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Extracellular vesicles as a promising tool in neuropsychiatric pharmacotherapy application and monitoring

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Abstract:	This review deals with the application of extracellular vesicles (EVs) in the treatment of various neuropsychiatric disorders, including mood disorders, neurodegeneration, psychosis, neurological insults and injuries, epilepsy and substance use disorders. The main challenges of most neuropsychiatric pharmaceuticals nowadays are how to reach the central nervous system at therapeutic concentration and maintain it long enough and how to avoid undesirable side effects caused by unsatisfying toxicity. Extracellular vesicles, as very important mediators of intercellular communication, can have a variety of therapeutic qualities. They can act neuroprotective, regenerative and anti-inflammatory, but they also have characteristics of a good drug delivery system, including their nano- scale size, biological safety and abilities to cross BBB, to pack drugs within the lipid bilayer, and not to trigger an immunological response. Besides, due to their presence in readily accessible biofluids, they are good candidates for biomarkers of the disease, its progression and therapy response monitoring. Alternations in EVs' cargo profiles can reflect the pathogenesis of neuropsychiatric disorders, but they could also affect the disease outcomes. In the future, EVs could help physicians to tailor treatment strategies for individual patients, however, more extensive studies are needed to standardize isolation, purification and production procedures, increase efficacy of drug loading and limit unwanted effects of innate EVs' content.
Opposed Reviewers:	
Response to Reviewers:	Editor and Reviewer comments: 1. Introduction. Could you restructure the introduction? Currently, it mixes an explanation of potential biomarkers with a discussion of EVs as an application, making the flow less coherent. We have incorporated your suggestion and revised the 'Introduction' section by delineating more clearly the two EV-based therapeutic approaches: (1) the use of EVs as direct therapeutic agents or as drug delivery systems, and (2) their application as therapeutic biomarkers. 2. Are there any studies on EV-based therapies for mood or psychotic disorders? This review primarily discusses EV-based therapies in the context of neurodegenerative diseases, while the use of EVs as biomarkers spans both psychiatric and neurodegenerative conditions. If no studies exist on EV-based therapies for mood or psychotic disorders, could you briefly address the possible reasons in the conclusion?" Thank you for bringing this to our attention. As noted, there is indeed a limited number

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	of published studies addressing the use of EVs as direct therapeutics or drug delivery systems in psychiatric disorders. While we initially acknowledged this in the ‘Introduction’ section, we have now also included a discussion in the ‘Conclusion’ section to explore potential reasons for this gap. The revised sections have been highlighted in red for clarity.

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Highlights

- content of EVs reflects the pathogenesis of neuropsychiatric disorders
- EV profile affects the outcomes of neuropsychiatric disorders
- EVs can be used as a direct treatment of neuropsychiatric disorders
- EVs can serve as vehicles of pharmaceuticals used in neuropsychiatry
- isolation, purification and production procedures of EVs need to be standardized

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Abstract

This review deals with the application of extracellular vesicles (EVs) in the treatment of various neuropsychiatric disorders, including mood disorders, neurodegeneration, psychosis, neurological insults and injuries, epilepsy and substance use disorders. The main challenges of most neuropsychiatric pharmaceuticals nowadays are how to reach the central nervous system at therapeutic concentration and maintain it long enough and how to avoid undesirable side effects caused by unsatisfying toxicity. Extracellular vesicles, as very important mediators of intercellular communication, can have a variety of therapeutic qualities. They can act neuroprotective, regenerative and anti-inflammatory, but they also have characteristics of a good drug delivery system, including their nano- scale size, biological safety and abilities to cross BBB, to pack drugs within the lipid bilayer, and not to trigger an immunological response. Besides, due to their presence in readily accessible biofluids, they are good candidates for biomarkers of the disease, its progression and therapy response monitoring. Alternations in EVs' cargo profiles can reflect the pathogenesis of neuropsychiatric disorders, but they could also affect the disease outcomes. In the future, EVs could help physicians to tailor treatment strategies for individual patients, however, more extensive studies are needed to standardize isolation, purification and production procedures, increase efficacy of drug loading and limit unwanted effects of innate EVs' content.

Keywords: mood disorders, psychosis, neurodegeneration, substance use disorders, neurological insults and injuries, epilepsy, exosomes

Introduction

Extracellular vesicles (EVs) are cell-derived lipid bound vesicles with a critical role in mediating cell-to-cell communication (Yáñez-Mó et al., 2015). Although very heterogeneous, EVs can be classified according to their biogenesis, release pathways, size, content and function into three main subtypes, including exosomes, microvesicles (MVs) and apoptotic bodies (Théry et al., 2009).

Although not completely clear, there are several known physiological purposes of EVs. Accumulation of EVs' cargo is a functional process that enables them to participate in mechanism-driven intercellular communication. They transfer signaling components and genetic material, which can induce targeted responses in recipient cells (Khan et al., 2011; Tomasoni et al., 2013). By carrying the cargo within the bi-lipid membrane, EVs are protecting it from enzymatic degradation by RNAse, trypsin and other substances (Koga et al., 2011). By transferring specific ligands, receptors, inflammatory cytokines or presenting antigens between cells, EVs can mediate immunological response (Popēna et al., 2018; Zhou et al., 2020), coagulation (Gasecka et al., 2019) and cancer invasiveness and metastasis (Higginbotham et al., 2011). Uptake of EVs by cells is based on several mechanisms, including phagocytosis (Chen et al., 2018), fusion through lipid rafts (Svensson et al., 2013) or receptor interaction (Segura et al., 2005), presentation of biologically active molecules (Zhang et al., 2006) and endocytosis (Mulcahy et al., 2014).

This review deals with the application of EVs in different neurological and psychiatric disorders (addressed as neuropsychiatric disorders throughout the following text). We broadly classified EV-based therapeutic approaches into two categories: (1) the application of EVs either as direct therapeutic agents or as drug delivery vehicles, and (2) their use as therapeutic biomarkers.

Although we are living in a time when substantial progress is being made in the field of neuropsychiatric medications, there is a great percentage of current medications with unsatisfying responses of patients, as well as new therapeutic strategies that fail due to their inefficacy, unsatisfying toxicity profile and undefined dose-response relationship (Correll et al., 2023). The main challenge of most neuropsychiatric pharmaceuticals is how to reach the central nervous system (CNS) at therapeutic concentration and maintain it long enough since the blood brain barrier (BBB) prevents around 98% of small-molecules and all macromolecular pharmaceuticals from entering the brain (Banks, 2016). Although the exact mechanisms are still not clear (Ramos-Zaldívar et al., 2022), it was shown that EVs cross the BBB, and do so at varying rates (Banks et al., 2020). Extracellular vesicles can have a variety of therapeutic qualities depending on the parent cell type. They can act neuroprotective (Kojima et al., 2018), regenerative (Rajan et al., 2016) and anti-inflammatory (Long et al., 2017), but they also have characteristics of a good drug delivery system, including their nano- scale size, biological safety and abilities to cross BBB, to pack drugs within the lipid bilayer, and not to trigger an immunological response (Rufino-Ramos et al., 2017). Given their ability to carry bioactive compounds and penetrate biological barriers, EVs are increasingly being investigated as possible therapeutic agents.

Furthermore, modern medicine is in need of some new, reliable therapeutic biomarkers, crucial in the clinical development and clinical practice of neuropsychiatric therapies. They could help identify patients who are more likely to respond to specific treatment and provide a more objective measure for selecting and tailoring appropriate therapy for specific symptoms. Currently this field is largely focused on peripheral molecular markers, which are easier to determine than those in CNS. The limitation of these studies is that the changes observed in the periphery cannot be easily linked to those that actually occur in the CNS. Therein lies the great potential of EV-based research which are already implying that EVs could reflect the localized and systemic changes in CNS (Bravo-Miana et al., 2024).

However, there are also disadvantages of EVs based therapy application and monitoring that must be mentioned. Some of them are lack of standardized isolation, purification and production protocols, limited efficacy of drug loading or unwanted effects of innate EVs contents (Rufino-Ramos et al., 2017).

In this paper, we aimed to review the published literature dealing with the pros and cons of EVs usage in treatment (direct or as a drug vehicle) and treatment efficacy monitoring in neuropsychiatric disorders, including mood disorders, psychosis, neurodegeneration, neurological insults and injuries, epilepsy and substance use disorders (Table 1). It is evident that studies dealing with EVs as direct therapeutics or drug delivery systems are mostly preclinical animal studies primarily focused on neurological and substance use disorder. Human studies are more represented among studies reporting EVs as a tool for therapy monitoring, mostly in psychiatric conditions such as depression and psychosis.

Extracellular vesicles as biomarkers of therapy response in neuropsychiatric disorders

Extracellular vesicles were isolated from nearly all mammalian cell types and can be found in a variety of biological fluids (Akers et al., 2013; Grigor'eva et al., 2016; Lässer et al., 2011; Shi et al., 2015), which caused an increasing interest in EVs as potential carriers of diagnostic and prognostic biomarkers for different diseases (Melo et al., 2015; Sandfeld-Paulsen et al., 2016; Zhou et al., 2006). Since EVs act as vehicles of intercellular communication, they reflect the condition and any active pathological process of cells producing them (Yuana et al., 2013). The biggest potential of EVs in neuropsychiatry lies in their ability to reflect the localized and systemic changes in CNS. These characteristics make them useful as peripheral therapeutic biomarkers for monitoring the therapy response associated with molecular changes occurring in the CNS. Most of the studies describing EV-based therapy monitoring are human studies dealing with different psychiatric diagnoses (Table 1).

Mood disorders

Antidepressant therapy (ADT), including selective serotonin reuptake inhibitors (SSRIs), helps in the preservation of neuroplasticity and reduces the negative effects of major depressive disorder (MDD) by raising brain-derived neurotrophic factor (BDNF) expression (Chakrapani et al., 2020; Zhou et al., 2017). It is now clear that EVs may play an important role in monitoring the treatment of MDD because they carry biomarkers, which reflect biochemical changes during ADT. BDNF and pro-BDNF concentrations in exosomes vary during ADT, indicating that exosomes may be useful, yet non-invasive, markers for monitoring ADT response (Gelle et al., 2021). Neuron-derived EVs (NDEVs) exhibit alterations in size and miRNA composition with regard to the ADT response. Patients with MDD who responded to escitalopram therapy had an increase in the size of NDEVs, with specific NDEVs miRNAs (miR-21-5p, miR-30d-5p, and miR-486-5p) highly associated with improved outcomes after therapy (Saeedi et al., 2021). A recent study indicated that fluoxetine treatment altered the expression of specific miRNAs in serum exosomes of rats exposed to chronic unpredictable mild stress, reversing some alterations caused by it (Fang et al., 2020). This modification includes miR-1b overexpression and miR-122-5p downregulation, and these miRNAs are connected to pathways like MAPK, Wnt, and mTOR, which play important roles in neuroplasticity, neuronal survival, and the overall stress response.

Extracellular vesicles act as molecular messengers, enhancing the observation of systemic and brain-specific responses to SSRIs, offering a key tool for enhancing comprehension in mood disorders and therapeutic research. Normalization of EV cargo could be associated with a successful response to SSRIs, whereas persisting anomalies might indicate resistance to pharmacotherapy. Goetzl et al. reported that

mitochondrial protein levels in NDEVs varied depending on how individuals with MDD responded to SSRI therapy. Proteins such as cyclophilin D and mitofusin-2, which are required for mitochondrial activity, were lower in MDD patients than in healthy controls, but protein levels returned to normal in MDD patients who responded to SSRI treatment after eight weeks (Goetzl et al., 2021). Administering fluoxetine following prolonged stress in rats resulted in substantial alterations in neurotransmitter levels and microRNA expression in EVs. Fluoxetine enhanced performance on the forced swim test and elevated the expression of essential microRNAs such as miR-16, miR-21, miR-146a, and miR-223, which are implicated in inflammation and stress response (Estévez-Cabrera et al., 2023). Specifically, miR-16 regulates serotonin transporter (SERT) and is involved in fluoxetine's antidepressive effects. A study by Hung et al. (2021) reports that patients who experienced remission following ADT exhibited elevated levels of various exosomal microRNAs (let-7e, miR-21-5p, miR-145, miR-146a, and miR-155). Additionally, prior to therapy, remission patients had reduced levels of these microRNAs in comparison to individuals who did not attain remission (Hung et al., 2021). Exosomal miRNAs isolated from blood plasma samples of individuals with treatment-resistant depression showed an aberrant expression profile. It was specifically shown that two miRNAs, has-miR-335-5p and has-miR-1292-3p, had significant expression differences between TRD patients and healthy controls (L. Di Li et al., 2021).

A recent study noted that infliximab, a TNF-α antagonist, reduced neuroinflammatory biomarkers in individuals with bipolar disorder (BD), particularly among those with a history of childhood trauma. They also observed a decrease in the signaling proteins, TNFR1 and NF-κB, in NDEVs (Mansur et al., 2020). The decrease was associated with improvements in depressive symptoms. This study implies that infliximab reduces systemic inflammation and interacts with neuronal inflammatory pathways, which are considered to be crucial in the development of the pathophysiology of BD.

Psychotic disorders

Studies that investigated the potential of EVs in monitoring antipsychotic treatment have mainly focused on miRNAs and different proteins that can be found in circulating EVs. MiR-233 was found to be expressed in astrocytes and secreted through exosomes, with antipsychotics controlling its cellular and exosomal localization in cortical neurons and astrocytes (Amoah et al., 2020). These results suggest that EV miRNAs could be regulated by antipsychotics and used as readily accessible and non-invasive biomarkers of treatment outcome. Tsoporis et al. (2022) reported decreased levels of DJ-1 protein (Parkinsonism-associated deglycase) and increased miR203a-3p levels in whole blood samples and blood-derived exosomes of antipsychotic naïve schizophrenia patients. After 6 weeks of olanzapine monotherapy, the level of both DJ-1 and miR203a-3p in exosomes normalized, suggesting that DJ-1 and miR203a-3p could serve as potential biomarkers for schizophrenia and its response to antipsychotic therapy (Tsoporis et al., 2022). A global expression analysis of miRNAs obtained from plasma exosomes of patients with TRS treated with clozapine revealed 13 up- and 18 downregulated miRNAs (Funahashi et al., 2023). Among the upregulated miRNAs, miR-675-3p expression was successfully validated by qPCR analysis, showing higher expression of miR-675-3p in TRS compared to healthy controls (Funahashi et al., 2023). Interestingly, decreased expression of the same miRNA was detected in the non-TRS group when compared to healthy controls (Funahashi et al., 2023). To additionally analyze the possible effect of clozapine therapy on miR-675-3p, an *in vitro* study using SH-SY5Y cells was conducted. The results revealed that the treatment with clozapine upregulates the expression of miR-675-3p in exosomes (Funahashi et al., 2023). A recent study published by Tu et al. (2024) used EVs isolated from individuals who received olanzapine treatment for 3 months and injected them into rats in order to investigate the glucose-

regulating function *in vivo*. They demonstrated that circulating EVs, particularly those rich in miR-486-5p, could be associated with interindividual differences in insulin sensitivity among patients receiving olanzapine treatment (Tu et al., 2024). MiR-486-5p was also linked to insulin resistance since it impairs glucose regulation by disrupting the AKT-GLUT4 signaling pathway (Tu et al., 2024). The study suggested that miR-486-5p-rich EVs could serve as biomarkers for predicting susceptibility to olanzapine-induced insulin resistance. Clozapine treatment is known to be associated with the risk of idiosyncratic drug-induced agranulocytosis (IDIAG) (X.-H. Li et al., 2020). Most of the patients experience a transient immune response in the beginning of clozapine treatment (Blackman et al., 2021). It was suggested that EVs, which are released in response to clozapine, play an important role in the proinflammatory response associated with IDIAG (Sernoskie et al., 2024). Clozapine-exposed EVs were found to be more immunogenic, inducing inflammasome activation and a stronger proinflammatory response compared to olanzapine-exposed EVs (Sernoskie et al., 2024). Clozapine, but not olanzapine, was found to significantly increase the release and immunogenicity of EVs, which may contribute to the early immune activation leading to clozapine-induced IDIAG (Sernoskie et al., 2024).

Another EV cargo investigated due to its possible association with schizophrenia are metabolites. A study by Du et al. detected 25 metabolites that were significantly altered in patients with schizophrenia (Du et al., 2021). These metabolites were associated with amino acid metabolism (phenylalanine, tyrosine, tryptophan) and glycerol phospholipid metabolic pathways, which goes in line with the hypothesis of membrane phospholipid dysfunction in schizophrenia (Du et al., 2021). However, the results of this study also suggest that these metabolites were not influenced by the antipsychotic treatment (Du et al., 2021).

Proteins, another frequent EV molecular cargo, could also have biomarker potential in diagnosing schizophrenia and predicting treatment response to antipsychotics. Plasma-derived EVs from individuals diagnosed with chronic or first-episode schizophrenia, patients with bipolar disorder, and subjects with major depressive disorder were analyzed in order to determine a novel EV-based protein biomarker panel for diagnosing chronic schizophrenia and distinguish it from bipolar disorder and major depressive disorder (Xue et al., 2024). Results suggested that EVs containing complement proteins (C3, C4A, C4B, C4BPA, C4BPB, and PROS1) were significantly elevated in schizophrenia patients compared to controls (Xue et al., 2024). Additionally, these EV-derived complement proteins outperformed plasma counterparts in predicting antipsychotic responses (Xue et al., 2024).

Neurodegenerative disorders

One study evaluated changes of NDEVs parameters following treatment with cerebrolysin, donepezil, or a combination of both drugs, in Alzheimer's disease (AD) patients enrolled in a randomized clinical trial (Alvarez et al., 2022). In this study, authors demonstrated synergistic reduction of plasma NDEVs Aβ-42 after cerebrolysin and donepezil treatment and that combination therapy reduced NDEVs levels of total tau, P-T181-tau, and P-S396-tau more effectively than monotherapies in mild to moderately severe AD patients. This study suggests that these NDEVs markers could be useful for monitoring the effects of anti-AD drugs.

In clinical research, Luo et al. investigated the therapeutic effects of pramipexole, a non-ergoline dopamine agonist, in patients with Parkinson's disease (PD) (Luo et al., 2016). They examined α-syn levels in serum-derived EVs and identified a strong correlation between reduced α-syn levels and positive therapeutic response, suggesting that α-syn levels in serum-derived EVs could serve as a non-invasive biomarker for evaluating pramipexole's efficacy (Luo et al., 2016). In another study, Athauda et al. explored the use of CNS-derived EVs from the serum of PD patients as biomarkers for monitoring 60-week treatment with exenatide (Athauda et al., 2019), a glucagon-like peptide 1 agonist repurposed from type

II diabetes therapy for PD. Their findings showed that exenatide activated the insulin signaling pathway by phosphorylating IRS-1 in neural-derived EVs, which in turn activated the Akt and mTOR pathways, leading to improved motor function in PD patients. The study also found that IRS-1 phosphorylation in serum-derived neuronal EVs correlated with mTOR activation and motor improvements, suggesting that IRS-1 in EVs could be a valuable biomarker for tracking the efficacy of treatments targeting neuronal pathways (Athauda et al., 2019).

Regarding clinical research in multiple sclerosis (MS), studies concerning EVs as biomarkers for therapy response have conflicting results. For instance, some studies on monocyte-derived EVs indicated a reduction of interferon-beta (INF-β) in EVs over time (Blonda et al., 2017), while others found no significant effect (Dalla Costa et al., 2018). MS patients undergoing treatment with natalizumab, a recombinant humanized monoclonal antibody that prevents cell transendothelial migration to the CNS (Selewski et al., 2010), exhibited higher levels of plasma EVs derived from monocytes, leukocytes, and platelets compared to non-treated patients (Dalla Costa et al., 2018; Sáenz-Cuesta et al., 2018). The next investigational drug, fingolimod, which downregulates sphingosine 1-phosphate receptors in lymphocytes, limits CNS infiltration by reducing their migration, and inhibits acid sphingomyelinase, an enzyme involved in EV production (Dawson and Qin, 2011). In MS patients, fingolimod decreased monocyte-derived EVs at 3, 6, and 12 months (Amoruso et al., 2018; Dalla Costa et al., 2018). Moreover, altered miRNA profiles in EVs of fingolimod responders versus non-responders further suggest their potential as biomarkers for monitoring treatment response (Ebrahimkhani et al., 2020). In another study, teriflunomide was shown to reduce B and T cell proliferation by inhibiting dihydroorotate dehydrogenase and progressively decrease monocyte-derived EV production from the second month of treatment, with more significant reductions at 6 and 12 months (Blonda et al., 2017). Conversely, glatiramer acetate, an immunomodulatory drug that mimics myelin basic protein, did not affect monocyte-derived EV levels in MS patients after 3 or 12 months of treatment (Dalla Costa et al., 2018).

Extracellular vesicles as direct therapeutics or indirect drug delivery systems in neuropsychiatric disorders

A great deal of EVs' role is to act as carriers protecting and delivering the cargo to specified intracellular regions in a target-specific manner through the plasma membrane (Luo et al., 2021). They are able to cross biological barriers, including BBB (Morad et al., 2019) and, due to their cellular origin, have significantly lower immunogenicity and toxicity (Xue et al., 2020) than conventional nanocarriers. Because of these qualities, EVs are used as carriers to deliver therapeutic agents to specified areas including CNS. Either their innate content can have direct therapeutic effect, or they can serve as vehicles of external therapeutic agents. More precisely, we can differentiate between native EVs, hybrid EVs, which are modified with external drugs or surface ligands, and extracellular vesicle-liposome hybrids (Sato et al., 2024). Despite the great scientific efforts to utilize EVs as smart drug delivery systems, their clinical translation remains challenging (Clemmens and Lambert, 2018). Hence, most of the studies describing EVs as direct therapeutics or indirect drug delivery systems in neuropsychiatric disorders are animal studies and usually this kind of therapeutic approach targets neurological over psychiatric disorders (Table 1). Psychiatric disorders in which direct EV-based therapy has been considered were MDD and substance use disorders (SUDs). We found only one study reporting EVs as a direct antidepressant therapy. It describes EVs derived from *Lactobacillus plantarum* (L-EVs) as antidepressant therapy enhancing the BDNF expression in the hippocampus, which is usually reduced in MDD (Choi et al., 2019). It was observed that

the use of L-EVs as a therapy reduces depressive behavior in mice, with an efficacy comparable to the heterocyclic antidepressant imipramine. Findings suggest that L-EVs may be beneficial in treating MDD by alleviating depressive symptoms and promoting neuroplasticity (Choi et al., 2019).

Substance use disorders

The study of Chivero et al. (2020) loaded dendritic cells derived EVs with miR-124 and used them as *in vitro* and *in vivo* treatments in a mouse model of cocaine administration. The results suggested that dendritic cell-derived EVs can deliver miR-124 to the brain and alleviate cocaine-mediated microglial activation. Together, these findings have implications for the development of EVs RNA-based therapeutics for the treatment of drug-related neurodegeneration, involving functional impairment of microglia. In addition, Liu and colleagues (Liu et al., 2015) showed that modified EVs, which expressed neuron-specific rabies viral glycoprotein (RVG) peptide on the membrane surface, were able to efficiently and specifically deliver opioid receptor mu (MOR) siRNA into Neuro2A cells and the brain in a mouse model of morphine addiction. The siRNA-loaded RVG exosomes significantly reduced MOR mRNA and protein expression levels and strongly inhibited morphine relapse, as evidenced by blocked condition place preference after re-exposure to morphine. This study also suggested clinical potential of EVs to serve as a gene therapy strategy for the transfer of siRNA across the BBB, which might represent more effective treatment for opioid addiction compared to treatment with naltrexone and methadone (Liu et al., 2015). A more recent study provided evidence that rhynchophylline (Rhy)-treated EVs exert protective effects against methamphetamine-induced dependence through the EV-encapsulated miR-183-5p-mediated inhibition of neuregulin-1 (NRG1) expression, supporting EVs therapeutic potential in drug addiction. Authors observed that Rhy-EVs inhibited the effects induced by methamphetamine dependence and displayed neuroprotective effects on the methamphetamine-induced damage in the hippocampus of dependent mice (Zhou et al., 2021).

The study of Ezquer and colleagues (Ezquer et al., 2019) demonstrated that intranasal administration of exosomes derived from activated human MSCs to alcohol-consuming rats reached the brain and inhibited chronic alcohol intake and relapse-like 'binge' drinking, reversed both alcohol-induced hippocampal oxidative stress and neuroinflammation, as well as increased glutamate transporter GLT1 expression in nucleus accumbens (Ezquer et al., 2019). Moreoever, recent findings have shown that intravenous administration of MSC-EVs from adipose tissue ameliorated neuroinflammation by decreasing the expression of inflammatory genes (e.g., COX-2, iNOS, MIP-1α, NF-κB, CX3CL1, and MCP-1), myelin and synaptic structural alterations (e.g., irregular myelin fiber shapes, interlaminar splitting of myelin sheaths, reduction in both postsynaptic thickness and synaptic vesicle number) in prefrontal cortex, as well as spatio-temporal memory dysfunction and recognition memory deficits, induced by binge-like ethanol treatment in adolescent mice (Mellado et al., 2023).

Alzheimer's disease

One of the first studies exploring the use of EVs as drug carriers was conducted by Alvarez-Erviti et al. (2011). They demonstrated that EVs loaded with small interfering RNAs (siRNA) targeting BACE1, a protease involved in the formation of amyloid-beta (Aβ) aggregates, could reduce the mRNA and protein levels of BACE1 in Alzheimer's disease (AD) mouse models. This study represented a major advancement toward using EVs for drug delivery in neurodegenerative disorders (Pan et al., 2023).

Stem cell-derived EVs have been proposed as a potential AD treatment due to their anti-oxidant, anti-apoptotic and immunomodulatory properties (Lee et al., 2019). Extracellular vesicles derived from mesenchymal stem cells (MSCs-EV) ought to have a promising therapeutic potential due to its ability to

navigate to target cells, fuse with them and deliver therapeutic cargo, usually containing proteins and miRNA (Xie et al., 2019). Because of their role in modulating inflammation and maintaining neuronal survival and function, MSC-EVs have been found to be particularly promising for the treatment of AD (Palanisamy et al., 2023). They can be easily harvested from different adult tissues, including bone marrow, adipose tissue, peripheral blood, as well as neonatal tissues such as the umbilical cord or placenta (Hass et al., 2011). Several studies showed the neuroprotective potential of MSC-EVs in an animal model of AD, where they have been effective in protecting neurons against oxidative stress and synaptic damage caused by Aβ accumulation (de Godoy et al., 2018; Ma et al., 2020). Additionally, MSC-EV has shown encouraging therapeutic effects by clearing abnormal protein accumulation (Cone et al., 2021; Elia et al., 2019; Sha et al., 2021; Yang et al., 2020), reducing neuronal loss (Ma et al., 2020; Wang and Yang, 2021), improving synaptic transmission and neuronal function (Gomes et al., 2022; Wang et al., 2021, 2018), and increasing neurogenesis (Ma et al., 2020; Reza-Zaldivar et al., 2019), in both *in vivo* and *in vitro* studies. Although the number of *in vitro* and *in vivo* studies on MSC-EVs is increasing, clinical evaluations remain limited. There are few EV-based therapeutics for AD that have reached clinical trials. One of the studies registered as NCT04388982 has progressed to phase I/II clinical trials (Xie et al., 2023). This trial involved nine participants who were divided into three groups and received intranasal MSC-derived exosomes at different dosages over a 12-week period. After measuring cognitive function using the Alzheimer's Disease Assessment Scale-Cognitive Section (ADAS-cog) and Montreal Cognitive Assessment (MoCA), in the medium dose group, improved cognitive performance was reported. While there were no significant changes in amyloid or tau deposition across all groups, there was a slight reduction in hippocampal shrinkage in the medium-dose group (Xie et al., 2023).

While MSC have broader regenerative and anti-inflammatory effects, neuronal stem cells (NSC) are more specifically designed for the CNS environment and offer more targeted potential in neural repair by differentiating into both neurons and glia cells (Reynolds and Weiss, 1992). Neuronal cell-derived extracellular vesicles play a crucial role as carriers of various miRNAs and proteins important for neuroprotection, neuronal plasticity and neuroregeneration (Vogel et al., 2018; Zhong et al., 2023). So far, the therapeutic potential of NDEVs has been explored in various models of NDs, especially AD, with promising outcomes. Studies on 5×FAD and APP/PS1 transgenic mice demonstrated neuroprotective efficacy of NDEVs by enhancing mitochondrial function, synaptic activity, reducing inflammatory response and improving cognitive performances (Apodaca et al., 2021). Additionally, NDEVs have demonstrated positive effects in reducing AD-related neuropathology by reducing Aβ accumulation. It is well known that NDEVs levels of Aβ, total tau, phosphorylated at threonine 181 (P-T181-tau), and tau phosphorylated at serine 396 (P-S396-tau) increased in AD patients compared to controls (Fiandaca et al., 2015; Jia et al., 2019; Nam et al., 2020).

Parkinson's disease

Recent research suggests that intranasal administration of EVs derived from human exfoliated deciduous teeth (SHEDs) could alleviate gait impairments, reduce contralateral rotation, and normalize tyrosine hydroxylase expression in the striatum and substantia nigra in a PD rat model (Narbute et al., 2019). Similarly, Chen et al. found that EVs from human umbilical cord MSCs protect dopaminergic neurons and reduce asymmetric rotation in a rat model of PD (Chen et al., 2020). Further studies have shown that human umbilical cord MSC-EVs enriched with miRNA-106b inhibit neuronal apoptosis, enhance autophagy, as well as improve behavior and increase DA levels in PD models (Bai et al., 2021; Zhang et al., 2023). Additionally, bone marrow MSCs (BM-MSCs) EVs enriched with Wnt5 have been

shown to improve climbing speed and rotation behavior in rats, potentially by repairing DA nerve damage and modulating inflammation (Li et al., 2022). These EVs also positively affect circadian rhythm-related genes and neurotransmitter levels, suggesting benefits for sleep disturbances associated with PD (Li et al., 2023). EVs are also effective for delivering therapeutic agents in PD. Peng et al. developed a nanocarrier combined with MSC-derived exosomes to transport curcumin into the brain of a PD mouse model, which is found to reduce α-syn aggregates, restore neuronal function, and alleviate neuroinflammation (Peng et al., 2022).

Huntington disease (HD)

One of the novel approaches, miRNA-based therapy, was shown to be very effective in HD (Ananbeh et al., 2021). In particular, miR-124 promotes neurogenesis and BDNF expression by downregulating REST transcription factor, and it is one of the most downregulated miRNAs in HD (Buckley et al., 2010). In a study conducted by Lee et al. (2017), exosomes containing miR-124 were injected into the striatum of transgenic HD mice, reducing REST protein expression. However, no significant behavioral improvement was visible. Further studies have investigated exosome use in delivering therapeutic molecules. For example, in the N171-82Q, BACHD and YAC128 HD mouse models, intravenous administration of exosomes loaded with siRNAs targeting HTT exon 1 transcript significantly reduced mHTT expression in the brain (Zhang et al., 2021). Similar outcomes were observed in other study, where chemically stabilized siRNAs were loaded into exosomes, leading to a significant reduction of mHTT expression in cultured cortical neurons and in mice brains (Didiot et al., 2016).

Multiple sclerosis

Riazifar et al. demonstrated that intravenous administration of MSC-derived exosomes, stimulated by interferon-beta (INF-β), the first approved treatment for MS, decreased neuroinflammation, increased regulatory T cells in the spinal cord, and reduced demyelination in experimental autoimmune encephalomyelitis (EAE) mice, a widely used model for studying brain inflammation and demyelination (Riazifar et al., 2019). Additionally, Castella et al. found that modified microglia-derived EVs expressing a protein that increased absorption by myeloid cells and astrocytes also improved EAE outcomes (Casella et al., 2018). Furthermore, MSC-EVs combined with a myelin-specific DNA aptamer were shown to promote both immunomodulatory effects and remyelination in EAE (Hosseini Shamili et al., 2019). Similarly, modified EVs carrying peptide cargoes that target pathogenic cells have proven effective in preventing EAE (Manu et al., 2021). Clark et al. further demonstrated that placental MSC-EVs promoted oligodendrocyte precursor cell differentiation and new myelin production in EAE models (Clark et al., 2019). In support of these findings, a meta-analysis by Xun et al. confirmed improved functional outcomes in MS animals treated with MSC-EVs, indicating their promising therapeutic potential (Xun et al., 2022). Moreover, human adipose tissue-derived MSCs (hAdMSCs) administered intravenously were found to improve motor function, promote remyelination, and control neuroinflammation in a primary progressive MS mouse model (Laso-García et al., 2018). Additionally, Jafarinia et al. also reported that hAdMSC-derived EVs effectively reduced T cell proliferation, demyelination, and leukocyte infiltration in EAE models (Jafarinia et al., 2020). However, Farinazzo et al. observed that EVs derived from adipose stem cells only had a protective effect before disease onset in EAE but not during the active phase (Farinazzo et al., 2018).

Amyotrophic lateral sclerosis

Unlike PD and MS, where both preclinical studies and clinical trials have explored the potential of EVs for therapy and monitoring, in amyotrophic lateral sclerosis (ALS) only preclinical studies have been conducted. Bonafede et al. investigated the therapeutic potential of exosomes derived from adipose stem cells (ASC-exosomes) in the superoxide dismutase 1 G93A (SOD1(G93A)) mouse model, the most widely used in vivo model for ALS (Bonafede et al., 2020). The study showed that ASC-exosomes protected lumbar motor neurons, muscle and neuromuscular junctions, as well as improved motor function and decreased activation of glial cells (Bonafede et al., 2020). Additionally, these exosomes demonstrated the ability to target and migrate to damaged barin areas of the treated animals (Bonafede et al., 2020). Another study by Garbuzova-Davis and Borlongan found that EVs derived from human bone marrow endothelial progenitor cells alleviated cellular damage in mouse brain endothelial cell line bEnd.3 (mBEC) exposed to ALS mouse plasma, further supporting the potential of EV-based therapies for ALS (Garbuzova-Davis and Borlongan, 2021).

Neurological insults and injuries

Different types of mechanisms can lead to secondary brain damage following acute insults to CNS like stroke, traumatic brain injury (TBI) and spinal cord injury (SCI).

Current brain stroke treatments have many limitations, which indicates the urgency for new therapeutic options. The most recent and innovative therapeutic strategy involves the transplantation of stem cells that release EVs or, even more effectively, treatment with isolated cell-free EVs that contain anti-inflammatory factors, which helps reduce neuroinflammation, cellular damage and promote neurogenesis. This effect of exosome treatment has been demonstrated in Wistar rats almost a decade ago (Xin et al., 2013; Zhang et al., 2015). The capability of EVs to mediate intercellular exchange among brain cells is supported by a growing number of evidence. Microglia utilize EVs to regulate the level of synaptic proteins in recipient neurons, but also to propagate inflammatory and degenerative signals in response to tissue damage and disease (Cabrera-Pastor, 2024; Raffaele et al., 2021; Schnatz et al., 2021). Li et al. (2021) showed that, in mice, glial scar formation after stroke can be reduced via M2 microglial small EVs through tail intravenous injections. Intracerebral infusion of microglia-derived EVs restores protective microglia/macrophages functions, limiting their senescence during the post-stroke phase in mice (Raffaele et al., 2021).

Recently, an emerging amount of research focuses on the role of exosomes as vectors containing miRNA, siRNA, mRNA, peptides, and synthetic drugs for cell therapy against neuro-inflammatory and neurodegenerative diseases (Pascual et al., 2020). For example, Wang et al. (2020) concluded that enrichment of miR126 enhanced the therapeutic efficacy of exosomes released from endothelial progenitor cells (EPC-EXs) on ischemic stroke by attenuating acute injury and promoting neurological function recovery in mice. There is also a mention that EV-derived miR-98 can act as an intercellular signal mediating neurons and microglia communication during the brain remodeling after ischemic stroke (Yang et al., 2021). Research shows that EVs originating from human umbilical vein endothelial cells (HUVECs) are absorbed by astrocytes during cerebral ischemia-reperfusion injury and promote the restoration of neurological function. In this case, miR-155-5p carried by HUVEC-EVs modulated the c-Fos/AP-1 signaling pathway in astrocytes to protect brain tissue (Gao et al., 2023). In the last few years, fields like nanotechnology and neuroregeneration have emerged with solutions like the usage of hydrogel-delivered EVs. It is now known that it is possible to stably incorporate EVs into the hydrogels and that they can be controllably released in response to the brain microenvironment after stroke in mice. Injection of EV-

hydrogels into the ischemic mouse brain enhanced EVs retention, promoted angiogenesis, and improved neurobehavioral recovery (Gu et al., 2023; Jiang et al., 2022).

It is known that inflammation plays a crucial role after TBI. Different mechanisms that include EVs are considered to play a role in the activation of the immune response. For example, some suggest that exosomes carry bioactive cytokines, inflammasome components and that they can regulate Toll-like receptor signaling and IL-1β production (Haneklaus et al., 2013). Xu et al. (2020) found that BDNF-induced MSC-derived exosomes (MSCs-Exo) can improve cell migration and inhibit apoptosis better than MSCs-Exo in rats after TBI, and the mechanism may be related to the high expression of miR-216a-5p. One study showed that acute intravenous injections of human NSC-EVs increased the migration of endogenous NSCs to the lesion site and increased VEGF activity in male rats after TBI, which promoted recovery of motor function. Interestingly, the therapeutic benefit of NSC-EVs following TBI was significant in male rats but variable in females (Sun et al., 2020). Another study presented a promising neuroprotective peptide NR2B9c in the form of an engineered RVG29-conjugated exosome. This form had higher neuron targeting efficiency compared to naïve exosomes both *in vivo* and *in vitro*. They showed that intravenous administration of RVG-ExoNR2B9c significantly improved behavioral outcomes and reduced the lesion volume after TBI injury in mice (Haroon et al., 2024).

Regarding SCI, there is a significant amount of studies that have been published during the last few years and they focused mostly on exosome-loaed hydrogels (Chen et al., 2023; Cheng et al., 2021; Han et al., 2022; Nazerian et al., 2023; Wang et al., 2023). For example, Li et al. (2020) report usage of human MSCs-Exo immobilized in a peptide-modified adhesive hydrogel (Exo-pGel) that exhibit efficient retention and sustained release in the host nerve tissues. Fang et al. (2023) developed a device incorporating mesenchymal stem cells and porous microneedles that enables the delivery of extracellular vesicles to the injured spinal cord.

When it comes to EVs as drug carriers, Fan et al. (2020) have successfully loaded resveratrol into exosomes secreted by microglia *in vitro*. They showed that exosome-encapsulated resveratrol improved the stability of resveratrol and reduced its degradation. Furthermore, exosome-encapsulated resveratrol displayed greater improvement in the locomotor function of rats than free resveratrol after SCI. This year, a small clinical trial study was conducted to evaluate the safety and potential effects of intrathecal administration of exosomes derived from human umbilical cord MSCs (HUC-MSCs) in 8 patients with SCI (Akhlaghpasand et al., 2024).

Epilepsy

Nowadays there is a growing interest in the role of neuroinflammation in the pathology of epilepsy and especially in status epilepticus (SE) (Foiadelli et al., 2023). Namely, a SE episode contributes to acute neuroinflammation, which progresses into chronic neuroinflammation, which again contributes to the occurrence of spontaneous seizures. To break this vicious circle, inflammation-inhibiting drugs are considered in achieving seizure control. It was already shown that MSC-Exo achieve a strong anti-inflammatory effect when applied as a treatment in several neurological diseases (Doeppner et al., 2015; Kim et al., 2016; Xin et al., 2013). A group of authors (Long et al., 2017) conducted a study in which a pilocarpine-induced mouse model of SE was subjected to intranasal treatment of human bone marrow-derived MSC-Exo. The effects of exosomes administration were a decrease in neuronal loss, significantly reduced inflammation in the hippocampal area, as well as long-term preservation of normal hippocampal neurogenesis, cognition and memory (Long et al., 2017). Similar results were observed *in vitro* and during the intraventricular application of human umbilical cord MSC-Exo in a pilocarpine-induced mouse model

of SE (Xian et al., 2019). The study reported an association of the treatment with the reduction in pro-inflammatory cytokine expression, attenuation of learning and memory deficits and decreased expression of astrogliosis markers (Xian et al., 2019).

It was already shown that epileptic seizures could be triggered by a disrupted balance between the excitatory-inhibitory neurotransmission as a consequence of increased activity of excitatory glutamatergic neurons and/or lower activity of inhibitory GABAergic interneurons (Righes Marafiga et al., 2021). Further studies, based on the idea of direct reduction of excitatory neurons or induction of inhibitory neurotransmission as a tool for controlling seizures, showed that transplantation of GABAergic interneuron progenitors can improve seizure control (Upadhya et al., 2022). Encouraged by those results, Ballal et al. (2024) conducted an experiment with direct intranasal delivery of exogenous GABA to the brain of a rat epilepsy model through EVs from human GABA-producing cells and their progenitors. Their results indicated that exogenous GABA delivered to the brain by EVs from GABAergic interneurons and medial ganglionic eminence cells significantly reduces total seizures, stage V seizures, and total time spent in seizure activity (Ballal et al., 2024).

Although not many, there are results indicating EVs as a promising new therapeutic approach in epilepsy. There are some additional studies whose results may point a direction in which further studies should go. For example, *in silico* analysis using the LINCS database (Subramanian et al., 2017) showed that anti-seizure drugs, including carbamazepine, primidone and gabapentin, alter the expression of EV-related genes (Karttunen et al., 2019). However, research of therapeutic capacities of EVs in epilepsy, as well as the effects of anti-seizure medications on EVs profiles, is still in its early stages.

Conclusion

Based on the studies reviewed, it can be concluded that changes in EVs' content are likely associated with the development of various neuropsychiatric disorders. These alternations in EV cargo profiles not only reflect the underlying disease processes, but they could also affect the disease outcomes. One of the key advantages of EVs is their detectability in easily accessible biofluids. Obtained from plasma or serum, EVs offer a valuable, non-invasive means for monitoring therapeutic responses. This could eventually support personalized treatment approaches by helping physicians tailor therapies to individual needs.

Moreover, EVs possess several inherent therapeutic benefits, including their small size, biological safety, ability to cross the blood–brain barrier, and other previously mentioned properties. These features make them promising candidates for developing novel EV-based therapies, either as direct treatments or as drug delivery vehicles for neuropsychiatric disorders. However, these EV-based therapy approaches are currently predominantly focused on neurological conditions, with limited exploration in the psychiatric domain. This imbalance can be attributed to several factors. As outlined in Table 1, EVs are mainly used to deliver their endogenous cargo which often exhibits neuroprotective or neuroregenerative properties. Such strategies are more beneficial in neurological conditions involving structural brain damage but less so in psychiatric disorders characterized primarily by functional dysregulation. Moreover, the pathophysiology of psychiatric disorders remains highly complex and incompletely understood, making the identification of precise therapeutic targets more challenging compared to neurological disorders, which tend to have more clearly defined neurobiological underpinnings. Most current research involving EVs, either as therapeutic agents or drug delivery systems, remains at the preclinical stage, primarily using animal models. The development of such models further highlights the disparity. Neurological models

often replicate specific structural and functional deficits, providing relatively accurate disease analogs. In contrast, psychiatric models typically reflect limited behavioral or emotional phenotypes often based on partially understood brain dysfunctions. This makes it more challenging to design and target effective pharmacological treatments in psychiatric contexts.

Despite significant progress in the field of EV-based therapies for neuropsychiatric disorders, and bearing in mind that a lot of therapeutic strategies have failed in clinical trials, there are still many challenges ahead. Key challenges are the development of isolation methods in order to generate clinical-grade EVs (Hering and Shetty, 2023) and the identification of specific surface markers or cargo content to distinguish between different EV subtypes, which could improve the design of EVs for therapeutic use (Gomes et al., 2022). Finally, prior to clinical application of EVs, it is essential to determine the optimal dosage, the most beneficial administration route and investigate the effect of repeated administration to avoid adverse effects and ensure maximum therapeutic effectiveness (Liew et al., 2017). Further, more extensive studies should help us to gain enough knowledge to address those elements and to properly exploit the potential of EVs by translating them into the clinic.

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Graphical Abstract

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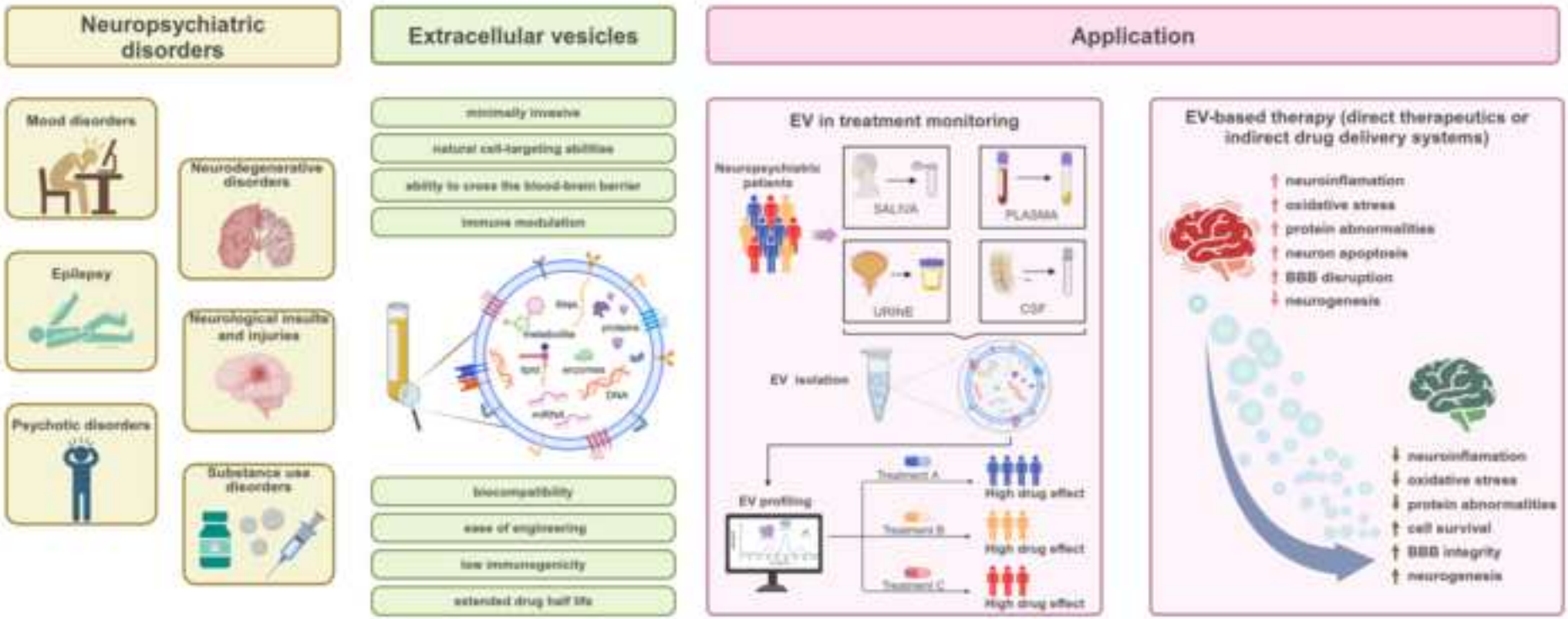


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Table 1. Overview of the literature data dealing with the usage of EVs in the treatment of neuropsychiatric disorders with summarized reported information about subjects and EV content applied in specific therapy approach.

Study	Subject	EV origin	EV content	Neuropsychiatric disorder
Therapy response				
Alvarez et al., 2022	Human	Neurons	Innate Aβ42, total tau, P-T181-tau, P-S396-tau, neurogranin, REST	Alzheimer's disease
Mansur et al., 2020	Human	Neurons	Innate signaling proteins, TNFR1, NF-κB	Bipolar disorder
Ananbeh et al., 2021	Pig/Human	Plasma	Innate mHTT protein fragments	Huntington's disease
Estévez-Cabrera et al., 2023	Rat	Serum	Innate miR-16, miR-21, miR-146a, miR-223	Major depressive disorder
Fang et al., 2020	Rat	Serum	Innate miR-455-3p, miR-122-5p	
Gelle et al., 2020	Human	Exosomes	Innate BDNF & pro-BDNF	
Goetzl et al. 2021	Human	Neurons	Innate NRF2, CYPD, MFN2	
Di Li et al., 2021	Human	Plasma	Innate has-miR-355-5p and has-miR-1292-3p	
Hung et al., 2021	Human	Exosomes	Innate let-7e, miR-21-5p, miR-145, miR-146a, miR-155	
Saeedi et al., 2021	Human	Neurons	Innate miR-21-5p, miR-30d-5p, and miR-486-5p	
Amoruso et al., 2018	Human	Microvesicles	Innate IL-1β	Multiple sclerosis
Blonda et al., 2017	Human	Microvesicles	Innate IL-1β, IL-6, TNF-α, Caspase-1	
Dalla Costa et al., 2018	Human	Plasma	Innate IL-1β, IL-6, TREM2	
Ebrahimkhani et al., 2020	Human	Serum	miR-150-5p, miR-130b-3p, miR-548e-3p	
Sáenz-Cuesta et al., 2018	Human	Plasma	Innate miRNA, cytokines, proteins	
Athauda et al., 2019	Human	Neurons	Innate IRS-1, Akt and mTOR signaling proteins	Parkinson's disease
Luo et al., 2016	Human	Serum	Innate α-Syn	
Amoah et al., 2020	Human	Exosomes	Innate miR-223	Psychosis
Du et al., 2021	Human	Serum	Innate metabolites	Schizophrenia
Funahashi et al., 2023	Human	Plasma	Innate miR-675-3p	
Sernoskie et al., 2024	Rat	Serum	Innate proteins related to inflammation and stress response	
Tsoporis et al., 2022	Human	Blood	Innate DJ-1 protein, miR-203a-3p	
Tu et al., 2024	Rat	Plasma	Innate miR-486-5p	
Xue et al., 2024	Human	Plasma	Innate C3, C4, C4BPA, PROS1	
Drug vehicle				
Alvarez-Erviti et al., 2011	Mouse	Dendritic cells	Exogenous siRNA	Alzheimer's disease

Ballal et al., 2024	Rat	Neural stem cells	Exogenous GABA	Epilepsy
Didiot et al., 2016	Mouse	U87 glioblastoma cells	Exogenous siRNA	Huntington's disease
Lee et al., 2017	Mouse	HEK 293T cells	Exogenous miR-124	
Direct treatment				
Choi et al., 2019	Mouse	*L. plantarum*	Exogenous BDNF, Sirt1, CREB	Major depressive disorder
Chivero et al. 2020	Mouse	Dendritic cells	Exogenous miR-124	Substance use disorders
Ezquer et al., 2019	Rat	Mesenchymal stem cells	Innate AoE	
Liu et al., 2015	Mouse	HEK293T cells	Exogenous siRNA	
Mellado et al., 2023	Mouse	Mesenchymal stem cells	Innate COX-2, iNOS, MIP-1α, NF-κB, CX3CL1, and MCP-1	
Zhou et al., 2021	Mouse	H9c2 cells	Exogenous miR-183-5p	
Apodaca et al., 2021	Mouse	Neural stem cells	Exogenous miRNAs and neuroprotective proteins	Alzheimer's disease
Cone et al., 2021	Mouse	Bone marrow	Innate proteins, Syntenin-1, CD63	
de Godoy et al., 2018	Rat	Mesenchymal stem cells	Innate AoE, IL-6, IL-10, VEGF	
Elia et al., 2019	Mouse	Bone marrow	Innate NEP	
Ma et al., 2020	Mouse	Adipose tissue	Innate miRNAs, NEP, neuroplastin and eIF5A	
Reza-Zaldivar et al., 2019	Mouse	Mesenchymal stem cells	Innate BDNF	
Sha et al., 2021	Rat	Bone marrow	Innate miR-29c-3p	
Wang et al., 2018	Mouse	Mesenchymal stem cells	Innate proteins and factors (iNOS mRNA)	
Wang et al., 2021	Mouse	Mesenchymal stem cells	Innate neuroprotective proteins	
Xie et al., 2023	Human	Allogenic human adipose mesenchymal stromal cells	Innate miRNAs and neuroprotective proteins	
Yang et al., 2020	Mouse	Umbilical cord	Innate NEP, IDE, HSP70, HSP90, miRNAs	
Bonafede et al., 2020	Mouse	Adipose tissue	Innate proteins, miRNA	Amyotrophic lateral sclerosis
Garbuzova-Davis and Borlongan, 2021	Mouse	Bone marrow	Innate angiogenic factors, proteins	
Casella et al., 2018	Mouse	BV2 microglia cells	Exogenous IL4, Cre recombinase and Mfg-e8	Multiple sclerosis
Clark et al., 2019	Mouse	Placental mesenchymal stem cells	Innate BDNF, HGF, VEGF	
Farinazzo et al., 2018	Mouse	Adipose tissue	Innate HSP70, CD9, TSG101	
Hosseini Shamili et al., 2019	Mouse	Mesenchymal stem cells	Exogenous LJM-3064 aptamer	
Jafarinia et al., 2020	Mouse	Adipose tissue	Innate immunomodulatory molecules, cytokines	
Laso-García et al., 2018	Mouse	Mesenchymal stem cells	Innate cytokines, chemokines and growth factors	

Riazifar et al., 2019	Mouse	Mesenchymal stem cells	Innate HSP90, SOD1, β-Actin, mRNA	
Xun et al., 2022	Mouse	Mesenchymal stem cells	Innate immunomodulatory molecules, IL-17, IFN-γ	
Bai et al., 2021	Rat	Mesenchymal stem cells	Innate miR-106b	Parkinson's disease
Chen et al., 2020	Rat	Mesenchymal stromal cells	Innate proteins, miRNA	
Li et al., 2022	Rat	Bone marrow	Innate Wnt5a, proteins, miRNA	
Narbute et al., 2019	Rat	Exfoliated deciduous teeth	Innate proteins, miRNA, AoE	
Peng et al., 2022	Mouse	Mesenchymal stem cells	Exogenous curcumin and miR-133b inhibitor	
Zhang et al., 2023	Rat	Umbilical cord	Innate proteins, miRNA	
Gao et al., 2023	Mouse	Umbilical vein endothelial cells	Innate miR-155-5p	Brain stroke
Gu et al., 2023	Mouse	Neural stem cells	Innate RNA, proteins, lipids, cytokines	
Jiang et al., 2022	Mouse	Neural stem cells	Innate miR-126, let-7f, VEGF-A	
Li et al., 2021	Mouse	Microglia	Innate miR-124	
Raffaele et al., 2021	Mouse	Microglia	Innate tmTNF	
Wang et al., 2020	Mouse	Endothelial progenitor cells	Exogenous miR-126	
Xin et al., 2013	Rat	Mesenchymal stem cells	mRNA, miRNA, proteins	
Yang et al., 2021	Rat	Neurons	Innate miR-98	
Long et al., 2017	Mouse	Mesenchymal stem cells	Innate miRNAs, proteins and AIF	Epilepsy
Xian et al., 2019	Mouse	Mesenchymal stem cells	Innate mRNA, miRNA and proteins	
Akhlaghpasand et al., 2024	Human	Umbilical cord	Innate proteins, miRNA, cytokines	Spinal cord injury
Fan et al., 2020	Rat	Microglia	Exogenous Resveratrol	
Fang et al., 2023	Rat	Mesenchymal stem cells	Innate proteins, miRNA	
Li et al., 2020	Rat	Mesenchymal stem cells	Innate miRNA, proteins	
Haroon et al., 2024	Rat	BV2 microglia cells	Exogenous NR2B9c peptide	Traumatic brain injury
Sun et al., 2020	Rat	Neural stem cells	Innate VEGFR2, nestin	
Xu et al., 2020	Rat	Mesenchymal stem cells	Innate miR-216a-5p	
Zhang et al., 2015	Rat	Mesenchymal stem cells	Innate mRNA, miRNA, proteins, lipids	

Aβ - amyloid-β; BDNF – brain derived neurotrophic factor; CREB - cAMP response element-binding protein; CYPD - cyclophilin D; eIF5A - eukaryotic translation initiation factor 5A; GABA - gamma-aminobutyric acid; HSP - heat shock protein; HGF - hepatocyte growth factor; iNOS - inducible nitric oxide synthase; IFN-γ - interferon gamma; IL- interleukin; miR – microRNA; MFN2 - mitofusin 2; Mfg-e8 - milk fat globule epidermal growth factor 8; mHTT - mutant huntingtin;

NEP – neprilysin; NF-κB - nuclear factor kappa B; REST - RE1-silencing transcription factor; Sirt1- Sirtuin 1; siRNA - small interfering RNA; SOD1 - superoxide dismutase-1; TNF - tumor necrosis factor-alpha; TREM2 - triggering receptor expressed on myeloid cells 2; VEGF - vascular endothelial growth factor

Declaration of Interest Statement

None to declare.

Ethical Statement

This paper is a review paper and no ethical considerations should be addresed.

Author contributions

Gordana Nedic Erjavec: Conceptualization, Supervision, Visualization, Investigation, Writing - original draft, Writing - review & editing. ***Nikola Balic***: Investigation, Visualization, Writing - original draft, Writing - review & editing. ***Matea Nikolac Perkovic, Tina Milos, Barbara Vuic, Dubravka Svob Strac***: Writing - original draft

Extracellular vesicles as a promising tool in neuropsychiatric pharmacotherapy application and monitoring

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