

PHARMACOLOGICAL CHAPERONES AS THERAPEUTIC MODULATORS: A NEW ERA IN PROTEIN MISFOLDING DISEASE MANAGEMENT

Parasa Likhita Suma

KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, Andhra Pradesh, India.

Corresponding Author Email: likhitasuma773@gmail.com

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ABSTRACT

Protein misfolding is a central molecular event in many rare genetic and neurodegenerative diseases, leading to the production of unstable, dysfunctional proteins that are often rapidly degraded or form toxic aggregates. Over the past two decades, pharmacological chaperones have emerged as a novel class of small-molecule therapeutics aimed at correcting this defect. These compounds work by selectively binding to misfolded or unstable proteins, stabilizing their structure and assisting in their proper folding, trafficking, and eventual functionality within the cell. Unlike traditional enzyme replacement therapies, pharmacological chaperones act intracellularly and have the potential to cross biological barriers, including the blood-brain barrier, thereby increasing their utility in systemic and neurologic disorders. This review explores the molecular mechanisms by which pharmacological chaperones exert their action and highlights their clinical application across a range of diseases, including Fabry disease, transthyretin amyloid cardiomyopathy and Gaucher disease. In addition to disease-specific benefits, this article discusses broader therapeutic implications and the advantages pharmacological chaperones offer over conventional treatments. Despite their promise, challenges such as mutation specificity, limited organ targeting, potential for enzyme inhibition, and the need for long-term safety data remain areas of active investigation. As our understanding of protein folding disorders expands and technologies for drug discovery improve, pharmacological chaperones are meant to become essential tools in precision medicine especially in many rare conditions.

INTRODUCTION

Pharmacological chaperone is a term that has been in use since 20 years. The main characteristic feature of a pharmacological chaperone is its ability to bind to misfolded

proteins and stabilizing them.¹ Protein misfolding and aggregation are the primary causes of a large number of neurodegenerative diseases like Alzheimer's disease, Parkinson's disease, Huntington's

disease, Creutzfeldt–Jakob disease and also cystic fibrosis, Gaucher’s disease and many other degenerative disorders. Many p53-mediated cancers are also the caused due to protein misfolding.² The destabilization of the alpha helical structure and the simultaneous formation of a beta sheet cause formation of aggregate protein molecules.³ These pharmacological chaperones stabilize the proteins against thermal denaturation or proteolytic degradation and also prevent aggregation.⁴ Most of the effective pharmacological chaperones include cofactor mimetics, ligand mimetics, catalytic inhibitors, stabilized helical peptides, and secondary structure mimetics.⁵ Molecular mechanisms behind many protein conformational diseases are intricate and polyfactorial. Various events are associated with conformational diseases such loss of characteristic function, toxic gain of function, functional degradation, and improper localization.⁶

At molecular level substrate inhibitor binds to a mutant lysosomal misfolded protein as a kind of chaperone, to normalise molecular folding at the endoplasmic reticulum or Golgi compartment in somatic cells, resulting in formation of a stable molecular complex. The chaperone itself, doesnot refold the target protein, but induces the equilibrium toward the natural correct folding after binding to the active site of mutant protein reversibly. The protein-chaperone complex is safely transported to the lysosome, where it breaks down under the acidic condition and the mutant enzyme remains stabilized both structurally and functionally.⁷

Identifying pharmacological chaperones for particular protein targets is difficult due to various factors, including the properties of

protein surfaces, the absence of appropriate chemical libraries, and the limited availability of effective high-throughput screening (HTS) techniques.⁵

PHARMACOLOGICAL CHAPERONES AND THEIR MECHANISM OF ACTION

Pharmacological chaperones are low-molecular-weight chemicals that specifically bind to unstable or misfolded proteins, stabilizing them in a functioning state. This stabilization facilitates proper protein folding and intracellular trafficking, ultimately restoring biological activity in circumstances where genetic mutations disrupt protein structure or localization.^{8,9}

These compounds are especially beneficial in diseases that cause protein misfolding and degradation, such as lysosomal storage disorders, cystic fibrosis, and some neurodegenerative ailments.^{10,11} In many of these illnesses, mutant proteins fail to fold properly in the endoplasmic reticulum (ER) and are thus targeted for ER-associated destruction (ERAD), despite having potential enzymatic or structural function if folded correctly.¹²

Pharmacological chaperones work by reversibly binding to the active site or an allosteric region of the mutant protein. This interaction increases thermodynamic stability, allowing the protein to bypass the cellular quality control system, exit the ER, and travel to its physiological destination—usually the lysosome or plasma membrane. When the protein reaches its intended site, the chaperone may detach, restoring native protein activity.^{13,14} Unlike enzyme replacement treatment, which obtains functional enzymes from outside sources, pharmacological chaperones act

intracellularly and are typically orally accessible. They can also traverse the blood-brain barrier, which provides therapeutic benefits in disorders involving the central nervous system.¹⁵ However, chaperone

therapy is mutation-specific and works best when the protein retains residual activity but is misfolded or unstable.^{9,13}

Major differences between Chemical and Pharmacological Chaperones

CHARACTER	CHEMICAL CHAPERONE	PHARMACOLOGICAL CHAPERONE
Molecule type	General	Designed to target
Specificity	Non Specific	Target Sspecific
Mechanism	General stabilisation	Structural stabilisation
Potential	Minimal	Promising

Table 1: The chaperone molecules are chemical entities that bind to proteins. Pharmacological chaperones are sub classification of chemical chaperones. The characteristic differences between chemical and pharmacological chaperones are represented.¹⁶

Effect of pharmacological chaperones on Dopamine

Sutton *et al.* (2022) conducted an investigation ability of pharmacological chaperones to effect dopamine transporter (DAT), a protein implicated in dopamine transporter deficiency syndrome (DTDS). This condition arises from genetic mutations that prevent DAT from reaching the cell surface, leading to serious motor impairments. They observed that the presence of a secondary amine in bupropion and a rigid isoquinuclidine structure in ibogaine were key for functional recovery. This work emphasizes the importance of molecular conformation of pharmacological chaperones in therapeutic design.¹⁷

Effect of pharmacological chaperones on Ischemic stroke

Chaperones play a critical role in counteracting oxidative stress during ischemic stroke. The ATP-dependent and ATP-independent chaperones protect cellular proteins under stress conditions, especially in energy-deprived zones of the brain. Key families such as heat shock proteins and small chaperones like Hero proteins and Sigma-1 receptors contribute by promoting protein folding, preventing aggregation, modulating mitochondrial function, and activating antioxidant pathways. Their effective role in ischemia suggests potential for therapeutic targeting and significant expression during the onset of stroke.¹⁸

Effect of pharmacological chaperones on Opioid tolerance

Repeated opioid use, particularly morphine, can lead to tolerance through mechanisms involving endoplasmic reticulum stress and the unfolded protein response, which disrupts proper mu-opioid receptor (MOR) signaling. 4-phenylbutyric acid (PBA) and tauroursodeoxycholic acid (TUDCA) when tested in mice have significantly mitigated the development of morphine tolerance without affecting baseline analgesia. Even after tolerance had developed, coadministration of PBA restored morphine's analgesic efficacy.¹⁹

PHARMACOLOGICAL CHAPERONES IN RARE DISEASES

Milgastat in Fabry Disease

Fabry disease defined as a rare lysosomal disorder is characterised by deficient or reduced α -galactosidase activity due to mutations in the GLA gene. Migalastat is the first approved pharmacological chaperone which stabilizes mutant forms of α -galactosidase A enzyme by binding to it reversibly and increases its lysosomal activity. Once in lysosomes, migalastat separates from α -galactosidase A as a result of the more acidic pH and higher concentration of substrates finally allowing the enzyme to break down GL-3. After dissociation from the enzyme, migalastat is rapidly removed from the cell and excreted.²⁰

Tafamidis in Transthyretin Amyloid Cardiomyopathy

Tafamidis is a selective transthyretin (TTR) stabilizer that functions as a pharmacological chaperone, binding to the thyroxine-binding sites of the TTR tetramer. In patients with

transthyretin amyloid cardiomyopathy, this stabilization delays the accumulation of amyloid deposits in cardiac tissue, thereby preventing progressive heart failure and related complications. A recent multicenter observational study by Masri *et al.* (2025) assessed long-term tafamidis outcomes in diverse U.S. population with transthyretin amyloid cardiomyopathy. Among 624 patients, tafamidis was associated with a 65-month survival probability of 54.1%.²¹

Ambroxol in Gaucher Disease

Gaucher disease is a lysosomal storage disorder caused due to β -glucocerebrosidase deficiency. Glucosylceramide and glucosylsphingosine, accumulate in the monocyte lineage of the reticuloendothelial system mainly in the liver, spleen, bone marrow and central nervous system. Pharmacological chaperone therapies for the treatment of Gaucher disease were first studied in the 1990s. Ambroxol is an oral mucolytic available as an over the counter medication. Later it was discovered to act as a pharmacological chaperone for mutant GCase when taken at a high dose by binding to the misfolded GCase and correcting its folding and inducing functional recovery.²²

CHALLENGES DUE TO PHARMACOLOGICAL CHAPERONES

Although pharmacological chaperones have emerged as a promising approach for treating certain protein misfolding disorders, several limitations continue to prevent their broader implementation. One major issue is the selective nature of their effectiveness, such as mutation specificity in which only a subset of genetic variants produce misfolded proteins. That has limited enzymatic activity thus narrowing the scope of treatable patients.²³

Another challenge involves enzyme inhibition, particularly with compounds that bind to the active site, which can unintentionally reduce enzymatic function at higher concentrations or in non-target tissues.²⁴ Limited distribution to certain organs, especially the central nervous system, also restricts the use of many chaperones in diseases with neurological involvement due to poor blood-brain barrier penetration.²⁵

Furthermore, long-term safety and effectiveness remain under-investigated, and whether these therapies can sustain clinical benefit over time is still being studied.²⁶ A revised classification system has recently been suggested to distinguish between chaperones that act alone and those used alongside enzyme replacement therapies (ERT).²⁶ Finally, combination therapies with ERT, while being potentially more effective also adds complexity to treatment.²⁷

CONCLUSION

Pharmacological chaperones represent a transformative step toward the management of protein misfolding disorders, offering a precision-based approach that addresses the molecular origin of disease. Unlike therapies that merely replace or bypass defective proteins, chaperones intervene at the folding stage, helping mutant proteins gain a functional structure and restoring their physiological role. This unique mechanism enables intracellular action and permits crossing of the blood-brain barrier.

The success of agents such as tafamidis in transthyretin amyloid cardiomyopathy and migalastat in Fabry disease has validated this therapeutic concept in clinical settings, showing that pharmacological chaperones

can improve survival, reduce disease burden, and offer oral alternatives to invasive treatments like enzyme replacement therapy. In Gaucher disease, repurposing ambroxol as a chaperone has further demonstrated the potential of existing molecules to be redirected toward rare disorders with unmet needs.

The efficacy of pharmacological chaperones is highly mutation dependent. For moving forward, a deeper understanding of protein folding pathways, combined with advances in high-throughput screening and structure-based drug design, will be essential for identifying and optimizing chaperones for a broader range of diseases. Additionally, strategies such as combining pharmacological chaperones with gene therapy, antisense oligonucleotides, or enzyme replacement therapy may enhance therapeutic outcomes.

In conclusion, pharmacological chaperones are more than a conceptual innovation. They are a practical and evolving reality in modern medicine. Their ability to restore protein homeostasis places them at the forefront of therapeutic development for rare and conformational diseases.

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