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The microRNA profile of brain-derived extracellular vesicles: A promising step forward in developing pharmacodynamic biomarkers for psychiatric disorders

Mojtaba Oraki Kohshour [a,b], Urs Heilbronner [a], Thorsten Mueller [a], Moritz Rossner [c], Sergi Papiol [a,d,*], Thomas G. Schulze [a,e,f]

[a] Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich 80336, Germany
[b] Department of Immunology, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[c] Section of Molecular Neurobiology, Department of Psychiatry and Psychotherapy, LMU University Hospital, LMU Munich, Munich 80336, Germany
[d] Max Planck Institute of Psychiatry, Munich 80804, Germany
[e] Department of Psychiatry and Behavioral Sciences, Norton College of Medicine, SUNY Upstate Medical University, Syracuse, NY, USA
[f] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, Baltimore, MD, USA

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ABSTRACT

MicroRNAs (miRNAs) have the potential to affect drug metabolism, and some drugs affect cellular miRNA expression. miRNAs are found inside extracellular vesicles (EVs), and the profile of these EV-miRNAs can change across different diseases and disease states. Consequently, in recent years EV-miRNAs have attracted increasing attention as possible non-invasive biomarkers. For example, analyzing the miRNA expression profile of brain-derived EVs in blood may allow us to non-invasively assess miRNA dysregulation and thus to gain knowledge about the pathophysiology of psychiatric disorders and identify potential new predictive targets. We searched PubMed for all studies related to the effects of psychiatric medications on EV-miRNAs and identified 14 relevant articles. Taken together, findings indicate that certain EV-miRNAs may be targets for psychiatric medications and that antipsychotics such as olanzapine and antidepressants such as fluoxetine may alter the expression levels of particular EV-miRNAs. If confirmed and replicated, these findings may lead to the suggested miRNA profiles being used as pharmacodynamic biomarkers. However, heterogeneities and uncertainties remain regarding the role of EV-miRNAs in psychiatric disorders and their interaction with neuronal gene expression and drugs. This minireview summarizes some of the findings on the effects of psychiatric medications on EV-miRNAs and describes the potential role of EV-miRNAs as pharmacodynamic biomarkers for psychiatric disorders.

1. Introduction

1.1. Relevance of microRNAs

Eukaryotic genes are regulated at the post-transcriptional level through an RNA interference process, an evolutionary conserved mechanism of gene silencing that regulates gene expression and function (Carthew and Sontheimer, 2009; Terasawa et al., 2011). The central RNA interference players include 18- to 25-nucleotide non-coding RNA molecules known as microRNAs (miRNAs), which may make up 2% of mammalian genomes (Koturbash et al., 2015; Terasawa et al., 2011). As a class of small, single-stranded RNAs, miRNAs are bioactive molecules that can epigenetically regulate gene expression in cells (Funahashi et al., 2023; Nedaeinia et al., 2017).

According to the latest version of the miRBase database (v22.1) (www.mirbase.org), the human genome contains 1917 annotated precursors and 2654 mature sequences of miRNAs that regulate thousands of protein-coding genes (Kozomara et al., 2019). More than 30% of human genes are estimated to be targets of miRNAs, indicating that miRNAs have extensive effects on the transcriptome and proteome (Yao et al., 2019). About 70% of all miRNAs in the human body are found in the central nervous system, where they play important roles in controlling neurogenesis and neuroplasticity by affecting messenger RNA function in the brain (Barnett et al., 2023; Oraki Kohshour et al., 2023). In brain cells, dysregulation of miRNAs affects synaptic plasticity and is associated with major psychiatric disorders (Amoah et al., 2020; Barnett

* Corresponding author at: Institute of Psychiatric Phenomics and Genomics (IPPG), LMU University Hospital, LMU Munich, Munich 80336, Germany.
E-mail address: Sergi.Papiol@med.uni-muenchen.de (S. Papiol).

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et al., 2023; Estévez-Cabrera et al., 2023). For instance, miRNA expression profiling of the superior temporal gyrus and dorsolateral prefrontal cortex showed a significant increase in global miRNA expression in schizophrenia (SCZ) (Beveridge et al., 2010).

The role of miRNAs as post-transcriptional regulators of gene expression has attracted increasing interest in the past decade because this role may make miRNAs suitable as therapeutic biomarkers or potential targets in a range of conditions, including psychiatric disorders (O'Connor et al., 2012). Some miRNAs have been shown to have antidepressant actions. A study on a chronic mild stress model in mice reported that miRNA-207 (miR-207) from EVs derived from natural killer cells mitigated symptoms of depression (Li et al., 2020). The suggested molecular mechanism behind this effect involves targeting the Toll-like receptor 4 (TLR4) interactor and blocking the nuclear factor kappa B (NF-κB) signaling pathway in astrocytes (Li et al., 2020). Furthermore, medications such as fluoxetine (FLX) have been shown to impact miRNA expression profiles, and research has found that miRNAs may affect the metabolism of medications such as olanzapine (Koturbash et al., 2015; Santarelli et al., 2013). Accordingly, specific miRNA profiles may contribute to drug resistance in individuals with a particular drug-resistance phenotype (Pérez-Rodríguez et al., 2023).

1.2. Extracellular vesicles

As tiny intercellular messengers, extracellular vesicles (EVs) are membrane-bound nanoparticles that are secreted by most cell types (Samanta et al., 2018). They are found in numerous bodily fluids, including plasma and serum, cerebrospinal fluid, and urine, and play a role in physiological and pathological functions through cell-to-cell communication and long-range signaling processes (Conlan et al., 2017; Kano et al., 2021). EV cell-to-cell communication transfers diverse bioactive molecules, such as proteins and miRNAs, from the origin (parent) cells to recipient cells (Kano et al., 2021). When they arrive at the recipient cells, EVs merge with the plasma membrane and release their cargo, and miRNA they deliver (EV-miRNAs) may post-transcriptionally suppress target genes (Amoah et al., 2020). When introduced into brain cells, EV-miRNAs may impact the expression of important genes linked to neuronal pathways and synaptic activity and ultimately play a role in the etiology of mental disorders (Amoah et al., 2020).

In the central nervous system, neurons and glia produce EVs in response to pathophysiological stimuli, allowing these cells to exchange chemical signals that regulate distinct physiological processes, such as synaptic plasticity, a process referred to as generalized cross-talk (Barnett et al., 2023; Caruso Bavisotto et al., 2019; Cioanca et al., 2023). According to in vitro and in vivo (i.e., mouse model) research, neuron-derived EV (NDEV)-miRNAs alter expression of the glutamate receptor GLT1 in astrocytes (Morel et al., 2013), and Schwann cells provide trophic support by using EVs to transfer resources to damaged axons (Lopez-Verrilli and Court, 2012). Moreover, research has indicated that neurons may use EVs to eliminate unwanted products (Caruso Bavisotto et al., 2019).

1.3. EV-miRNAs in psychopharmacology

Alterations in the expression profile of miRNAs within cells and subsequently within EVs may have implications for the use of EV-miRNAs as biomarkers to determine the efficacy of drugs (Amoah et al., 2020; Hung et al., 2021; Koturbash et al., 2015). In individuals with first-episode, drug-naïve SCZ, serum-derived EV-miRNAs appear to be useful for diagnosing treatment resistance (Du et al., 2019). Furthermore, the analysis of miRNAs in NDEVs from the blood of individuals with major depressive disorder (MDD) offers a new and non-invasive way to assess molecular changes associated with treatment effectiveness (Saeedi et al., 2021). Therefore, analyzing the contents of brain-derived EVs (BDEVs) in the blood of individuals with psychiatric disorders may represent a potential non-invasive approach to obtain information on the gene expression profiles of brain cells, e.g., misexpression of miRNAs. Such an approach may deepen our understanding of the pathophysiology of psychiatric disorders and reveal new pharmacological interventions for them (Fig. 1) (Amoah et al., 2020; Funahashi et al., 2023).

In this vein, this article reviews and summarizes research on the effects of psychiatric medications on EV-miRNAs with the aim to highlight the potential of EV-miRNAs, in particular BDEV-miRNAs, as pharmacodynamic biomarkers for psychiatric disorders.

2. Method

To identify all types of studies that investigated the effects of psychiatric medications on EV-derived miRNAs (the inclusion criterion), we performed a literature search in PubMed, the most widely used search platform for medical literature and largest bibliographic index for the life sciences (Misra and Ravindran, 2022; Willinsky and Quint-Rapoport, 2007). We included articles published in English by the end of August 2024 and excluded studies on miRNAs not derived from EVs. Because antipsychotics, antidepressants, mood stabilizers, and benzodiazepines are the most common classes of psychiatric medications, our search used the following strings: i) extracellular vesicle OR exosome AND miRNA AND antipsychotic (7 hits); (ii) extracellular vesicle OR exosome AND miRNA AND antidepressant (18 hits); iii) extracellular vesicle OR exosome AND miRNA AND "mood stabilizer" (0 hits); and iv) extracellular vesicle OR exosome AND miRNA AND benzodiazepine (1 hits). We also searched PubMed by using the name of the most current medications in each category (e.g., olanzapine, haloperidol, and quetiapine as antipsychotics; FLX, citalopram, and sertraline as antidepressants; lithium and lamotrigine as mood stabilizer; and clonazepam, diazepam, and alprazolam as benzodiazepine); however, this search yielded only one additional relevant article (related to lithium). After narrowing down the search results, we identified 13 publications that were duplicates, not relevant to the topic of interest, or were types of review articles that did not contain additional information, leaving a total of 14 (including the lithium-related one) relevant articles.

3. Results

Table 1 shows some of the EV-miRNAs associated with psychiatric medications and the potential role of these EV-miRNAs as biomarkers. The main findings of the reviewed studies are presented according to medication type below:

3.1. Antipsychotics and EV-miRNAs

Tsoporis et al. (Tsoporis et al., 2022) found that in individuals with SCZ, executive functioning deficits correlate with both higher levels of reactive oxygen species and lower levels of antioxidant-related proteins, and they hypothesized that this so-called redox imbalance is involved in the pathogenesis of the disorder. The multifunctional protein DJ-1 (Parkinson's disease protein 7 [PARK7]) protects neurons from oxidative damage caused by reactive oxygen species and has an antioxidant role in Parkinson disease and other diseases that involve neurodegeneration, and the 3′ untranslated region of DJ-1 mRNA is targeted by miR-203a-3p (Tsoporis et al., 2022). In this study, at baseline blood-derived EVs of individuals with first-episode antipsychotic-naïve SCZ ($n = 11$ cases) showed lower levels of DJ-1 mRNA and protein and higher levels of miR203a-3p than healthy controls (HC; $n = 10$), but after six weeks of olanzapine treatment, miR203a-3p and DJ-1 in blood-derived EVs from the individuals with SCZ were restored to the levels observed in the HC.

An in vitro cell line-based study on SH-SY5Y cells—a cloned subline of a neuroblastoma cell—found that miR-675–3p was upregulated in SH-SY5Y–derived EVs treated with clozapine (Funahashi et al., 2023).

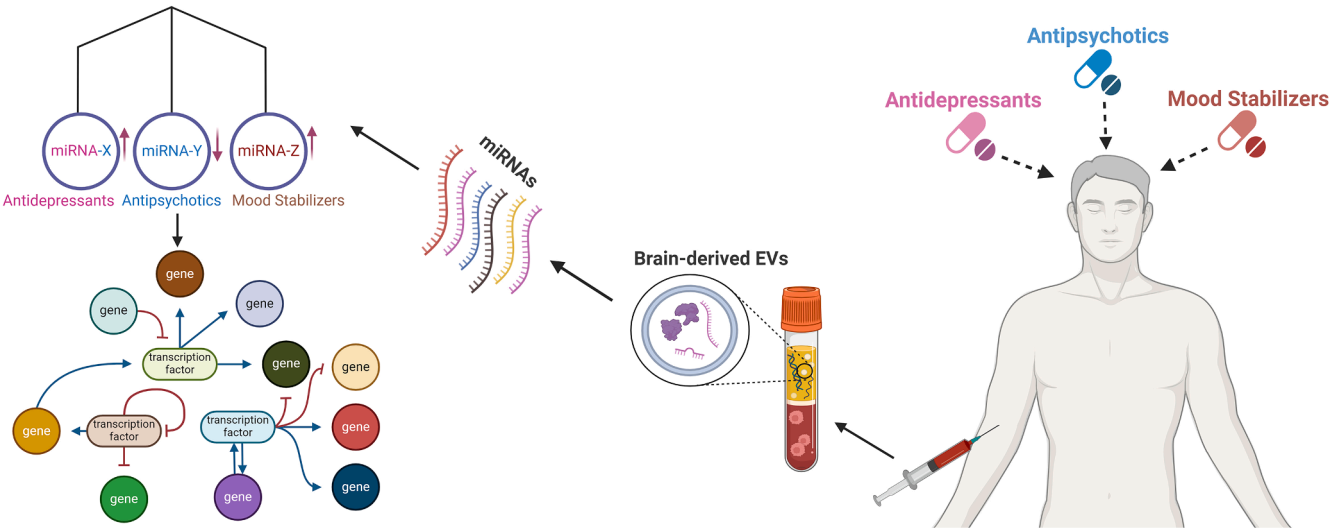

Fig. 1. Analysis of profiles of microRNAs in brain-derived extracellular vesicles in blood may represent a pharmacodynamic biomarker approach for evaluating psychiatric disorders and their treatment. By analyzing the microRNA (miRNA) expression profile in brain-derived extracellular vesicles and interpreting the involved signaling pathways in target cells, we may be able to non-invasively evaluate how psychiatric medications affect miRNAs. This ability would further our understanding of miRNA expression profiles and their potential use as pharmacodynamic biomarkers for mental health disorders. (Created with BioRender.com).
EVs, extracellular vesicles; miRNA, microRNA

Table 1
microRNAs in extracellular vesicles that may be pharmacodynamic biomarkers for psychiatric disorders.

Disorder	Sample size	EV source	miRNAs	Medication (Type)	Effect	Author, year
SCZ	–	SH-SY5Y cells	miR–675–3p	Clozapine (Antipsychotic)	Clozapine upregulated miR–675–3p	Funahashi et al., 2023 (Funahashi et al., 2023)
SCZ	11 FEP antipsychotic-naïve cases, 10 HC	Plasma	miR-203a-3p	Olanzapine (Antipsychotic)	miR203a-3p returned to normal levels with olanzapine treatment	Tsoporis et al., 2022 (Tsoporis et al., 2022)
SCZ BD	–	Culture of mouse cortical neurons and astrocytes	miR-223	Olanzapine, Haloperidol (Antipsychotic)	Olanzapine and haloperidol changed the expression of miR-223 in a cell-specific manner	Amoah et al., 2019 (Amoah et al., 2020)
MDD	31 cases	Serum	miR-1202	Paroxetine, Sertraline, Escitalopram (Antidepressant)	Lower level of miR-1202 was associated with higher sensitivity to antidepressants	Han et al., 2024 (Han et al., 2024)
Depression (CUMS rat model)	24 three-month-old male Wistar rats	Plasma	miR-16, miR-21, miR-146a, miR-223	Fluoxetine (Antidepressant)	Fluoxetine increased the expression of miR-16, miR-21, miR-223, and miR-146a	Estévez-Cabrera et al., 2023 (Estévez-Cabrera et al., 2023)
MDD	20 responders[a], 20 non-responders, 20 HC	Plasma-derived NDEVs	miR–21–5p, miR-30d-5p, miR486–5p	Escitalopram (Antidepressant)	Changes in the levels of miR–21–5p, miR-30d-5p, and miR486–5p were associated with the response to escitalopram	Saeedi et al., 2021 (Saeedi et al., 2021)
MDD	52 MDD, 31 HC	Serum	let-7e, miR–21–5p, miR-223, miR-145, miR-146a, miR-155	Various antidepressants	Acceptable discrimination between remission and non-remission groups was shown by pre-treatment levels of let-7e, miR-146a, and miR-145	Hung et al., 2021 (Hung et al., 2021)

[a] Responders to escitalopram treatment
BD, bipolar disorder; CUMS, chronic unpredictable mild stress; EV, extracellular vesicle; FEP, first-episode psychosis patients; HC, healthy controls; MDD, major depressive disorder; miRNA, microRNA; NDEV, neuron-derived extracellular vesicles; SCZ, schizophrenia.

This miRNA may control apoptosis by regulating genes linked to the immune system. One target of miR-675–3p is Myocyte Enhancer Factor 2C (*MEF2C*), which has been reported to be a risk gene for SCZ (Funahashi et al., 2023). Cultures of mouse cortical neuronal cells and astrocytes revealed that olanzapine and haloperidol induce a decrease in miR-223 expression in NDEVs and an increase in astrocyte-derived EVs (Amoah et al., 2020). Individuals with psychosis due to SCZ or bipolar disorder appear to have a significant increase in miR-223 in the orbitofrontal cortex and plasma (Amoah et al., 2020; Zhao et al., 2019). MiR-223 targets glutamate ionotropic receptors, including N-methyl-D-aspartate-type subunit 2B (coded by *GRIN2B* or *NR2B*) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid-type subunit 2 (coded by *GRIA2* or *GLUR2*) (Amoah et al., 2020; Zhao et al., 2019). Because miR-223 is a significant regulator of *GLUR2* and *NR2B* expression and its secretion in EVs can be controlled by antipsychotics, it may be useful in treating excitotoxic neuronal disorders (Amoah et al., 2020; Harraz et al., 2012).

According to the study by Tu et al. (Tu et al., 2024), miR-486–5p in plasma-derived EVs may be responsible for the interindividual differences in how olanzapine affects insulin sensitivity. The results of the study showed that olanzapine directly causes overexpression of miR-486–5p, which in turn is linked to impaired insulin-dependent glucose absorption. Furthermore, the authors proposed that elevated levels of EV-miR-486–5p indicate a higher risk of developing insulin resistance as an adverse effect of olanzapine.

3.2. Antidepressants and EV-miRNAs

Alterations in the expression of three NDEV-derived miRNAs were shown to predict response to antidepressants (Saeedi et al., 2021). In NDEVs from plasma of individuals with MDD (20 responders, 20 non-responders) and 20 HC, changes in the levels of miR-21–5p, miR-30d-5p, and miR486–5p were found to be associated with the response to escitalopram (area under the curve [AUC], 0.8254; specificity, 84%; sensitivity, 76%). These miRNAs appear to control the mitogen-activated protein kinase pathway, which has been linked to the effectiveness of antidepressants (Saeedi et al., 2021). In addition, evaluation of serum-derived EVs from individuals with MDD who were treated with different antidepressants for six weeks indicated that downregulation of miR-1202 expression may be associated with improved treatment response (Han et al., 2024a).

The antidepressant effect of FLX was examined in a study on plasma-derived EVs from rats that underwent six weeks of chronic unpredictable mild stress (CUMS) (Estévez-Cabrera et al., 2023). The results showed that CUMS reduced the expression of miR-16, miR-21, miR-223, miR-144, and miR-155, all of which are involved in modulating neuroinflammation. Furthermore, administration of FLX (CUMS + FLX group), which has anti-inflammatory and antioxidant effects (Estévez-Cabrera et al., 2023), increased the expression of miR-16, miR-21, miR-223, and miR-146a. A different study on CUMS rats compared the miRNAs in serum-derived EVs between the CUMS + FLX and CUMS + Vehicle groups and found 18 upregulated miRNAs (e.g., miR-1b) and 11 downregulated miRNAs (e.g., miR-122–5p) in the former group (Fang et al., 2020). Some of these miRNAs are involved in neuroplasticity and the stress response (Fang et al., 2020). FLX may control serotoninergic neurotransmission and neuroinflammatory processes by regulating miRNA expression, particularly that of miR-16, which has a role in serotonin transporter expression, stress, and inflammation (Estévez-Cabrera et al., 2023). Part of the anti-inflammatory actions of FLX and the influence of FLX on serotonin transporter expression may be reflected in the alterations of the miRNA profile in blood-derived EVs (Estévez-Cabrera et al., 2023).

Another study aimed to determine the potential of EV-miRNAs to predict antidepressant response in individuals with MDD ($n = 52$) by focusing on serum-derived EV-miRNAs involved in the TLR4 signaling pathways (as negative regulatory miRNAs that prevent TLR-induced cytokine storms), including let-7e, miR-21–5p, miR-223, miR-145, miR-146a, and miR-155 (Hung et al., 2021). Individuals with MDD were given one of a range of antidepressants, depending on their clinical characteristics. The findings indicated that the antidepressants upregulated the miRNAs and that pre-treatment levels of let-7e, miR-21–5p, miR-145, miR-146a, and miR-155 were significantly lower in the remission group than in the non-remission group. Furthermore, acceptable discrimination between the remission and non-remission groups was shown by let-7e, miR-146a, and miR-145 (AUC = 0.789, 0.759, and 0.711, respectively). The authors suggested that the pre-treatment levels of these EV-miRNAs can be used to predict whether antidepressants will lead to remission (Hung et al., 2021). In contrast, another study found that levels of various miRNAs, including miR-26a, miR-494, miR-30c, and miR-101, in plasma-derived EVs of individuals with depression were the same before and after escitalopram treatment (Homorogan et al., 2021).

The results of a study that investigated whether antidepressant treatment affects the relationship between brain structural variations and serum-derived EV-miR-146a-5p in individuals with MDD suggested that antidepressant treatment may lessen the impact of this miRNA on cortical atrophy (Deng et al., 2023). Furthermore, a different study showed that reduced levels of serum-derived EV-miR-1202 in individuals with MDD are linked to aberrant Brodmann area 44 connectivity in the striatal-thalamic region and that the antidepressant-related reduction of connectivity in this region is dependent on miR-1202 levels (Han et al., 2024b). A study by Kim et al. (Kim et al., 2022) introduced serum-derived EV-miR-137 as an miRNA with high potential as a diagnostic biomarker for methamphetamine abstinence syndrome and showed that antidepressant treatment did not affect the reduction in miR-137 resulting from methamphetamine abstinence.

3.3. Mood-stabilizers and EV-miRNAs

A study that used EVs derived from mesenchymal stem cells in a stroke mouse model showed that preconditioning the cells with lithium altered the levels of several EV-miRNAs; for example, the study found a significant increase in miR-1906, which has been identified as a new regulator of the TLR4 (Haupt et al., 2021). TLR4 downregulation by such EVs subsequently suppresses the NF-κB signaling pathway and inflammation (Haupt et al., 2021). New therapeutic approaches in mental disorders, which involve neuroinflammation, may take advantage of this anti-inflammatory effect of lithium (Dunn et al., 2020).

4. Discussion

In this minireview, we highlighted the findings of studies on the effects of psychiatric medications on EV-miRNAs and thereby focused on the possible use of EV-miRNAs as pharmacodynamic biomarkers for psychiatric disorders.

The role of EV-miRNAs in psychiatric disorders, their interactions with neuronal gene expression, and their responses to treatment are still poorly understood (Amoah et al., 2020). Antipsychotics and antidepressants appear to be able to regulate miRNA expression, thereby reversing effects previously induced by miRNAs, such as downregulation of the glutamate receptor gene (Amoah et al., 2020; Sarkami et al., 2023). A possible way to decipher the biomarker role of miRNAs in pharmaceutical approaches to treating brain disorders may be to analyze BDEV-derived miRNAs in responder and non-responder phenotypes while accounting for environmental factors and other relevant covariates.

One of the controversial topics in EV research is the evaluation of BDEVs in the periphery. For example, there appears to be some degree of uncertainty regarding how to use the specific surface markers of EVs to determine the cell type from which the EV originated (Norman et al., 2021; Théry et al., 2018; Younas et al., 2022). There is also a lack of standardization with regard to techniques for isolating pure populations of BDEVs from blood (Théry et al., 2018; Younas et al., 2022). In addition, some miRNAs are transported also outside of EVs and are present in the other blood compartments, so researchers must pay close attention to the sensitivity and purity rate of EV isolation techniques to enable accurate interpretation of results related to the EV cargo (Homorogan et al., 2021; Théry et al., 2018). To isolate BDEVs from the blood and determine the signaling pathways within brain cells, more sophisticated and integrated EV isolation methods appear to be required. If the above issues are solved, BDEV analysis holds unprecedented promise because—in contrast to the findings from other peripheral EVs, which may or may not be useful in describing brain processes—it can provide reliable and detailed information about the current biochemical states of brain cells (Saeedi et al., 2021). miRNAs usually work in concert to inhibit targets and control molecular pathways, and the miRNA-gene regulatory network may be more complex when many miRNAs regulate the same gene (estimates indicate that a single miRNA can influence more than 200 messenger RNAs) (Koturbash et al., 2015; Saeedi et al., 2021). For this reason, interpretation of the detected regulatory networks requires both improved algorithms to profile miRNAs identified in next-generation sequencing data and smart strategies based on significant miRNA profiles and their interaction networks. Accordingly, by determining all functional endogenous molecular sponges of miRNAs that may affect the regulation of mRNA expression, we may be able to increase the reliability of diagnostic and therapeutic biomarker panels predicated from the activity and network of “competitive endogenous RNA” (ceRNA) (Du et al., 2023; Salmena et al., 2011). By using

cutting-edge molecular techniques to engineer cell lines that generate and release EVs containing the desired miRNAs (e.g., lentiviral transduction of miR34a into the HEK293T cell line genome, which causes loading of miR34a into the secreted EVs (Sarkami et al., 2023)), we may be able to study the impacts of specific miRNAs on the cellular and molecular mechanisms involved in the response to medications.

The major limitation of this minireview is that we only searched for literature in the PubMed database; widening our search to include additional databases may have yielded more than the 14 relevant papers we identified.

5. The integrative findings and conclusion

Our findings indicate that there is still a lack of replicated research on the association of psychiatric medications with EV-miRNAs in terms of the pharmacodynamic biomarker role of these miRNAs. As shown in Table 1, findings vary and were obtained in different situations. Certain EV-miRNAs have been introduced as potential targets for psychiatric medications; however, the respective findings need to be replicated. A common message from the few currently available studies is that psychiatric medications appear to have the potential to change EV-miRNAs expression and that such changes may contribute to their therapeutic effects (i.e., to better or worse treatment response). For example, pretreatment levels of specific EV-miRNAs could be an indication for clustering the patients based on drug response. Future studies may provide a deeper understanding of the biomarker role of BDEV-miRNAs in relation to the degree of response to a particular psychiatric medication, or to the lack thereof. Such studies should address a variety of demographic and clinical variables, physiological and pathological circumstances, and environmental stimuli that may influence EV biogenesis and their cargo loading within parent cells. However, to date we are still unable to confidently isolate a pure subgroup of EVs (e.g., astrocyte- or oligodendrocyte-derived EVs). Additionally, researchers should not overlook the significance of other non-coding RNAs because changes in such RNAs can impact the expression and activity of miRNAs. Thus, future studies should thoroughly investigate each potential RNA involved in the response to psychiatric medications to introduce valid RNA profiles in this regard.

Overall, defining replicated and validated BDEV-miRNA profiles for psychiatric medications may help to improve indication-based guidelines for treating mental health disorders more effectively, which in turn would promote patient health and reduce additional expenses to healthcare systems. Researching the therapeutic and biomarker potential of BDEV-miRNAs in psychiatric disorders by performing studies with large sample sizes and advanced designs, applying comprehensive approaches to evaluate the relevant players, and decoding the intercellular cross-talk between these players may result in the development of more valid biomarkers and of potent medications that target certain molecules and have high therapeutic efficiency and fewer adverse effects.

CRediT authorship contribution statement

Mojtaba Oraki Kohshour: Conceptualization, Investigation, Writing - original draft, and Writing – review & editing. **Urs Heilbronner:** Writing – review & editing. **Thorsten Mueller:** Writing – review & editing. **Moritz Rossner:** Writing – review & editing. **Sergi Papiol:** Supervision and Writing – review & editing. **Thomas G. Schulze:** Supervision, Funding acquisition, Project administration, and Writing - review & editing.

Declaration of competing interest

The authors declare that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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