial approaches, but in medical practice, antidepressant drugs are the most common therapy and are among the most prescribed medications in North America and in Europe(2). While they have demonstrated effectiveness, on average, 30 to 40% of patients do not achieve response even following several adequate trials(3). Despite the heterogeneity in response to antidepressants, guidelines for MDD treatment remain general, non-specific, and do not take into account individual characteristics or variability. This is mainly due to the lack of empirically validated predictors of response. Poor response to treatment has severe individual, economic and social consequences for both patients and their families. Thus, there is a great need in not only identifying biomarkers associated with MDD but also those that predict response to antidepressant treatment.

There is growing evidence suggesting that microRNAs (miRNAs), play an important role regulating brain processes, and may underlie psychopathological states such as depression(4). Several studies suggest that miRNAs are involved in the pathophysiology of major depression and regulate the activity of several genes, which in turn, affect various functional pathways which are relevant to the etiology of mood disorders and their treatments(5). In addition, numerous findings suggest that miRNAs could be used as potential biomarkers of disease state, trait or could act as mediators of response to treatment(6). In this review, we discuss the growing field investigating microRNAs as prospective biomarkers of major depression and antidepressant treatment. After reviewing the current literature, we also propose a research agenda to progress knowledge in this field.

MicroRNA Regulation

Regulation of gene expression can occur at different levels. For instance, regulation can happen at the level of the gene, where, for example, a repressor molecule may bind a promoter region and

decrease the amount of RNA a gene generates. Regulation can also occur at the level of RNA. RNA is generated in the nucleus and transported to the cytoplasm where RNA molecules become the template for protein synthesis. At many different points during this process, RNA can be altered or degraded. Proteins can also undergo modification and regulation after translation from RNA molecules. In this way, the multiple levels of gene expression from DNA to protein can be regulated by multiple different mechanisms, giving an organism a precise number of gene products(7). Different types of noncoding RNA have been identified and traditionally classified according to size into mainly two groups: long and small noncoding RNA(8). Among these, miRNAs are ones that have received most of the attention and will be the focus of this review. For an in-depth review on other types of noncoding RNA, please see Esteller(9) and St. Laurent *et al*(10).

MicroRNAs are small, non-coding, single stranded, RNA transcripts that play an important role in the posttranscriptional regulation of messenger RNA. Since their discovery in the early 90s, miRNAs have revolutionized our understanding of gene regulation and have been the subject of growing interest in psychopathology(11). After their transcription and maturation, miRNAs are loaded into the RNA-induced silencing complex (RISC). Within this complex miRNAs serve as a primer, directing the RISC to complementary sequences within mRNA transcripts, which leads to either mRNA degradation or translational repression(12) (**Figure 1**). For a comprehensive review on miRNA biogenesis and function, please see(13). MiRNAs are abundantly expressed in the brain, reflecting their widespread and diverse influence on central nervous system (CNS) functioning(14). They play important roles in a variety of key processes such as neuronal differentiation and survival, brain development, synaptic plasticity and neurogenesis(15-18). Given that miRNAs play an important function in the regulation of essential brain processes, there has been growing interest in the role of miRNAs in psychiatric disorders and their treatment(19, 20). Furthermore, miRNAs can be stably transported in blood and other fluids in exosomes(21) or by lipoproteins(22). Recently, there has been considerable interest to identify circulating miRNAs signatures correlating with pathological states or biomarkers of treatment

response(23). In psychiatry, there are a growing number of studies investigating peripheral miRNA changes associated MDD and its treatment (**Figure 1, Tables 1-3**).

MicroRNAs as Biomarkers of MDD

The first studies, in humans, exploring the expression of miRNAs in psychiatric disorders came from postmortem studies. In 2007, Perkins *et al*, reported 16 differentially expressed miRNAs in the prefrontal cortex of individuals who suffered from schizophrenia(24). Their study was followed by several independent groups investigating miRNA changes in MDD brains(25-35). These studies are summarized in **Table 1**. In 2012, Belzeaux and colleagues performed the first study investigating miRNA changes in depressed patients and healthy controls, using peripheral blood samples(36). The authors found a dysregulation in the expression of 14 miRNAs in peripheral blood mononuclear cells (PBMCs), from depressed patients as compared to psychiatrically healthy controls. Follow-up studies using PBMCs(37), blood monocytes(38), blood leukocytes(39), cerebral spinal fluid (CSF)(40), plasma(41) and serum(42) found additional miRNAs dysregulated in depressed patients. However, there was no overlap between the top findings in these studies and the miRNAs reported by Belzeaux *et al*. However, this could be explained by methodological differences across studies. On the other hand, studies using whole blood show higher consistency across studies. For example, miR-132 was shown to be upregulated in depressed patients in two independent studies(43, 44). In addition, miRNA members of the Let-7 and miR-34 families were shown to be dysregulated in several studies using blood samples from MDD patients(39, 42, 45, 46). Although encouraging, these findings were not predictive of treatment response and suggest that these miRNAs could only be used as disease biomarkers of MDD. A summary of dysregulated miRNAs, source of tissue, quantification method, sample size, and diagnosis criteria can be found in **Table 2**.

MicroRNAs as Biomarkers of Treatment Response

In 2012, Bocchio-Chiavetto *et al* performed the first study, looking at miRNA changes after antidepressant treatment, in a small group of patients(47). Using a PCR-based array, they identified a

group of 30 miRNAs dysregulated after escitalopram treatment. More recently, Baudry *et al* found that miR-16 explains antidepressant action of fluoxetine in the raphe and locus coeruleus of mice(48). Follow up work suggest that the same miRNA mediates adult neurogenesis in rodent hippocampus(49). Additional studies, performed by others, have shown decreased levels of miR-16 in cerebrospinal fluid samples from depressed patients as compared to controls(40), baseline differences between responders and non-responders, as well as changes after antidepressant treatment(50).

Another promising finding, uncovered a key role for miR-135a in the molecular mechanisms underlying the therapeutic actions of SSRIs using both human samples and animal models of depression(51). In this study, they determined the specific miRNA “fingerprint” of 5HT neurons and identified a strong microRNA-target interaction between miR-135a, and both serotonin transporter and serotonin receptor-1a transcripts. Intriguingly, miR-135a levels were upregulated following administration of 5HT-linked antidepressants. Mice expressing higher or lower levels of miR-135a demonstrated major alternations in anxiety and depression-like behaviors, 5HT levels, metabolism and behavioral response to antidepressant treatment. Finally, miR-135a levels in blood and brain of depressed human patients were significantly lower. Likewise, He and colleagues found that miR-124 was decreased after treatment with various types of antidepressants(52). Furthermore, Belzeaux *et al*, reported changes in the expression of several miRNAs (miR-20b, miR-433, miR-409, miR-485, miR-133a, miR-145 and miR-331) after antidepressant response(36).

Our group has conducted several studies looking at the role of microRNAs in major depression and antidepressant treatment. Using postmortem brain samples from depressed patients, we found an up-regulation of miR-185, a miRNA involved in the regulation of the *tropomyosin receptor kinase B* (TrkB), the preferred receptor of the brain-derived neurotrophic factor (BDNF) and a key player in the neurotrophic hypothesis of depression(26). In addition, we reported an up-regulation of four miRNAs (miR-320c, miR-195, miR-34c-5p and miR-139-5p) that regulate the expression of the polyamine genes SAT1 and SMOX3(28). These results are of interest given that we have previously reported decreased

TrkB, SAT1 and SMOX levels in depressed brains. Furthermore, using a high-throughput approach, we identified miR-1202, a primate-specific and brain-enriched miRNA that was decreased in brains from depressed individuals(29). We showed that miR-1202 regulates the expression of the glutamate metabotropic receptor 4 (GRM4), a class III glutamatergic receptor that was proposed as a new target for antidepressant development. We also found that expression levels of miR-1202 predicted AD treatment response, using blood samples from depressed patients. Moreover, a recent study focusing on a genetic variant in the GRM4 gene, within the binding site of miR-1202, provided additional evidence for an association between miR-1202, GRM4 and MDD(53). In a series of molecular and brain imaging follow-up studies, we found that changes in miR-1202 levels during antidepressant treatment were correlated with changes in brain activity(54). In addition, in two independent cohorts of depressed patients who received eight weeks of antidepressant therapy, responders to treatment displayed lower baseline miR-1202 levels compared to non-responders(50).

Finally, using small RNA-sequencing, we identified miR-146a-5p, miR-146b-5p, miR-24-3p and miR-425-3p as potential markers of antidepressant response(35). These results were replicated using two independent clinical trials of MDD, a well-characterized animal model of depression, and postmortem human brains from depressed patients. Using a combination of bioinformatics, mRNA studies and functional in vitro experiments, we showed significant dysregulation of genes involved in MAPK/Wnt signaling pathways. Interestingly, an independent study performed by Enatescu and colleagues, showed a consistent dysregulation of miR-146a-5p, miR-146b-5p, and miR-24-3p in peripheral samples from depressed patients before and after antidepressant treatment(55). Similarly, others have shown an association between these miRNAs and MDD in peripheral samples(36, 38, 45). In addition, we also reported an association of these microRNAs and the MAPK/Wnt signaling pathways. The results of our studies and others, suggest a potential role for miRNAs as a new venue for potential treatment of MDD. **Table 3** shows a summary of the most relevant findings from studies looking at miRNAs as biomarkers of treatment response. **Figure 1** highlights the most consistent findings across studies.

Future Directions

Despite the prevalence and burden of MDD, our understanding of the pathophysiology remains rudimentary. Several molecules reported to be dysregulated in MDD have been signaled as potential biomarkers, however, a validated biomarker has yet to be identified. Antidepressants are the most common treatment for MDD, yet roughly one third of patients experience an inadequate response to treatment after several attempts. This affects patient care, economic and social outcomes of MDD, and the development of new medication, as it occludes efficiency data of new molecules in clinical trials. Thus, there is a great need in not only identifying biomarkers of MDD but also those that can predict response to antidepressant treatment. In light of what has been described in this review, miRNAs have emerged as an important player in the pathophysiology of MDD and antidepressant treatment. Our findings and results from others support the hypothesis that 1) targeting miRNAs directly could be therapeutically beneficial for MDD, and 2) miRNAs are potential biomarkers of depression and its treatment. Several studies point at miRNAs as an ideal biomarker to study peripherally as they are excreted by cells and are stably transported through circulation in exosomes. However, important questions still remain about the validity of conducting expression studies in peripheral samples, sensitivity and specificity of biomarkers, source of biomarker signatures, mechanistic links between antidepressants and microRNAs, and new methodologies for reliable quantification.

One of the central questions is whether or not these studies are representative of gene changes taking place in the brain. This question is particularly important for investigating the etiological mechanisms using peripheral samples, such as those comparing lymphocyte expression patterns between cases and controls. On the other hand, peripheral studies of drug response have value beyond a proxy model of CNS phenomena, given that both peripheral and central processes are involved in the individual response to treatment(56-60). A few studies have assessed how representative peripheral expression studies are of CNS gene expression(61-63), and while there are important differences they also found significant similarities between the investigated peripheral tissues and brain material(61, 63).

These encouraging results suggest that when used cautiously and thoughtfully, peripheral-based expression studies may be a useful and practical surrogate for gene expression in the CNS. In addition, several lines of evidence suggest that MDD is a systemic illness(64, 65), so even if peripheral samples would not be good surrogates of the CNS, there is still value to study peripheral samples per se because we could detect peripheral processes that may be etiologically relevant to depression and contribute to antidepressant response, including side effect profiles. Ultimately, investigating gene functional changes associated with MDD, as well as the molecular factors regulating these changes, will provide valuable information to identify molecular mechanisms associated with MDD, as well as valid biomarkers, and novel treatment targets.

Furthermore, future studies will need to address the sensitivity and specificity of miRNAs, as well as their usefulness for early prediction. From the clinical application perspective identifying a single miRNA as a sole and reliable biomarker of depression is unrealistic. Thus, we need to shift our attention from individual biomarker signature studies to a more complex and realistic scenario of network regulation. As such, a more efficient strategy would be to develop a biomarker panel composed of several signatures including molecular, imaging, and clinical data to better dissect a complex mood disorder such as major depression. Another important issue is the source of a biomarker signature. The miRNA findings in peripheral blood samples of MDD subjects so far have been very exciting, and indicate the possibility of developing biomarkers in a non-invasive manner. Nevertheless, a lot more work is needed in this aspect, since miRNAs may be expressed differently in various blood cell types. In addition, whether miRNAs in a specific blood cell-type truly represent brain-derived miRNAs, is unclear at the present time. In this regard, measuring miRNAs in exosomes may be an alternate and better approach. It is also unclear how miRNA levels in the periphery and the brain interact during antidepressant treatment. It can be hypothesized that peripheral miRNAs may be able to reach the brain in free form or in microvesicles, based on studies that have shown that exosomes can cross the blood-brain barrier and deliver several molecules, including miRNAs(66, 67). Alternatively, changes observed in blood might

reflect neuroendocrine or neuroimmune responses elicited by the brain. Indeed, several miRNAs appear to modulate both immune and neuronal processes and may mediate the interaction between these systems. These exciting discoveries suggest that circulating miRNAs in humans may act as molecular signals between cells and tissues, and correlate with pathological states. There is also an urgent need to establish a mechanistic link between the effects of antidepressant treatment on miRNA expression to develop early diagnostic tools, preventive strategies, and effective pharmacological treatment for mood disorders. Finally, the techniques used to quantify miRNAs, which are still time-consuming, will have to be improved, both in terms of reproducibility, speed, cost, and standardization.

Conclusion

Overall, we believe miRNAs hold significant promise as biomarkers for depression and the use of peripheral tissues such as blood could be a valid and promising method of examining their dynamic role in mental disorders and their treatment but further research is still needed.

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Conflicts of Interest

Juan Pablo Lopez, Aron Kos and Gustavo Turecki declare no conflicts of interest.

Figure and Table Legends

Figure 1. MicroRNAs and antidepressant treatment. A number of selected miRNAs which were consistently identified in central and peripheral tissues in humans and rodents. Within the cell, miRNAs are transcribed from the genome as pri-miRNA transcripts. Through processing by the Drosha/DGCR8 complex a pre-miRNA transcript is transported to the cytosol. Here it is digested by Dicer and incorporated into the RNA induced silencing complex (RISC). These miRISC complexes can target mRNA transcripts leading to their cleavage or translational repression. Circulating miRNAs are excreted from cellular populations. These can occur in a number different complexes, namely high-density-lipoprotein (HDL), exosomes, microvesicles, or within miRNA silencing complexes (miRISC). The blue upward arrow denotes an increase while a red downward arrow denotes a decrease in the respective miRNA.

Table 1. Human postmortem. Studies in which microRNAs have been associated with major depression.

Table 2. Human peripheral samples. Studies in which microRNAs have been associated with major depression.

Table 3. Human peripheral samples. Studies in which microRNAs have been associated with response to antidepressant treatment.

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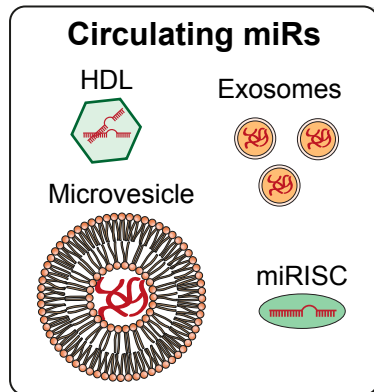
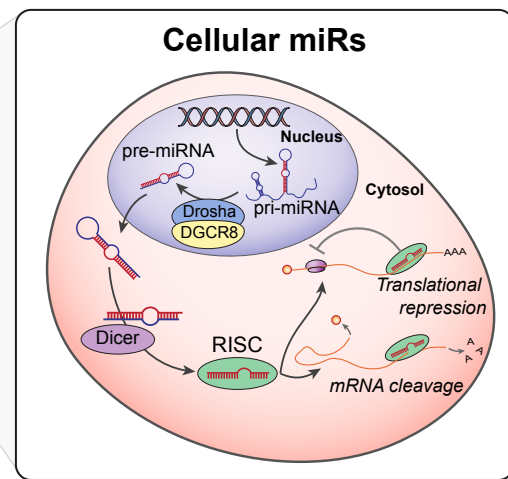
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Human

↑ **miR-1202**
Lopez, et al.

↑ **miR-135a, miR-16**
Issler, et al.

↑ **miR-1202**
Lopez, et al.
Fiori, et al.



↑ **miR-16**
Fiori, et al.
Baudry, et al.
Lunay, et al.

↑ **miR-135a**
Issler, et al.
Fiori, et al.

↓ **miR-146a-5p, miR-146b-5p, miR-24-3p, miR-425-3p**
Enatescu, et al., Lopez et al.

↓ **miR-124**
He, et al.



Rodent

Table 1. Human postmortem. Studies in which microRNAs have been associated with major depression.

MicroRNA	Brain Region	Quantification Method	Sample Size (n)	Criteria	Results	Study
miR-106b, miR-212, miR-24, miR-30e, miR-20b, miR-26b, miR-29a, miR-29b, miR-29c, miR-30a-5p, miR-30b, miR-30d, miR-195, miR-9-3p, miR-7, miR-92	Frontal cortex (BA9)	Microarray	36	SCZ vs Controls	1 miRNAs upregulated and 15 downregulated in Schizophrenia	Perkins et al, 2007
miR-142-5p, miR-137, miR-489, miR-148b, miR-101, miR-324-5p, miR-301a, miR-146a, miR-335, miR-494, miR20b, miR-376a, miR-190, miR-155, miR-660, miR-130a, miR-27a, miR-497, miR-10a, miR-20a, miR-142-3p	Frontal cortex (BA9)	qPCR-based Array	35	MDD vs Controls	21 miRNAs downregulated in MDD	Smalheiser et al, 2012
miR-185	Anterior prefrontal cortex (BA10)	Microarray and qPCR	63	MDD vs Controls	1 miRNA upregulated in MDD	Maussion et al, 2012
miR-508-3p, miR-152-3p	Anterior prefrontal cortex (BA10)	qPCR-based Array	30	MDD vs Controls	2 miRNAs downregulated in MDD	Smalheiser et al, 2014
miR-34c-5p, miR-139-5p, miR-195, miR-320c	Ventrolateral prefrontal cortex (BA44)	qPCR	31	MDD vs Controls	4 miRNAs upregulated in MDD	Lopez et al, 2014
miR-1202	Ventrolateral prefrontal cortex (BA44)	Microarray and qPCR	104	MDD vs Controls	1 miRNA downregulated in MDD	Lopez et al, 2014
miR-511, miR-340	Basolateral amygdala (BLA)	qPCR	37	MDD vs Controls	2 miRNAs upregulated in MDD	Maheu et al, 2015
miR-326	Midbrain	qPCR	13	MDD vs Controls	1 miRNA downregulated in MDD	Aschrafi et al, 2016
miR-34a	Anterior cingulate cortex (BA24)	qPCR	29	MDD vs Controls	1 miRNA downregulated in MDD	Azevedo et al, 2016
miR-218	Ventrolateral prefrontal cortex (BA44)	qPCR	82	MDD vs Controls	1 miRNA downregulated in MDD	Torres-Berrio et al, 2017
miR-124	Dorsolateral prefrontal cortex (BA46)	qPCR	30	MDD vs Controls	1 miRNA upregulated in MDD	Roy et al, 2017
miR-146a-5p, miR-146b-5p, miR-24-3p, miR-425-3p	Ventrolateral prefrontal cortex (BA44)	qPCR	52	MDD vs Controls	4 miRNAs upregulated in MDD	Lopez et al, 2017

BA Brodmann Area, *SCZ* Schizophrenia, *MDD* Major Depressive Disorder, *qPCR* Quantitative Polymerase Chain Reaction.

Table 2. Human peripheral samples. Studies in which microRNAs have been associated with major depression.

MicroRNA	Tissue Source	Quantification Method	Sample Size (n)	Criteria	Results	Study
miR-589, miR-579, miR-941, miR-133a, miR-494, miR-107, miR-148a, miR-652, miR-425-3p, miR-517b, miR-636, miR-1243, miR-381, miR-200c	PBMCs	Microarray	29	MDD vs Controls	9 miRNAs upregulated and 5 downregulated in MDD	Belzeaux et al. 2012
miR-146a, miR-212	Blood Monocytes	qPCR-based Array	60	Postpartum Psychosis (PP) vs Controls	2 miRNAs downregulated in PP	Weigelt et al. 2013
miR-266, miR-1972, miR-4485, miR-4498, miR-4743	PBMCs	Microarray	127	MDD vs Controls	5 miRNAs upregulated in MDD	Fan et al, 2014
miR-1202	Whole Blood	qPCR	50	MDD vs Controls	1 miRNA downregulated in MDD	Lopez et al, 2014
miR-221-3p, miR-34a-5p, Let-7d-3p	CSF, Serum	qPCR-based Array	65	MDD vs Controls	3 miRNAs upregulated in MDD	Wan et al, 2015
miR-16	CSF	qPCR	66	MDD vs Controls	1 miRNA downregulated in MDD	Song et al, 2015
miR-132	Whole Blood	qPCR	60	MDD vs Controls	1 miRNA upregulated in MDD	Su et al, 2015
miR-320a	Plasma	qPCR	91	MDD vs Controls	1 miRNA downregulated in MDD	Camkurt et al, 2015
miR-34b-5p, miR-34c-5p	Blood Leukocytes	qPCR	64	MDD vs Controls	2 miRNAs upregulated in MDD	Sun et al, 2016
Let-7a-5p, Let-7d-5p, Let-7f-5p, miR-24-3p, miR-425-3p, miR-140-3p, miR-30d-5p, miR-330-5p, miR-378a-5p, miR-21-3p, miR-330-3p, miR-345-5p	Whole Blood	Microarray	60	MDD, BPD vs Controls	5 miRNAs in MDD, 5 miRNAs in BPD, 2 miRNAs both MDD and BPD	Maffioletti et al, 2016
Let-7b, Let-7c	Whole Blood	Microarray, qPCR	60	MDD vs Controls	2 miRNAs downregulated in MDD	Gururajan et al, 2016
miR-132	Whole Blood	qPCR	135	MDD vs Controls	1 miRNA upregulated in MDD	Liu et al, 2016

PBMCs Peripheral Blood Mononuclear Cells, *MDD* Major Depressive Disorder, *PP* Postpartum Psychosis, *CSF* Cerebral Spinal Fluid, *BPD* Bipolar Disorder, *qPCR* Quantitative Polymerase Chain Reaction.

Table 3. Human peripheral samples. Studies in which microRNAs have been associated with response to antidepressant treatment.

MicroRNA	Tissue Source	Quantification Method	Treatment	Duration	Sample Size (n)	Criteria	Results	Study
miR-130b, miR-505, miR-29-b, miR-26b, miR-22, miR26a, miR-664, miR-494, Let-7d, Let-7g, Let-7e, Let-7f, miR-34c-5p, miR-629, miR-106b, miR-103, miR-191, miR-128, miR-502-3p, miR-374b, miR-132, miR-30d, miR-500, miR-770-5p, miR-589, miR-183, miR-574-3p, miR-140-3p, miR-335, miR-361	Whole Blood	qPCR-based Array	Escitalopram (SSRI)	12 Weeks	10	RES vs NRES	28 miRNAs upregulated and 2 downregulated after treatment	Bocchio-Chiavetto, 2012
miR-20b-3p, miR-433, miR-409-3p, miR-410, miR-485-3p, miR-133a, miR-145, miR-331-5p	PBMCs	Microarray	Personalized Treatment	8 Weeks	9	RES vs NRES	7 miRNAs upregulated and 1 downregulated after treatment	Belzeaux et al. 2012
miR-1202	Whole Blood	Microarray and qPCR	Citalopram (TCA)	8 Weeks	32	REM vs NRES	Upregulated after treatment	Lopez et al, 2014
miR-135a	Whole Blood	qPCR-based Array & qPCR	CBT or Escitalopram (SSRI)	12 Weeks	24	RES vs NRES	Upregulated after treatment	Issler et al, 2014
miR-124	PBMCs	qPCR	Personalized Treatment	8 Weeks	32	RES vs NRES	Downregulated after treatment	He et al, 2016
miR-146a-5p, miR-146b-5p, miR-24-3p, miR-425-3p	Whole Blood	Small RNA Sequencing	Duloxetine (SNRI), Escitalopram (SSRI), Nortriptyline (SNRI) or Placebo	8 Weeks	477	RES vs NRES	Downregulated after treatment	Lopez et al, 2017
miR-146a-5p, miR-146b-5p, miR-24-3p	Plasma	Small RNA Sequencing	Escitalopram (SSRI)	8 Weeks	158	RES vs NRES	Downregulated after treatment	Lopez et al, 2017
miR-146a-5p, miR-146b-5p, miR-24-3p,	Plasma	qPCR-based Array	Escitalopram (SSRI)	12 Weeks	5	RES vs NRES	Downregulated after treatment	Enatescu et al, 2017
miR-503-3p, 215-5p, 3074-5p, 1180-3p, 324-5p, 6750-3p, 6511a-3p, 361-5p, 3173-5p, miR-2110, miR-3605-3p, miR-6881-3p, miR-30e-5p, miR-423-3p, miR-361-3p, miR-3184-5p, miR-636	Whole Blood	Small RNA Sequencing	Duloxetine (SNRI) or Placebo	8 Weeks	124	RES vs NRES	11 miRNAs upregulated and 7 downregulated after treatment	Lopez et al, 2017
miR-1202	White Blood Cells	qPCR	Escitalopram (SSRI) or Desvenlafaxine (SNRI)	8 Weeks	55	RES vs NRES	Upregulated after treatment	Fiori et al, 2017
miR-16, miR-1202, miR-135a	Whole Blood	High-sensitivity standard flow cytometer (Firefly BioWorks)	Duloxetine (SNRI)	8 Weeks	124	RES vs NRES	Upregulated after treatment	Fiori et al, 2017

SSRI Selective serotonin reuptake inhibitor, TCA Tricyclic antidepressants, SNRI Serotonin–norepinephrine reuptake inhibitor, RES Responders, REM Remitters, NRES Nonresponders, PBMCs Peripheral Blood Mononuclear Cells, MDD Major Depressive Disorder, qPCR Quantitative Polymerase Chain Reaction.