PPN

Personalized Psychiatry and Neurology

Review

mRNA-based Therapy for Neurodegenerative Diseases: Advantages and Limitations

Aisylu I. Ayupova[1], Alexandra Sharshakova[1], Albert A. Rizvanov[1,2*], Valeriya V. Solovyeva[1]

1 Institute of Fundamental Medicine and Biology, Kazan Federal University, Kazan, 420008, Russia;
2 Division of Medical and Biological Sciences, Tatarstan Academy of Sciences, Kazan, 420111, Russia;
* Correspondence: albert.rizvanov@kpfu.ru (A.A.R.)

Citation: Ayupova A.I., Sharshakova A., Rizvanov A.A., Solovyeva V.V. mRNA-based therapy for neurodegenerative diseases: advantages and limitations. *Personalized Psychiatry and Neurology* **2026**; *6 (2)*: 2-9. https://doi.org/10.52667/2712-9179-2026-6-2-2-9

Chief Editor: Nikolaj G. Neznanov, D Med Sci, Professor

Received: 25 March 2026
Accepted: 10 June 2026
Published: 15 June 2026

Publisher's Note: V.M. Bekhterev NMRC PN stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Abstract: mRNA-based therapy represents one of the most promising directions in modern biomedicine and is actively being investigated for the treatment of neurodegenerative diseases. In contrast to traditional gene therapy approaches based on DNA vectors, mRNA does not integrate into the host genome and does not require entry into the nucleus, thereby reducing the risk of mutagenesis and improving the safety profile of the method. This review provides an overview of the advantages and limitations of mRNA-based therapeutic approaches for neurodegenerative diseases. Key features of mRNA platforms are discussed, including the possibility of programmable expression of therapeutic proteins, the high flexibility of nucleotide sequence modification, and the relative simplicity of scalable production. Particular attention is given to mRNA delivery systems, especially lipid nanoparticles, which protect mRNA molecules from degradation and enhance the efficiency of intracellular delivery. The major limitations of this technology are also addressed, including the difficulty of crossing the blood-brain barrier, the low stability of mRNA, its potential immunogenicity, and the requirement for repeated administrations in the treatment of chronic diseases. In addition, current experimental strategies for the application of mRNA therapy are described, including protein replacement approaches, delivery of neuroprotective factors, and genome editing technologies. Overall, mRNA therapy holds considerable potential for the treatment of neurodegenerative disorders, however, its broad clinical implementation will require further improvements in delivery systems and enhanced stability of mRNA molecules.

Keywords: *mRNA, neurodegenerative diseases, delivery systems, lipid nanoparticles, intracellular delivery, neuroprotective factors*

1. INTRODUCTION

Messenger RNA (mRNA) is a type of single-stranded ribonucleic acid transcribed from a DNA template that carries the coding information required for protein synthesis, which is subsequently translated and processed into functional proteins [1]. mRNA-based therapy plays an important role in the treatment of various diseases. Unlike DNA-based therapeutics, mRNA transcripts demonstrate relatively high transfection efficiency and low toxicity, as they do not need to enter the nucleus to perform their function. Consequently, mRNA has recently emerged as a promising strategy for protein expression in the treatment of a wide range of diseases [2]. Importantly, mRNA does not carry the potential risk of accidental infection or insertional mutagenesis [3]. Furthermore, mRNA exhibits considerable potential for the treatment of diseases that require therapeutic protein expression and may provide higher therapeutic efficacy due to continuous translation into encoded proteins or peptides, thereby enabling more sustained expression compared with conventional transient protein or peptide therapeutics.

mRNA-based therapy possesses significant advantages that expand its potential application in the treatment of brain disorders. Through modification of mRNA molecules or their delivery using nanocarriers, it becomes possible to overcome the blood-brain barrier (BBB) or bypass it by delivering mRNA via the cerebral lymphatic system, thereby increasing the concentration of mRNA in the target region while minimizing its effects on non-target cells or tissues. The design and optimization of mRNA sequences encoding specific proteins enable precise targeted therapy for brain

diseases [4]. mRNA also overcomes many of the limitations associated with post-translational modification, folding, assembly, and localization of exogenously expressed proteins. Owing to advances in synthetic mRNA technology, these therapeutic approaches aim to restore the expression of lost or dysfunctional proteins, thereby targeting the molecular mechanisms underlying neurodegenerative diseases (NDs). A hallmark of NDs is the loss or misfolding of key proteins required for neuronal function and survival. mRNA therapy offers a unique opportunity to achieve transient yet sustained expression of functional proteins directly in target cells [4].

The application of mRNA therapy for various diseases generally involves several key steps: identification of an appropriate therapeutic target, design of a corresponding mRNA sequence and its modification to enhance stability, followed by the use of a suitable delivery platform to transport the mRNA to the desired site for proper protein expression [2]. mRNA molecules facilitate the efficient translation of genetic information into proteins by ribosomes in the cytoplasm and can be engineered to produce virtually any therapeutic protein. Synthetic mRNA consists of five key structural elements: a 5′ cap responsible for ribosome recruitment, translation initiation, and stability; a 5′ untranslated region (5′ UTR) involved in the regulation of translation and stability; an open reading frame (ORF) encoding the protein of interest; a 3′ untranslated region (3′ UTR) that also contributes to translation and stability; and a polyadenylated poly(A) tail that supports ribosome initiation, translation, and mRNA stability [5].

Because mRNA molecules possess an overall negative charge, their penetration through the anionic cellular membrane is limited [6]. To overcome this limitation, various strategies have been developed during the preparation of mRNA-based therapeutics. These include the incorporation of modified nucleotides to enhance the stability of RNA transcripts, the application of immunosuppressive approaches to reduce immunogenicity, and the development of specialized delivery carriers that protect mRNA from degradation and improve the efficiency of intracellular delivery.

A wide range of vectors has been proposed for mRNA transport, including viral and non-viral systems, lipid nanoparticles (LNPs), polymer-based carriers, protein derivatives, and extracellular vesicles. Viral delivery approaches, particularly those based on adeno-associated virus (AAV), have demonstrated significant progress in the treatment of monogenic diseases. However, the use of AAV is associated with the activation of both innate and adaptive immune responses, the requirement for nuclear delivery of genetic material, and a potential risk of genomic integration [5].

As an alternative, natural exosomes — a subtype of extracellular vesicles characterized by a unique lipid bilayer structure and high biocompatibility — are being explored as carriers for mRNA delivery [7]. Exosomes are capable of crossing biological barriers, interacting specifically with target cells, and avoiding rapid clearance by the immune system, thereby enabling targeted delivery. However, a major limitation of natural exosomes is the difficulty associated with their isolation and purification; current technological approaches do not yet fully meet the demands of large-scale production [8].

In contrast to exosomes, LNP-based delivery systems offer several advantages, including a favorable safety profile and high loading capacity. LNPs induce a less pronounced immune response compared with AAV and allow repeated administration. Furthermore, the production of LNP components is technologically less complex and more scalable than the isolation of exosomes [4].

2. ADVANTAGES OF mRNA THERAPY FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

NDs are characterized by complex and cumulative pathogenic mechanisms, while currently available treatments are largely symptomatic. One of the key advantages of mRNA-based therapy is its versatility. Unlike the administration of pre-formed recombinant proteins, endogenous protein synthesis by cellular ribosomes directly from mRNA enables proper protein folding and the acquisition of necessary post-translational modifications, which are often technically difficult or impossible to reproduce in vitro [9]. Moreover, a single mRNA molecule can encode multiple polypeptide chains through the use of enzymatic processing systems or 2A peptides. Alternatively, a mixture of different mRNAs can be administered to simultaneously target multiple pathogenic pathways [10]. This feature is particularly important in the context of multifactorial NDs that require complex therapeutic interventions. Thus, mRNA can encode a wide range of proteins — from antigens and antibodies to growth factors and enzymes involved in tissue repair — providing this approach with a high degree of flexibility and adaptability [11].

The development of mRNA therapeutics primarily involves programming a nucleotide sequence encoding the target protein, which significantly accelerates the early stages of preclinical development. mRNA synthesis is performed in vitro without the need for cell culture or living organisms, thereby simplifying purification procedures and

facilitating large-scale production [12]. For example, during the COVID-19 pandemic, less than three months were required for mRNA vaccines to progress from the development stage to clinical trials [13]. Owing to the rapid modifiability of nucleotide sequences, mRNA therapeutics can be quickly adapted to emerging antigenic variants of pathogens or personalized according to the characteristics of individual patients. Such rapid development and flexibility in modifying therapeutic agents are difficult to achieve using conventional drug development approaches.

The delivery of mRNA into cells is primarily achieved using LNPs that do not contain viral proteins (**Figure 1**). Unlike viral vectors, LNPs rarely induce the production of vector-specific neutralizing antibodies; therefore, repeated administrations of mRNA are generally not associated with reduced therapeutic efficacy due to immune responses [12]. In addition, LNPs typically exhibit low immunogenicity, allowing multiple administrations of mRNA without a strong adaptive immune response [14]. The production of LNP-mRNA therapeutics is also relatively simple and readily scalable. Because mRNA synthesis is cell-free and nanoparticle assembly relies on chemical processes, these technologies can be rapidly adapted for industrial-scale manufacturing. Overall, the LNP-mRNA platform has demonstrated promising results in preclinical studies, and numerous clinical trials are currently evaluating its therapeutic potential for various NDs [15]. Another limitation associated with viral vectors, such as AAV, is their limited packaging capacity, which complicates the delivery of large proteins or multifunctional complexes [16]. In contrast, the mRNA platform does not have such restrictions, as very long mRNA molecules encoding complex multidomain proteins or enzymes can be synthesized. This capability opens new opportunities for implementing advanced therapeutic strategies, including the direct correction of pathogenic mutations within the body.

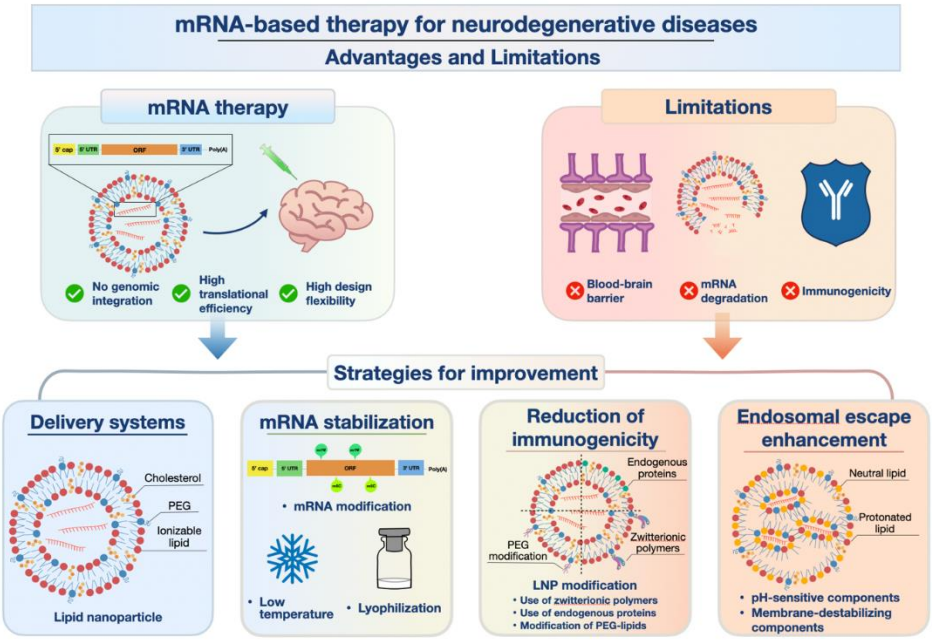

Figure 1. Schematic representation of the advantages, limitations, and optimization strategies of mRNA therapy in NDs.

One of the advantages of mRNA-based therapy is its relatively low production cost compared with gene therapy, primarily due to the absence of the expensive manufacturing processes required for viral vectors, which constitute a major component of overall costs and limit scalability. Owing to the technological simplicity, reproducibility of synthesis, and high throughput of production platforms, mRNA therapeutics demonstrate high economic efficiency and scalability when expanded to broader clinical applications [15,17].

Another distinctive feature of mRNA therapy is the use of cells as biological factories for protein production [1]. Continuous intracellular synthesis of the therapeutic protein can provide more stable and prolonged therapeutic levels compared with single administrations of recombinant proteins. This approach combines controllable pharmacotherapy with the ability to deliver high-molecular-weight biologically active compounds that otherwise poorly penetrate the blood-brain barrier when administered externally.

Delivery of mRNA via LNPs in NDs enables transient and programmable expression of therapeutic proteins in neurons and glial cells. mRNA-LNP formulations can restore deficient proteins, induce neuroprotective factors, promote the degradation of pathological aggregates, and stimulate immune-mediated clearance of toxic proteins. These properties make mRNA-based therapy particularly attractive for diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease [15].

Overall, the combination of these advantages makes mRNA therapy a promising approach for the treatment of NDs that require precise and multifactorial therapeutic interventions. The slow progression and complex pathogenesis of NDs make them particularly suitable targets for mRNA-based strategies. With further improvements in delivery systems and the accumulation of clinical evidence, mRNA therapy may play an important role in the future treatment of NDs [4].

3. LIMITATIONS OF mRNA THERAPY FOR THE TREATMENT OF NEURODEGENERATIVE DISEASES

Despite its considerable potential, the application of mRNA-based therapeutic approaches in NDs faces several significant challenges and limitations (**Figure 1**).

One of the major obstacles to the use of mRNA therapy in NDs is the difficulty of crossing the BBB. The BBB is formed by a monolayer of endothelial cells connected by tight junctions (claudin-5, occludin), surrounded by pericytes, astrocytic end-feet, and a specialized basement membrane. This structure results in extremely low paracellular permeability, selectively restricting the penetration of small molecules, proteins, and mRNA into the brain [20,25]. Strategies involving nanocarriers have been proposed to improve the delivery of mRNA across the BBB by enhancing molecular stability and enabling receptor-mediated transport through the engineering and surface functionalization of LNPs [26]. For instance, systemic delivery of LNPs optimized for BBB penetration resulted in widespread mRNA expression in neurons and astrocytes in the mouse brain [25]. In another study, LNPs modified with short targeting peptides capable of selectively interacting with receptors on endothelial cells and neurons significantly enhanced mRNA delivery to the brain while reducing its accumulation in the liver, thereby improving tissue specificity [27].

Another major limitation of mRNA-based therapy is the intrinsic instability of mRNA molecules. In the extracellular environment, mRNA is rapidly degraded by RNases, while its negatively charged structure hinders its passage across the cellular membrane, thereby limiting efficient translation of functional proteins [1,17]. To enhance stability and safety, various chemical and structural modifications of mRNA are employed, including the incorporation of modified nucleosides (e.g., replacement of uridine with pseudouridine or N1-methylpseudouridine (m1Ψ), and cytidine with 5-methylcytidine (m5C)), optimization of the 5′ cap structure and poly(A) tail length, and improvements in delivery systems, particularly LNPs [17]. Due to its limited stability, mRNA-based therapeutics require strict temperature-controlled storage conditions, which may complicate transportation and large-scale production. Therefore, the development of effective long-term storage methods for mRNA therapeutics remains highly relevant. For example, one study reported the development of lyophilized mRNA-LNP formulations that maintained structural integrity and biological activity after prolonged storage at room temperature [19].

A paradox of mRNA platforms lies in the fact that their key limitation — the intrinsic immunogenicity of mRNA molecules — represents an advantage in the context of vaccines, where immune activation is desirable. However, in therapeutic applications aimed at protein replacement, excessive immune activation becomes undesirable [11]. Unmodified mRNA can activate innate immune Toll-like receptors, induce cytokine production, and suppress its own translation, while impurities such as double-stranded RNA or DNA-RNA hybrid fragments may further increase the risk of inflammatory responses. The reduction of immunoreactivity can be achieved through chemical nucleoside modifications, optimization of the 5′ cap and poly(A) tail, careful purification procedures, and encapsulation in LNPs, which together improve stability and safety [11,17].

The transient nature of mRNA expression also complicates its broad clinical application in the treatment of chronic NDs. To maintain therapeutic protein levels, repeated injections at defined time intervals are required, which may lead to immune activation [1,18]. Even when LNPs are used, issues related to immunogenicity remain relevant. Polyethylene glycol (PEG), commonly included in LNP formulations, may cause allergic reactions, including anaphylaxis, and repeated administration may lead to the formation of anti-PEG antibodies, potentially reducing therapeutic efficacy and increasing the risk of adverse reactions [18,21]. To mitigate these effects, next-generation LNPs are being developed in which the architecture of PEG-containing nanoparticles is modified to reduce recognition by anti-PEG antibodies, PEG

is replaced with low-immunogenic zwitterionic polymers, or endogenous proteins are utilized to circumvent limitations associated with PEG-mediated immune recognition [28].

Even after successfully crossing the BBB, mRNA-containing nanoparticles are preferentially taken up by glial cells rather than neurons, resulting in reduced neuronal transfection efficiency. This significantly limits the therapeutic potential in diseases where neurons are the primary targets, such as Parkinson's disease or Alzheimer's disease [22]. Another major challenge is the endosomal trapping of approximately 99% of therapeutic RNA, which leads to its degradation. Consequently, strategies aimed at enhancing endosomal escape are being actively developed, including the use of LNPs containing pH-sensitive or membrane-destabilizing components [24,29].

Despite substantial progress in the development of mRNA platforms, their application in NDs remains limited by a combination of biological and technological barriers. Key challenges include the difficulty of crossing the BBB, preferential transfection of glial cells with insufficient neuronal specificity, the endosomal trapping effect, limited mRNA stability, immunogenicity, and the requirement for repeated administration in chronic diseases. Current research is focused on the development of next-generation LNPs with improved neurotropism, enhanced endosomal escape, reduced immunogenicity, and improved storage stability (Figure 1). Addressing these challenges is critical for the successful clinical translation of mRNA-based therapies in the field of neurodegenerative diseases.

4. PROSPECTS FOR THE APPLICATION OF mRNA THERAPY IN NEURODEGENERATIVE DISEASES

mRNA-based therapy can be applied to NDs through three main strategies: (i) replacement of defective proteins; (ii) expression of neuroprotective and anti-inflammatory factors; and (iii) delivery of genome-editing tools [4].

In the case of inherited monogenic NDs or neurometabolic disorders caused by genetic defects and resulting deficiencies of functional proteins, mRNA-based therapy can transiently restore the missing functional proteins in the central nervous system (CNS) without integrating into the genome [17,30]. For example, in a mouse model of arginase 1 (ARG1) deficiency, daily injections of mRNA encoding the ARG1 enzyme restored normal axonal myelination and prevented dysmyelination during the early postnatal period, demonstrating the potential of mRNA replacement therapy for metabolic and myelin disorders [31]. Another example of mRNA-loaded LNP therapy is the preclinical treatment of argininosuccinic aciduria, a rare inherited neurometabolic disease caused by mutations in the ASL gene. Dysfunction of this enzyme leads to ammonia accumulation and CNS damage, including developmental delay and cognitive impairment. In a mouse disease model, administration of LNPs containing mRNA encoding argininosuccinate lyase (ASL) restored urea cycle activity and improved animal survival, demonstrating the therapeutic potential of mRNA-based replacement therapy [32].

mRNA therapy aimed at delivering neurotrophic factors and immunomodulatory cytokines is also considered a promising strategy for the treatment of NDs, as these proteins can support neuronal survival, promote neuroregeneration, and reduce neuroinflammation. Such approaches are particularly relevant for diseases characterized by progressive neuronal loss and chronic inflammation, such as Parkinson's disease, Alzheimer's disease, and other neurodegenerative disorders [33]. For instance, intracerebral delivery of polymeric nanoparticles carrying mRNA encoding brain-derived neurotrophic factor (BDNF) to mice with an Alzheimer's disease model resulted in BDNF expression in astrocytes and improved cognitive function [34]. In another recent study, a novel LNP platform capable of delivering mRNA to the brain after systemic administration was developed. When loaded with mRNA encoding interleukin-12 (IL-12), these nanoparticles significantly suppressed tumor growth and increased survival in a mouse model of glioblastoma [35].

mRNA-based approaches are also being explored for the delivery of genome-editing components to correct the genetic causes of CNS disorders. For example, the administration of mRNA encoding the enzyme neprilysin (NEP) has been shown to reduce β-amyloid (Aβ) levels in the brains of mice by enhancing its degradation [36]. In other studies, glutathione-responsive nanocapsules were used to deliver Cas9 mRNA for the editing of genes associated with Alzheimer's disease. These nanocapsules were able to cross the BBB and enable in vivo editing of the APP gene [37]. In addition, an LNP-based system designed to deliver Cas9 mRNA and single-guide RNA (sgRNA) targeting the PLK1 gene achieved up to 70% gene editing efficiency in vivo, leading to apoptosis of tumor cells in a mouse model of glioblastoma [38].

mRNA therapy has also demonstrated promising results in combination strategies. For example, an mRNA vaccine targeting Aβ based on the MultiTEP platform and encapsulated in LNPs has been developed. In experiments involving

mice and non-human primates, the vaccine induced a strong humoral immune response resulting in the production of antibodies against pathological Aβ. These antibodies are believed to bind amyloid aggregates and promote their clearance in the CNS, potentially slowing the progression of Alzheimer's disease [39]. In another study, a dual mRNA therapy was tested in a mouse model of propionic acidemia, a rare neurometabolic disorder caused by deficiency of the enzyme propionyl-CoA carboxylase (PCC). Administration of LNPs containing mRNA resulted in a dose-dependent reduction in metabolic toxins and restoration of PCC activity [40].

Despite promising results in preclinical studies, the clinical application of mRNA therapy remains extremely limited. A phase I clinical trial is currently investigating the safety of a multi-antigen mRNA vaccine in patients with recurrent high-grade glioma (NCT07306299). The vaccine encodes several tumor antigens and is designed to induce an antitumor immune response.

At the same time, other RNA-based therapeutic approaches are being actively investigated in clinical trials. For example, strategies aimed at reducing the levels of huntingtin (HTT) mRNA using antisense oligonucleotides (ASOs) are being developed for the treatment of Huntington's disease [30]. Tominersen, an ASO-based therapy, demonstrated dose-dependent reductions in mutant HTT protein levels in the cerebrospinal fluid (CSF) during phase I and II clinical trials (NCT02519036). However, in the subsequent expanded phase III study (NCT03761849), treatment did not lead to improvements in clinical disease outcomes, and some patients experienced adverse clinical effects. Due to an unfavorable risk–benefit profile, the trial was halted. Subsequent analyses suggested that lower dosing regimens might be potentially beneficial in younger patients with less advanced neurodegeneration. Based on these findings, a new study (NCT05686551) has been initiated to reassess the efficacy of tominersen using modified dosing regimens and in patients at earlier stages of the disease [41,42].

Another ASO-based therapy, Tofersen, has been approved for the treatment of amyotrophic lateral sclerosis (ALS) caused by mutations in the superoxide dismutase 1 (SOD1) gene. Clinical trials demonstrated that intrathecal administration of Tofersen led to reductions in SOD1 protein levels in the CSF as well as decreased levels of neurofilament light chain (NfL) (NCT04972487) [43].

One of the earliest successful examples of RNA interference-based therapy is the treatment of hereditary transthyretin amyloidosis (ATTR). This disease is caused by mutations in the TTR gene, resulting in misfolding of the transthyretin protein and the formation of amyloid fibrils that accumulate in peripheral nerves and other tissues. The drug Patisiran is a small interfering RNA (siRNA) designed to suppress expression of the TTR gene. Delivery of Patisiran in the form of LPNs resulted in sustained reductions in serum transthyretin levels, which ultimately led to its clinical approval (NCT02939820) [30].

Thus, mRNA-based therapy for the treatment of NDs currently remains largely at the preclinical stage, and available clinical data are extremely limited. This is likely due to a number of technological and biological limitations discussed in this review. Nevertheless, the successful development of other RNA-based therapeutic approaches highlights the significant potential of this strategy and provides a foundation for the future clinical implementation of mRNA-based therapies.

5. CONCLUSION

mRNA-based therapy represents one of the most promising directions in modern biomedicine, offering fundamentally new opportunities for the treatment of NDs. The key advantages of this approach include high specificity and the ability to induce the synthesis of virtually any therapeutic protein directly within the patient's cells. This enables targeting of the major pathogenic mechanisms underlying NDs, including the replacement of lost protein functions, neutralization of toxic factors, and activation of neuroprotective pathways. In several aspects, such as target selectivity, the possibility of repeated administration, and the absence of genomic integration risk, mRNA technologies may offer potential advantages over both conventional small-molecule drugs and classical viral gene therapy systems.

At the same time, the current state of this technology remains far from optimal. Significant challenges persist, primarily related to the efficient delivery of mRNA to the CNS, the potential activation of immune responses, and the limited stability of mRNA molecules in vivo. Overcoming these barriers will require further advances in related fields, including nanotechnology-based delivery systems, chemical modification of mRNA, and studies on the interaction between mRNA therapeutics and the immune system.

Despite these limitations, the rapid progress in RNA technologies highlights the strong potential of this therapeutic approach. mRNA-based therapy is increasingly viewed as a promising complement to existing treatment strategies for NDs and may be used in combination with other therapeutic modalities, including conventional pharmacological agents. In the long term, the development of mRNA technologies may significantly expand the possibilities for the prevention and treatment of NDs, contributing to the development of more effective strategies for controlling and slowing the progression of these severe pathologies.

Author Contributions: A.I.A. and A.A.S. contributed to the investigation and the writing of the original draft. V.V.S. and A.A.R. contributed to the reviewing and editing of the manuscript. All authors have read and agreed to the published version of the manuscript.

Acknowledgments: This work/publication was funded by a grant from the Academy of Sciences of the Republic of Tatarstan provided to higher education institutions, scientific and other organizations to support human resource development plans in terms of encouraging their research and academic staff to defend doctoral dissertations and conduct research activities (Agreement No. 12/2025-PD-KFU dated December 22, 2025).

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Qin S., Tang X., Chen Y., et al. mRNA-Based Therapeutics: Powerful and Versatile Tools to Combat Diseases. *Signal Transduct Target Ther* **2022**; 7: 166. https://doi.org/10.1038/s41392-022-01007-w.
2. Xiao Y., Tang Z., Huang X., et al. Emerging mRNA Technologies: Delivery Strategies and Biomedical Applications. *Chem Soc Rev* **2022**; 51: 3828–3845. https://doi.org/10.1039/d1cs00617g.
3. Pardi N., Hogan M.J., Porter, F.W., Weissman, D. mRNA Vaccines - a New Era in Vaccinology. *Nat Rev Drug Discov* **2018**; 17: 261–279. https://doi.org/10.1038/nrd.2017.243.
4. Yang L., Li S., Hou C., Wang Z., et al. Recent Advances in mRNA-Based Therapeutics for Neurodegenerative Diseases and Brain Tumors. *Nanoscale* **2025**; 17: 3537–3548. https://doi.org/10.1039/d4nr04394d.
5. Parhiz H., Atochina-Vasserman E.N., Weissman D. mRNA-Based Therapeutics: Looking beyond COVID-19 Vaccines. *Lancet* **2024**; 403: 1192–1204. https://doi.org/10.1016/S0140-6736(23)02444-3.
6. Zhang C., Maruggi G., Shan H., Li J. Advances in mRNA Vaccines for Infectious Diseases. *Front Immunol* **2019**; 10: 594. https://doi.org/10.3389/fimmu.2019.00594.
7. Jafari D., Shajari S., Jafari R. V., et al. A. Designer Exosomes: A New Platform for Biotechnology Therapeutics. *BioDrugs* **2020**; 34: 567–586. https://doi.org/10.1007/s40259-020-00434-x.
8. Chavda V.P., Luo G., Bezbaruah R., et al. Unveiling the Promise: Exosomes as Game-Changers in Anti-Infective Therapy. *Exploration (Beijing)* **2024**; 4: 20230139. https://doi.org/10.1002/EXP.20230139.
9. Zhao Y., Gan L., Ke D., et al. Mechanisms and Research Advances in mRNA Antibody Drug-Mediated Passive Immunotherapy. *J Transl Med* **2023**; 21: 693. https://doi:10.1186/s12967-023-04553-1.
10. Chi H., Zhao S.-Q., Chen R.-Y., et al. Rapid Development of Double-Hit mRNA Antibody Cocktail against Orthopoxviruses. *Signal Transduct Target Ther* **2024**; 9: 69. https://doi:10.1038/s41392-024-01766-8.
11. Shi Y., Shi M., Wang Y., You J. Progress and Prospects of mRNA-Based Drugs in Pre-Clinical and Clinical Applications. *Signal Transduct Target Ther* **2024**; 9: 322. https://doi.org/10.1038/s41392-024-02002-z.
12. Wadhwa A., Aljabbari A., Lokras A., et al. Opportunities and Challenges in the Delivery of mRNA-Based Vaccines. *Pharmaceutics* **2020**; 12: 102. https://doi.org/10.3390/pharmaceutics12020102.
13. Lamb Y.N. BNT162b2 mRNA COVID-19 Vaccine: First Approval. *Drugs* **2021**; 81: 495–501. doi:10.1007/s40265-021-01480-7.
14. Kenjo E., Hozumi H., Makita Y., et al. Low Immunogenicity of LNP Allows Repeated Administrations of CRISPR-Cas9 mRNA into Skeletal Muscle in Mice. *Nat Commun* **2021**; 12:7101. https://doi.org/10.1038/s41467-021-26714-w.
15. Moosavi S.G., Rahiman N., Jaafari M.R., Arabi, L. Lipid Nanoparticle (LNP) Mediated mRNA Delivery in Neurodegenerative Diseases. *J Control Release* **2025**; 381: 113641. doi:10.1016/j.jconrel.2025.113641.
16. Zwi-Dantsis L., Mohamed S., Massaro G., Moeendarbary E. Adeno-Associated Virus Vectors: Principles, Practices, and Prospects in Gene Therapy. *Viruses* **2025**; 17: 239. https://doi.org/10.3390/v17020239.
17. Monfrini E., Baso G., Ronchi D., et al. Unleashing the Potential of mRNA Therapeutics for Inherited Neurological Diseases. *Brain* **2024**; 147: 2934–2945. https://doi.org/10.1093/brain/awae135.
18. Niazi, S.K. mRNA Therapeutics beyond Vaccines: Dosing Precision Challenges and Clinical Translation Framework. *RSC Pharm.* **2026**; 3: 10–21. https://doi.org/10.1039/D5PM00159E.
19. Ai L., Li Y., Zhou L., et al. Lyophilized mRNA-Lipid Nanoparticle Vaccines with Long-Term Stability and High Antigenicity against SARS-CoV-2. *Cell Discov* **2023**; 9: 9. https://doi.org/10.1038/s41421-022-00517-9.

20. Yang H.-M. Overcoming the Blood-Brain Barrier: Advanced Strategies in Targeted Drug Delivery for Neurodegenerative Diseases. *Pharmaceutics* **2025**; 17: 1041. https://doi.org/10.3390/pharmaceutics17081041.
21. Song J., Su D., Wu, H., Guo, J. Implications of Anaphylaxis Following mRNA-LNP Vaccines: It Is Urgent to Eliminate PEG and Find Alternatives. *Pharmaceutics* **2025**; 17: 798. https://doi.org/10.3390/pharmaceutics17060798.
22. Belaidi A.A., Furtado D.L., Alves F. et al. Engineering mRNA-LNP Medicines for the Ageing Brain: Opportunities and Challenges for Neurodegenerative Diseases. *Authorea Preprints* **2025**.
23. García-González N., Gonçalves-Sánchez J., Gómez-Nieto R. et al. Advances and Challenges in Gene Therapy for Neurodegenerative Diseases: A Systematic Review. *Int J Mol Sci* **2024**; 25: 12485, https://doi.org/10.3390/ijms252312485.
24. Chatterjee S., Kon E., Sharma P., Peer D. Endosomal Escape: A Bottleneck for LNP-Mediated Therapeutics. *Proc Natl Acad Sci U S A* **2024**; 121: e2307800120. https://doi.org/10.1073/pnas.2307800120.
25. Wang C., Xue Y., Markovic T., Li H., et al. Blood-Brain-Barrier-Crossing Lipid Nanoparticles for mRNA Delivery to the Central Nervous System. *Nat Mater* **2025**; 24: 1653–1663. https://doi.org/10.1038/s41563-024-02114-5.
26. Bhati V., Prasad S., Kabra A. RNA-Based Therapies for Neurodegenerative Disease: Targeting Molecular Mechanisms for Disease Modification. *Mol Cell Neurosci* **2025**; 133: 104010. https://doi.org/10.1016/j.mcn.2025.104010.
27. Han E.L., Tang S., Kim D. Murray et al. Peptide-Functionalized Lipid Nanoparticles for Targeted Systemic mRNA Delivery to the Brain. *Nano Lett* **2025**; 25: 800–810. https://doi.org/10.1021/acs.nanolett.4c05186.
28. Xiong S., Liu C. Breaking the PEG Barrier to Boost mRNA-LNP Therapeutics. *Nat Rev Mater* **2025**; 10: 799–800. https://doi.org/10.1038/s41578-025-00852-9.
29. Shahid U. Advances in RNA Therapeutics: Classes, *Innovations and Clinical Applications* **2025**.
30. Lee M.-J., Lee I., Wang K. Recent Advances in RNA Therapy and Its Carriers to Treat the Single-Gene Neurological Disorders. *Biomedicines* **2022**; 10: 158. https://doi.org/10.3390/biomedicines10010158.
31. Khoja S., Liu X.-B., Truong B., et al. Intermittent Lipid Nanoparticle mRNA Administration Prevents Cortical Dysmyelination Associated with Arginase Deficiency. *Mol Ther Nucleic Acids* **2022**; 28: 859–874. doi:10.1016/j.omtn.2022.04.012.
32. Gurung S., Timmermand O.V., Perocheau D. et al. mRNA Therapy Corrects Defective Glutathione Metabolism and Restores Ureagenesis in Preclinical Argininosuccinic Aciduria. *Sci Transl Med* **2024**; 16: eadh1334. doi:10.1126/scitranslmed.adh1334.
33. Chu Y., Boehringer A., Kordower J.H. The Future Neurotrophic Factor Therapy in Parkinson's Disease. In International Review of Movement Disorders. *Elsevier* **2024**; 7: 221–239. ISBN 978-0-443-31468-1.
34. Li H., Cao Y., Ye J. et al. Engineering Brain-Derived Neurotrophic Factor mRNA Delivery for the Treatment of Alzheimer's Disease. *Chemical Engineering Journal* **2023**; 466: 143152. https://doi.org/10.1016/j.cej.2023.143152.
35. Cao D., Hou X., Wang C., Wang S. et al. Lipid Nanoparticles for mRNA Delivery in Brain via Systemic Administration. *Sci Adv* **2025**; 11: eadw0730. https://doi.org/10.1126/sciadv.adw0730.
36. Lin C.-Y., Perche F., Ikegami M., et al. Messenger RNA-Based Therapeutics for Brain Diseases: An Animal Study for Augmenting Clearance of Beta-Amyloid by Intracerebral Administration of Neprilysin mRNA Loaded in Polyplex Nanomicelles. *J Control Release* **2016**; 235: 268–275. https://doi.org/10.1016/j.jconrel.2016.06.001.
37. Wang Y., Wang X., Xie R. et al. Overcoming the Blood-Brain Barrier for Gene Therapy via Systemic Administration of GSH-Responsive Silica Nanocapsules. *Adv Mater* **2023**; 35: e2208018. doi:10.1002/adma.202208018.
38. Rosenblum D., Gutkin A., Kedmi R., et al. CRISPR-Cas9 Genome Editing Using Targeted Lipid Nanoparticles for Cancer Therapy. *Sci Adv* **2020**; 6: eabc9450. https://doi.org/10.1126/sciadv.abc9450.
39. Hovakimyan A., Chilingaryan G., King O., et al. mRNA Vaccine for Alzheimer's Disease: Pilot Study. *Vaccines (Basel)* **2024**; 12: 659. https://doi.org/10.3390/vaccines12060659.
40. Jiang L., Park J.-S., Yin L., et al. Dual mRNA Therapy Restores Metabolic Function in Long-Term Studies in Mice with Propionic Acidemia. Nat Commun **2020;** 11: 5339. https://doi.org/10.1038/s41467-020-19156-3.
41. Farag M., Tabrizi S.J., Wild E.J. Huntington's Disease Clinical Trials Update: October 2025. *J Huntingtons Dis* **2026**; 15: 156–166. https://doi.org/10.1177/18796397251399751.
42. Piao X., Li D., Liu H., et al. Advances in Gene and Cellular Therapeutic Approaches for Huntington's Disease. *Protein Cell* **2025**; 16: 307–337. https://doi.org/10.1093/procel/pwae042.
43. Hamad A.A., Alkhawaldeh I.M., Nashwan A.J., et al. Tofersen for SOD1 Amyotrophic Lateral Sclerosis: A Systematic Review and Meta-Analysis. *Neurol Sci* **2025**; 46: 1977–1985. https://doi.org/10.1007/s10072-025-07994-2.