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Metals in medicine: unlocking new avenues for neurodegenerative disease treatment

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Neurodegenerative diseases (NDD) such as Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD), and amyotrophic lateral sclerosis (ALS) urgently demand novel therapeutics beyond symptomatic relief. Increasing evidence implicates dysregulation of metal ion homeostasis (e.g., iron, copper, zinc) in the pathogenesis of these diseases, contributing to oxidative stress and protein aggregation. Conventional therapies face limitations including poor brain bioavailability and inability to halt disease progression. In response, metal-based strategies are emerging as promising interventions. This mini-review highlights how restoring metal ion balance and leveraging inorganic chemistry can counter neurodegeneration. We discuss recent advances in metal complexes that target pathogenic pathways, metal-organic frameworks (MOFs) as sophisticated drug delivery scaffolds, and metallic nanoparticles engineered to cross the blood-brain barrier (BBB). These approaches offer unique capabilities to modulate disease processes and deliver multi-functional treatments. By exploring the roles of metal ions in neurobiology and surveying cutting-edge metal-containing therapeutics, we underscore the potential of metals in medicine to unlock new avenues for treating NDD.

KEYWORDS

neurodegenerative diseases, metal complexes, metal organic framework, metallic nanoparticles, metallopeptides, blood brain barrier, drug delivery, metal ion regulation

1 NDD and metal ions: a molecular connection between disease progression and therapy

NDD are a group of disorders characterized by gradual deterioration of nerve cells, leading to degenerative cognitive functions and motor impairments. Some of the main types of NDD include AD (Pantiya et al., 2020; Mittal and Agrawal, 2024; Wei et al., 2025), PD (Pantiya et al., 2020; Mittal and Agrawal, 2024; Wei et al., 2025), HD (Pantiya et al., 2020; Joshi et al., 2025), and ALS (Mittal and Agrawal, 2024; Wei et al., 2025). A

rising body of evidence have suggested that these diseases are often caused by abnormal protein accumulation (Sweeney et al., 2017), oxidative stress (Houldsworth, 2023), mitochondrial dysfunction (Joshi et al., 2025), and genetic mutations (Ogonowski et al., 2024). Symptoms commonly include memory loss, movement impairments, and behavioral changes. The incidence of NDD is projected to increase in parallel with rising life expectancy, imposing a substantial economic burden on public healthcare systems. In 2019, the worldwide cost of dementia (including AD) was estimated at approximately USD 1.3 trillion, equivalent to roughly 1.5% of the world's GDP (Wimo et al., 2023). In 2022, the economic burden of AD in Malaysia was estimated at USD 1.9 billion, accounting for approximately 0.47% of the nation's GDP (Ong et al., 2025). These enormous figure highlights the substantial economic impact of AD on societies globally and locally.

At present, there is no known cure for NDD, however, available treatments primarily focus on symptom management and decelerating disease progression. Ion imbalance plays a critical role in linking oxidative stress, cellular apoptosis, aging, and the pathogenesis of major health diseases. In addition, the homeostasis of metals, such as iron, copper, zinc and calcium for maintaining normal neurophysiological activity has been well established. As disruptions or dysfunctions in ion channel activity contribute to the disease progression, metal ion homeostasis-related signaling pathways have emerged as potential therapeutic targets for various neurological disorders (Xu et al., 2022; Zhang Y. Y. et al., 2023). Reviews have shown a potential risk of dyshomeostasis of calcium ion could heighten the risk of PD simply by disrupting interactions between subcellular organelles (e.g., endoplasmic reticulum, mitochondria, and lysosomes) (Xu et al., 2022). In addition, dysregulated iron homeostasis leading to abnormal iron accumulation in the brain regions has been correlated with the progression and severity of various NDD such as PD and AD (Maass et al., 2021; Wu D. et al., 2023). Conversely, exposure to cadmium and lead has been linked to an elevated risk of developing ALS (Peters et al., 2021).

Despite progress in current treatment approaches, significant challenges persist, including limited efficacy, adverse side effects, and the inability to halt disease progression. Growing evidence suggests that metal ions hold promise as therapeutic agents, offering innovative strategies to restore metal homeostasis and counteract disease pathology. Addressing these challenges demands ongoing research and innovation to refine metal-based therapeutics, enhance targeted delivery, and improve clinical translation, ultimately paving the way for more effective treatments and improved patient outcomes. This review next examines how metal dysregulation contributes to disease pathology and why current treatments fall short, in order to contextualize new metal-based therapeutic strategies.

2 Unraveling therapeutic pathways: mechanisms of action and the hurdles of current treatments

NDD are driven by complex, multifactorial mechanisms, including oxidative stress, protein misfolding, and

neuroinflammation (Wilson et al., 2023). Among these factors, metal dysregulation has emerged as a significant contributor to disease progression, affecting both oxidative balance and protein aggregation in the brain (Pamphlett and Bishop, 2023).

One key consequence of metal dysregulation is the accumulation of metals such as iron, copper, and zinc in specific brain regions, exacerbating neuronal damage. Meta-analyses have linked elevated iron and iron-related proteins to an increased risk of AD (Gong et al., 2023), while similar findings indicate a strong connection between iron accumulation and neurodegeneration (Vellingiri et al., 2022). The pathological effects of excess metal ions are largely mediated by oxidative stress (Chen et al., 2025). Redox-active metals such as iron contribute to the Fenton reaction, producing highly reactive hydroxyl radicals that ultimately result in neuronal death. Recent studies suggest that both iron and copper dysregulation contribute to PD by promoting α -synuclein aggregation through oxidative mechanisms, further accelerating neurodegeneration (Behl et al., 2022).

Beyond oxidative stress, disruptions in metal ion homeostasis influence key proteins involved in NDD. In AD, the toxic aggregation of Amyloid-beta ($A\beta$) and tau proteins has been linked to abnormal metal binding (Das et al., 2021). The function of metals such as zinc, copper and iron in promoting $A\beta$ aggregation was initially identified in early studies (Zatta et al., 2009) and later confirmed in subsequent investigations (Doroszkiwicz et al., 2023). Recent nuclear magnetic resonance studies have offered detailed insights into the structures and dynamics of metal- $A\beta$ complexes, shedding further light on their involvement in bulk protein aggregation (Abelein et al., 2022; Abelein, 2023).

While neuroinflammation is often considered a consequence of neurodegeneration, emerging evidence suggests it plays a crucial role in disease progression (Zhang W. et al., 2023). However, recent studies indicate that protein misfolding and aggregation may occur independently of neuroinflammation, suggesting that anti-inflammatory therapies alone may not be sufficient to halt disease progression (Matarazzo et al., 2024). This complexity underscores the need for multi-targeted therapeutic strategies.

Although significant research efforts have been made, finding effective disease-modifying therapies for NDD remains challenging. Existing treatments alleviate symptoms but do not prevent disease advancement, resulting in ongoing neurological deterioration (Akhtar et al., 2021). While numerous drug candidates have entered clinical trials, most fail due to issues with efficacy, safety, or drug delivery challenges (Zhang et al., 2024). For example, dalzanemdor, which was investigated for PD, AD, and HD, was discontinued in 2024 after failing to demonstrate significant benefits over placebo (Sage Therapeutics, 2024).

Traditional therapies also offer limited long-term benefits. For instance, levodopa, the gold standard treatment for PD, loses efficacy over time due to disease progression and the development of peripheral resistance (Beckers et al., 2022).

TABLE 1 Current treatment for neurodegenerative diseases and their limitations (Borovac, 2016; Hill et al., 2019; Parkinson's UK, 2025; Medscape, 2025).

Medication	Neurodegenerative diseases	Frequent adverse effects	Special caution
Amantadine	Parkinson's disease, Chorea of Huntington's disease, Lewy body dementia	1-10%: Headache, dizziness, drowsiness, fatigue, confusion, abnormal dreams, agitation, irritability, anxiety, nervousness, insomnia, ataxia, delirium, hallucinations, and depression	○ The benefits of treatment in Parkinson's disease tend to diminish over time, typically within several months. However, the abrupt discontinuation of the drug is strongly advised against, as it may lead to neuroleptic malignant syndrome (NMS)
Anticholinergics	Parkinson's disease	>10%: Dry mouth, dry skin, dental problems, constipation, blurred vision, hyperpyrexia (overheating), confusion, sedation, and dementia-like symptoms (especially with long-term use)	○ Side effects are more pronounced in the elderly population and may increase the risk of falls and injury ○ Increases the cumulative risk of cognitive impairment and mortality, especially in the elderly
Catechol-O-Methyl Transferase Inhibitors	Parkinson's disease	Diarrhea, elevated liver transaminases, discoloration of urine, and rhabdomyolysis	○ Because of the risk of liver disease, treatment with tolcapone should be discontinued within 3 weeks of initiation if no clinical benefit is seen ○ When used with levodopa/carbidopa, dyskinesias may occur
Cholinesterase Inhibitors	Alzheimer's disease and other dementias, rivastigmine is FDA-approved for Parkinson's disease dementia	>10%: Nausea, vomiting, diarrhea, loss of appetite, tired feeling, or sleep problems	○ Risk for seizures and impaired cardiac conduction
Dopamine Agonists	Parkinson's disease	Nausea, vomiting, orthostatic hypotension, headache, dizziness, and cardiac arrhythmia	○ Certain older dopamine agonists, known as 'ergot' derivatives, have been associated with an increased risk of heart and lung complications. Examples include bromocriptine, pergolide, and cabergoline
Dopamine Precursors	Parkinson's disease	>10%: Dyskinesias and involuntary movements, orthostatic hypotension, syncope, hypotension, dizziness, headache, gastric distress, depression with suicidal ideations, insomnia, anxiety, confusion, abnormal dreams and nightmares, and polyneuropathy	○ Motor fluctuations develop over time, with an estimated 10% annual risk associated with levodopa use. However, they can also appear as early as 5–6 months into therapy ○ Abrupt discontinuation of levodopa-containing medications is strongly discouraged to prevent the risk of NMS.
Memantine	Alzheimer's disease	1-10%: Dizziness, headache, confusion, constipation, cough, hypertension, backache, pain, somnolence, syncope, vomiting, dyspnea, fatigue	○ Caution is advised when using this medication in patients with pre-existing cardiovascular conditions (e.g., angina, bradycardia), as well as those with renal or hepatic impairment and seizure disorders ○ Use with extreme caution in patients with a known hypersensitivity to memantine or allergy to any of its derivatives
Riluzole	FDA-approved for amyotrophic lateral sclerosis	>10%: Oral hypoesthesia, asthenia, nausea (16%)	○ Severe neutropenia (absolute neutrophil count $<500/\text{mm}^3$) has been reported within the first 2 months of treatment ○ Cases of interstitial lung disease, including hypersensitivity pneumonitis, have been reported in patients undergoing treatment
Tetrabenazine	FDA-approved to treat chorea associated with Huntington disease	>10%: Sedation/somnolence, depression, anxiety, insomnia, akathisia (agitation and restlessness), fatigue, and nausea	○ Tetrabenazine possesses a black box warning for increasing the risk compared with placebo of suicidal thinking and depression in patients with Huntington's disease

Additionally, many available treatments cause adverse effects (Table 1). For instance, over 50% of patients receiving levodopa develop motor complications within 4 years of starting treatment (Warren Olanow et al., 2013).

One of the greatest obstacles in NDD treatment is the BBB, a highly selective membrane that restricts the entry of most therapeutic molecules into the central nervous

system (CNS) (Zlokovic, 2008; Wu D. et al., 2023). Since NDD involve progressive brain deterioration, effective treatments must cross the BBB to reach target sites. However, poor bioavailability in the CNS remains a critical limitation in delivering successful treatments (Akhtar et al., 2021). The next section explores such metal-based therapeutic avenues.

3 Translating metal-based therapeutics: applications across preclinical and clinical studies

3.1 Metal complexes in neurodegeneration: therapeutic roles in AD and PD

In light of the above challenges, researchers are exploring various metal-based compounds that target common pathological features like protein aggregation and metal ion imbalance.

Because of the critical roles of copper, zinc and iron accumulation in NDD, metal chelators have received considerable attention. For more detail on this approach, readers are referred to recent reviews (Sales et al., 2019; Vilella et al., 2020; Fasae et al., 2021; Du et al., 2024; Liu et al., 2024). Chelators, through binding to metal ions, prevent them from generating oxidative stress and from interacting with amyloid proteins, in turn inhibiting aggregation. In the context of NDD, a new class of chelators, characterized by a weaker affinity, named metal protein attenuating compounds (MPACs) are developed. MPACs are designed to cross the BBB and to remove excess accumulated metal ions (Zn^{2+} and Cu^{2+}) without disrupting bulk metal coordination and normal functioning of metalloenzymes and related biological processes. Following promising outcomes from preclinical studies in AD and PD models respectively, the 8-hydroxyquinoline derivatives PBT2 (Faux et al., 2010; Huntington Study Group Reach2HD Investigators, 2015; Villemagne et al., 2017) and PBT434 (Stamler et al., 2020; Levi and Volonté, 2023) have reached clinical trials (phase II in AD and HD patients and phase I respectively) (Figure 1). Similarly, Desferrioxamine (DFO), a chelator for trivalent ions (Figure 1) successfully entered AD phase II clinical trials, and, however, was discontinued due to the poor BBB penetration and systemic toxicity at high dosages.

Lithium-based treatments, which have long been used to treat psychiatric disorders (Cade, 1949), have been proposed to provide neuroprotection in neurodegenerative contexts (AD and PD, for example,) in *in vivo* studies (Lovestone et al., 1999; Alvarez et al., 2002; Su et al., 2004; Noble et al., 2005; Engel et al., 2006; Engel et al., 2008; Macdonald et al., 2008; Fiorentini et al., 2010; Leroy et al., 2010; Quiroz et al., 2010; Zhang et al., 2011; Forlenza et al., 2014; Lazzara and Kim, 2015; Gao et al., 2022) and were evaluated in a few clinical trials (Hampel et al., 2009; Forlenza et al., 2011).

Metallodrugs are also actively developed for the treatment of NDD, with diverse modes of action (MOA). The latest developments are described in several recent reviews (Liu et al., 2024; Florio et al., 2025). Most of those studied so far target A β species with the aim of inhibiting aggregation by interfering with the protein-metal ions interactions. Their interaction with such species, which can include coordination of protein side chains, can alter amyloid protein structures and aggregation states or stabilize non-toxic conformations. Antioxidant properties or inhibition of acetylcholinesterase are alternative modes of action.

Metal complexes evaluated in this context comprise platinum, ruthenium, iridium, gold, cobalt, vanadium, manganese/iron, copper and zinc complexes along with homo- and hetero-bimetallic species (Table 2). Promising results were obtained *in vitro* and in cellular models. However, few have been evaluated *in vivo*, often due to BBB crossing challenges.

A Pt (II) complex of a functionalized 8-BQ ligand (8-(1H-benzoimidazol-2-yl)-quinoline), **1**, was developed and demonstrated a reduction of A β toxicity in primary mouse cortical neuronal cell cultures (Kenche et al., 2013). The Pt (IV) corresponding prodrug, **2**, showed higher Pt levels in the brain of wild type mice compared to the Pt (II) complex (Figure 1). In a mouse model of AD (APP/PS1), a reduction in A β 42 levels and in plaque number was observed in the Pt (IV) treated group (Kenche et al., 2013). More recently, Co(III)-salnaph complexes showing A β aggregation inhibition properties (**3-4**), were delivered across BBB in mice (C57BL/6J and transgenic 5xFAD mice as AD model) by use of focused ultrasound and was shown to be well-tolerated (Figure 1) (Chan et al., 2021). Zinc complexes such as pine peptide-zinc chelates (Zhang Z. et al., 2023) and Zn(II)-based amide carboxylate (Waseem et al., 2022) were shown to have potential in AD treatment with improvements in memory and learning in AD murine models through reduction in acetylcholinesterase levels and antioxidant properties among others. Finally, the thiosemicarbazone-pyridylhydrazone Cu(II) complex CuL5 (Figure 1) demonstrated cognitive benefits despite increasing amyloid plaques in treated in 5xFAD mice (Choo et al., 2022).

Despite extensive research, few metal chelators or metal-based drugs have been evaluated *in vivo* so far. Further efforts are needed to translate promising *in vitro* results into preclinical and clinical evaluations to confirm their potential in reducing neurotoxicity in the treatment of NDD. To this aim, key chemical properties of the drug candidates such as pharmacokinetics require optimisation to limit toxicity and enhance BBB crossing ability.

3.2 Therapeutic potentials of MOFs: controlled drug release and metal ion homeostasis

Latterly, MOFs have garnered remarkable attention in biomedical applications. These materials composed of metals ions extensively coordinated with organic ligands are characterized with high crystallinity, porosity, and versatility for structural modification. Examples of well-established MOFs include MIL-100(Fe), ML-101(Cr), UiO-66, ZIF-8 etc. (Abánades Lázaro et al., 2024; Wang et al., 2024). Henceforth, MOFs have been prevalently investigated for their potential in drug delivery and metal ion regulation.

Harnessing MOFs as drug delivery system (DDS) generates merits including enhanced biocompatibility, controlled-release, stability, and targeting effect (Wang et al., 2024). Recently, encapsulation of hydrophobic quercetin within zeolitic imidazolate MOFs with Prussian blue coating (ZIF-8@PB-QCT) was designed for PD therapy. Intriguingly, functionalization with PB permits heat-stimulated release of QCT upon photoirradiation in near infrared region, improving penetration across BBB, hence uptake by neuronal cells. Ultimately, non-invasive delivery of ZIF-8@PB-QCT exerted protective effects against neurotoxins and mitochondrial damage, subsequently ameliorated locomotive ability of impaired mice (Liu et al., 2021). Likewise, ZIF-8 framework loaded with Kaempferol and bearing polydopamine coating was synthesized for Postoperative Neurocognitive Disorder treatment. Evidently, anti-inflammatory and anti-oxidative effects were

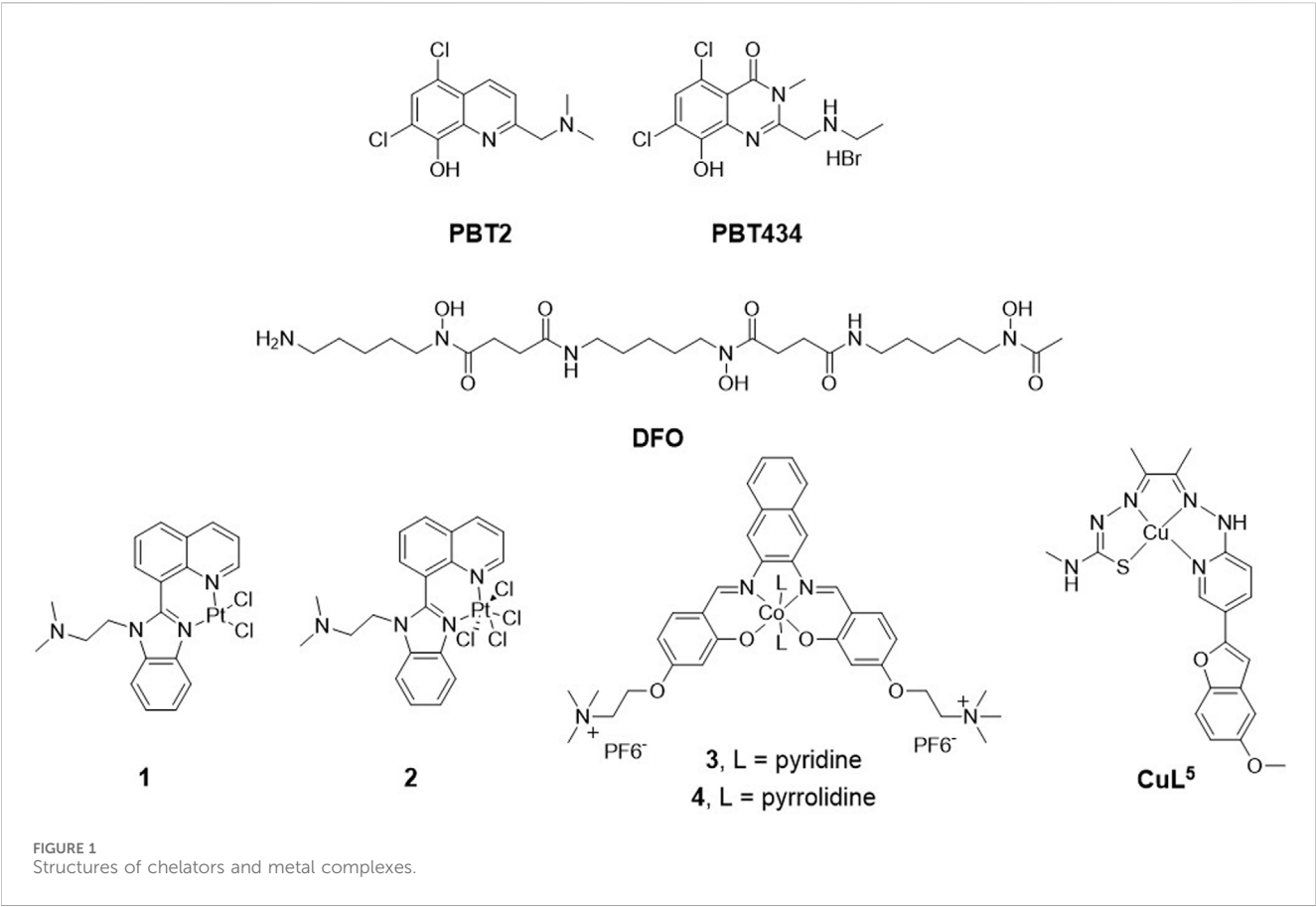


TABLE 2 Metal complexes assessed for neurodegenerative diseases.

Types of metal complexes	References
Platinum complexes	Florio et al. (2019a), Florio et al. (2019b), Manna et al. (2021), La Manna et al. (2022)
Ruthenium complexes	Batchelor et al. (2019), Gomes et al. (2019), Florio et al. (2020), Huffman et al. (2020), Kladnik et al. (2020), Liu et al. (2020), Almeida et al. (2021), Wall et al. (2021), Yawson et al. (2021), 2022; Cuccioloni et al. (2022), Singh et al. (2023), Wu C. Y. et al. (2023), Chen et al. (2024), Ehlbeck et al. (2024), La Manna et al. (2024b)
Iridium complexes	Kang et al. (2019)
Gold complexes	Huang et al. (2019)
Cobalt complexes	Gorantla et al. (2019), Iscen et al. (2019), Roberts et al. (2020)
Vanadium complexes	Dong et al. (2019), He et al. (2020), 2021; Rambaran et al. (2020), Drzeżdżon et al. (2021), Yao et al. (2023)
Manganese/iron complexes	Zhang et al. (2022)
Copper complexes	Choo et al. (2022), Zhang et al. (2021), Pyun et al. (2022), Pyun et al. (2023)
Zinc complexes	da Silva et al. (2021), Zafar et al. (2021b), Zafar et al. (2021a), Jahan et al. (2023), Sheikh et al. (2024)
Homo- and hetero- bimetallic species	Terán et al. (2023), La Manna et al. (2024a)

prominent during *in vivo* studies, with improvement in hippocampal neuron viability and cognitive function (Huang et al., 2024). Furthermore, a cyclodextrin-based MOFs modified with stigmasterol and lactoferrin was formulated for huperzine A delivery in AD treatment. The framework was dispersed in a hyaluronic acid/gelatin-tannic acid microneedle patch, subsequently delivered via nasal route. Inclusion of lactoferrin

improved targeting for intracerebral uptake while modified patch reduced aqueous degradation and toxicity. Impressively, microneedle-assisted MOFs delivery enhanced BBB penetration and accumulation of huperzine A, concurrently reducing clearance by nasal cilia. Overall, inhibition of neuronal oxidative damage and restoration of impaired mice’s neurological function was achieved (Ruan et al., 2024).

Intriguingly, biodegradation of MOFs has been optimized to stimulate controlled release of metal ions to cure deficiency. An investigation on MOF-74(Cu) elucidated the copper-release kinetics, shedding light on potential treatment against copper deficient neurological diseases including ALS and PD. Remarkably, zero-order controlled release of copper promoted brain accumulation, simultaneously minimizing liver intoxication for replenishment of body essential elements (Aguila-Rosas et al., 2024). Another study focused on alleviation of spinal cord injury (SCI) via exploiting ZIF-8 framework to induce neurodifferentiation of dental pulp stem cells (DPSCs), replenish Zn^{2+} levels, and trigger angiogenesis. Distinctly, combinatorial treatment with ZIF-8-DPSCs healed impaired neurons and rectified the locomotive ability of rats with SCI (Zhou et al., 2023).

In contrast, excessive accumulation of metal ions promotes the conformational change of A β peptides into aggregates, resulting in deterioration of neurological function and triggering the onset of AD (Abelein, 2023). In efforts to ameliorate AD, varying porphyrin-modified MOFs (PMOFs) were formulated to facilitate the removal of excessive copper (II) ions to restrict A β aggregation and neurotoxicity. In particular, Hafnium-based PMOFs demonstrated significant copper (II) chelation and singlet oxygen generation capacity upon photoirradiation at 450 nm. Evidently, treatment of Hf-PMOFs on AD transgenic roundworms rectified the locomotive ability, diminished paralysis and prolonged the lifespan (Yu et al., 2019).

3.3 Crossing the barrier: metallic nanoparticles in targeted CNS drug delivery

The treatment of NDD presents significant therapeutic challenges, primarily due to the formidable BBB. BBB is a highly selective semipermeable border of endothelial cells that protects the brain from harmful substances. It also simultaneously limits the entry of many potential therapeutics to the CNS, thus hindering its drug delivery effectiveness (Teleanu et al., 2018; Niu et al., 2019). Since the BBB restricts systemically administered compounds' access to the brain, large drug doses are required every time, unfortunately causing toxic effects (González-Domínguez et al., 2014).

Recent advancements in nanotechnology have introduced metal nanoparticles (MNPs) as promising vehicles for targeted drug delivery across the BBB, offering new avenues for NDD treatment (Sintov et al., 2016; Furtado et al., 2018; Abidi et al., 2023). The latest advances are thoroughly discussed in several recent reviews. These nanoparticles, including gold (Chang et al., 2021), silver (Qin et al., 2025), and iron oxide, exhibit unique physicochemical properties such as small size and large surface area. The desirable feature of metallic nanoparticles also includes the ability to be functionalized for a specific target. The ability to deliver drugs directly to the brain is enhanced, it improves bioavailability, and reduces side effects (Li et al., 2021; Scarpa et al., 2023).

Altering the size, shape, and surface chemistry of these nanoparticles can impact their participation in various transport mechanisms, such as receptor-mediated transcytosis and adsorptive-mediated transcytosis, in turn helping them cross

the BBB. Due to their nontoxic features, gold nanoparticles have been highlighted for their multifunctional capabilities, including the ability to undergo surface modifications and target specific brain regions (Chang et al., 2021; Silveira et al., 2021; Puranik et al., 2023; McLoughlin et al., 2024; Roghani et al., 2024). To improve drug delivery efficiency, these modifications can include functionalization with targeting ligands (Zhao et al., 2022; Roghani et al., 2024). For example, insulin-targeted gold nanoparticles (INS-GNPs) have been demonstrated to effectively cross the BBB, resulting in significant accumulation in the brain. Such results show the potential of INS-GNP as a delivery system for NDD treatments (Shilo et al., 2014; Betzer et al., 2019). INS-GNP demonstrated an accumulation exceeding five times that of untargeted gold nanoparticles by targeting insulin receptors.

The precision of drug delivery in AD and PD has also been proved by the functionalization of AuNP to specifically target pathological proteins such as Tau and α -synuclein (Tapia-Arellano et al., 2024). Silver nanoparticles (AgNPs) have been shown to enhance BBB permeability (Li et al., 2021). The interaction with endothelial cells modulates the expression of proteins that relate to oxidative stress and neurodegeneration (López-Espinosa et al., 2024). They have been shown to upregulate the proteins associated neurodisorders and downregulates those that sustain brain homeostasis. Consequently, AgNPs may facilitate drug delivery while potentially inducing neurotoxicity (Khan et al., 2019). Despite these concerns, their antimicrobial and anticancer properties make them promising for neurogenesis disease theragnostic (combining therapeutic and diagnostic capabilities) (Teixeira et al., 2025). Similar to AuNPs, AgNPs can also be designed to target specific molecular pathways involved in neurodegeneration (Ribeiro et al., 2022). The general goal is to improve their therapeutic potential while reducing adverse effects (Mistretta et al., 2023; López-Espinosa et al., 2024; Qin et al., 2025).

Other metal nanoparticles, such as those based on iron, copper or zinc (Jaragh-Alhaddad and Falahati, 2022), have been investigated for their magnetic characteristics. The presence of an external magnetic field makes it possible to guide the magnetic nanoparticles to specific brain areas (McLoughlin et al., 2024; Toader et al., 2024). These nanoparticles can be designed to be able to release drugs in a controlled manner (Kalaiselvi et al., 2020; Mendake et al., 2024). The potential of cerium nanoparticles in addressing treatment challenges associated with AD has also been explored (Hanzha et al., 2023). The brain-targeted nanoparticle, Ce/Zr-MOF@Cur-Lf, has been synthesized and described to improve drug transport across the BBB. Curcumin-loaded Ce/Zr-MOF@Cur-Lf can mitigate oxidative stress, a significant contributor to NDD (Yang et al., 2024).

Despite these advantages, the requirement for thorough safety and the scalability of the metallic nanoparticles production for clinical application need to be addressed (Rafati et al., 2024; Rehman et al., 2024). Overall, the integration of nanotechnology in NDD treatment holds significant promise since it offers innovative solutions to overcome the limitations posed by the BBB (Riccardi et al., 2021; Mistretta et al., 2023).

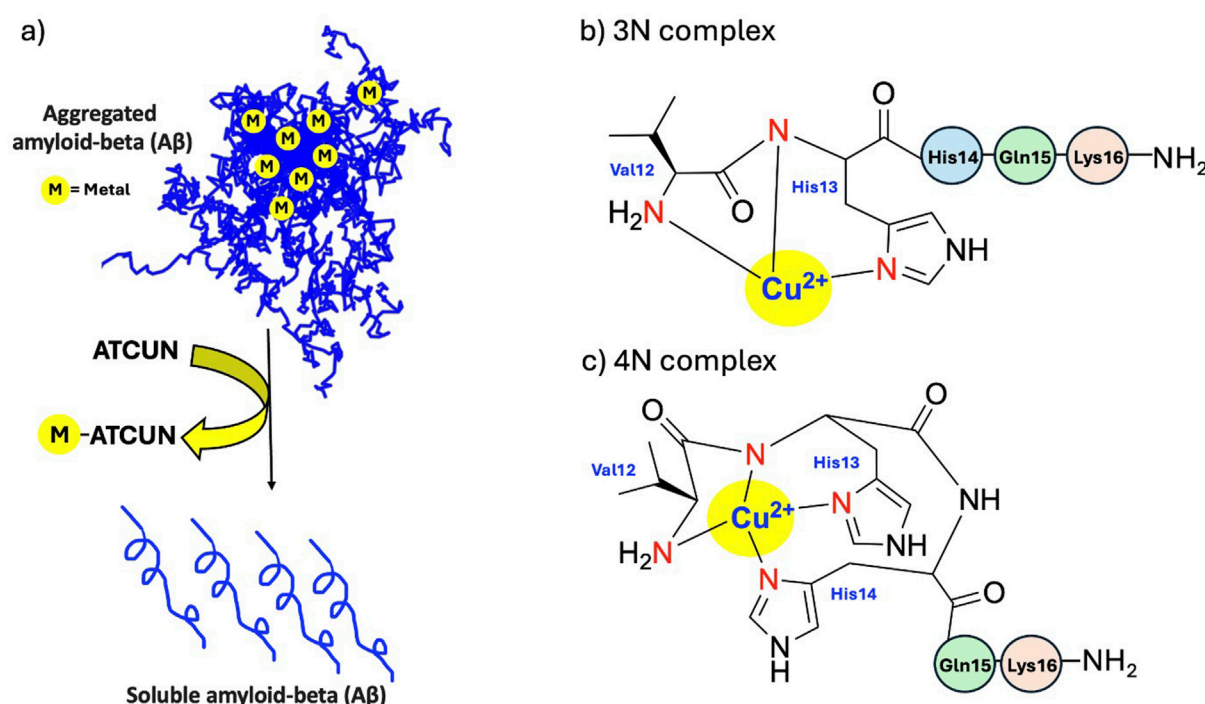


FIGURE 2
(a) Metal-ATCUN derivatives to remove excess metal ions and regulate metal homeostasis to prevent Aβ aggregation. **(b)** Val12 and His13 bind Cu²⁺ with 3N (ATCUN) and **(c)** Val12, His13 and His14 bind Cu²⁺ with 4N coordination modes, depending on the pH.

3.4 Exploring protein aggregation and metal imbalance in NDD using metallopeptides

Metallopeptides have been widely used to study and understand the underlying molecular mechanism that govern protein misfolding and metal homeostasis in the CNS. Studies have shown that the presence of metal ions tends to block the enzymes that break down Aβ and creates harmful free radicals which induce peptide conformation changes and lead to Aβ aggregation (Lovell et al., 1998; Dong et al., 2003; Miller et al., 2006; Tamano and Takeda, 2015). A recent NMR study revealed that metal-Aβ complexes inhibit fibril formation at low metal ion concentrations but promote amorphous aggregation at higher concentrations (Abelein, 2023). Several studies focus on using metal chelators, such as the amino-terminal copper and nickel binding site (ATCUN) to remove excess metal ions and regulate metal homeostasis to prevent Aβ aggregation, as illustrated in Figure 2a. Mital et al. examined how copper and zinc bind to the ATCUN motif that derived from Aβ(12–16) to better understand its coordination with metal ions (Mital et al., 2020). This study demonstrated that the 3N copper-peptide complex (Figure 2b) formed at low pH to a more stable 4N complex (Figure 2c) at pH above pH 6 monitored using UV-Vis and CD spectroscopy. Most of the copper-peptide complex formed at pH 7.4. Besides, Lefèvre et al. has also studied the sequence of ATCUN peptide in relation to its reactive oxygen species (ROS) activity in AD and found that all the eight synthesized ATCUN peptides formed the same thermodynamic complex with Cu(II) (Lefèvre et al., 2022). The addition of histidine at position 1 or 2 improved copper

uptake kinetics and the ability to prevent ROS formation, especially with motifs HWHG and HGHW.

In addition, Pandini et al. revealed that the addition of copper and zinc to nerve growth factor (NGF) and NGF (1–14) enhanced the phosphorylation of CREB, Akt and ERK, which are important signaling molecules involved in cell growth, survival and differentiation, but acetylated NGF (1–14) have no significant effect due to lower copper binding stability compared to NGF (1–14), highlighting the potential of metallopeptide in neurodisorder (Pandini et al., 2016). Russo et al. studied the neurotrophic activity of synthetic peptides based on the first 12 amino acids of BDNF N-terminal (HSDPARRGELSV, m-bdnf) and its dimer linked by a disulphide bridge (HSDPARRGELSV-CVSLEGRRAPDSH, d-bdnf), focusing on zinc ion modulation (Russo et al., 2022). D-bdnf was found to have activity like BDNF but loses effectiveness in promoting neuron growth when bound to zinc. Under acidic conditions, zinc binding decreases due to histidine protonation. A zinc preference for binding to the terminal histidine residues was also found. Besides, both d-bdnf and m-bdnf coordinated with only one Zn²⁺ ion despite having two histidine residues might be due to the higher flexibility compared to m-bdnf.

Tachykinins, a family of neuropeptides involved in various physiological and pathological processes, have been shown to possess excellent metal chelation properties with high binding affinity (Steinhoff et al., 2014). Metals such as Cu, Ag, Ni, and Zn have been studied for their binding to tachykinins and neuropeptides, including NKA, NKB, SP, NPG, and NPY (Pettit et al., 1991; Harford and Sarkar, 1997; Pietruszka et al., 2011; Russino et al., 2013; Grosas et al., 2014; Ye et al., 2018; Ben-

Shushan et al., 2020; Ben-Shushan and Miller, 2021a; Ben-Shushan and Miller, 2021b). These studies revealed that these tachykinins are potential metal chelators with high metal binding affinity. However, the experimental investigation into their role as metal chelators remains scarce. Recently, molecular modelling studies confirmed that three tachykinins can bind Cu^{2+} and Zn^{2+} ions, shedding light on their potential in metal ion interactions (Ben-Shushan et al., 2020).

4 Challenges and future perspectives

Metal-based therapies offer several compelling advantages over conventional approaches. Specificity can be heightened by designing complexes, MOFs or nanocarriers that target pathological hallmarks (for example, stimuli-responsive metal nanoparticles enable target-specific drug release in diseased neurons) (Behera et al., 2023). Such systems are often multifunctional, capable of concurrent therapeutic and diagnostic (theragnostic) roles or combined actions. In addition, pairing metal nanoparticles with chelators or other metal complexes can yield synergistic, multi-pronged effects (Behera et al., 2023). Furthermore, incorporating drugs into metal complexes or nanoscale metal frameworks can improve bioavailability and delivery to the brain.

Nanosystems have been shown to ferry drugs across the BBB more effectively than free small molecules (Mistretta et al., 2023), addressing a major limitation in neurodegenerative treatment. Customizing the surface properties of metallic nanoparticles further enhances their specificity and biocompatibility, as demonstrated with gold nanoparticles achieving targeted, prolonged action with minimal immune response (Chiang et al., 2024).

Despite these advantages, significant challenges remain before metal-based therapeutics can fully realize their potential. Toxicity is a foremost concern with many metal compounds that can induce off-target effects or oxidative damage if not carefully controlled. For instance, certain metal nanoparticles tend to release free metal ions or aggregate *in vivo*, which may trigger neuroinflammation and neuronal toxicity (Shahlaei et al., 2024). Ensuring stability of these agents under physiological conditions is crucial; premature degradation or uncontrolled metal release can not only reduce efficacy but also heighten side effects.

BBB penetration represents another double-edged sword. While innovative nanoformulations are being designed to cross the BBB, it is challenging to achieve sufficient brain uptake without disrupting the BBB's integrity or causing systemic issues (Shahlaei et al., 2024). Careful engineering is required so that delivery vehicles transit into the brain parenchyma efficiently yet safely. Moreover, the clinical translation of metal-based drugs is impeded by gaps in understanding their long-term behavior in the brain. For instance, nanoparticles accumulating in neural tissue might have unknown chronic effects (Shahlaei et al., 2024). Rigorous *in vivo* studies and safety assessments are needed to address these uncertainties.

Looking ahead, research is actively focused on overcoming these hurdles and enhancing the therapeutic promise of metal-based interventions. One key direction is improving biocompatibility: by using biologically friendly coatings or green synthesis methods, scientists aim to produce metal nanoparticles that evade immune detection and minimize toxicity (Chiang et al., 2024). Such surface modifications can also bolster particle stability and circulation time, ensuring the therapeutic payload reaches its target (Tan et al., 2025).

Another future avenue is personalized medicine. Given the patient-to-patient variability in metal metabolism and disease progression, tailoring treatments (for example, dosing of metal chelators or selecting specific metal-based agents) to an individual's genetic and biochemical profile could maximize efficacy and safety. In parallel, researchers are developing hybrid nanoplatforms that combine metal components with organic or biological molecules to harness the best attributes of each. These hybrids such as metal-polyphenol networks or metal-loaded exosome mimics offer the flexibility to integrate targeting ligands, responsive release mechanisms, and multi-drug payloads in one system, addressing multiple disease pathways simultaneously (Shahlaei et al., 2024).

Finally, the integration of artificial intelligence (AI) is poised to accelerate progress in this field. AI-driven drug discovery platforms can rapidly screen and optimize metal-based compounds, predicting properties like BBB permeability and toxicity before clinical testing (Nehmeh et al., 2024). By expediting the identification of promising metal complexes or nanomaterials and guiding rational design, machine learning tools may significantly shorten the development cycle for next generation neurotherapeutics.

5 Conclusion

In conclusion, metal-centered strategies are expanding the therapeutic toolkit for NDD, offering hope for more effective treatments. By capitalizing on their specificity and multifunctionality while diligently addressing safety and delivery challenges, future research will pave the way for metal-based medicines that can modify disease course. Interdisciplinary efforts uniting chemists, neuroscientists, clinicians, and data scientists will be essential to translate these innovative approaches from bench to bedside, ultimately unlocking new avenues to combat disorders like AD, PD, HD and ALS.

Author contributions

KT: Writing – original draft, Writing – review and editing. KC: Writing – original draft, Writing – review and editing. LW: Writing – original draft, Writing – review and editing. HB: Writing – original draft, Writing – review and editing. NA: Writing – original draft, Writing – review and editing. YC: Writing – original draft, Writing – review and editing. ML: Writing – original draft, Writing – review and editing.

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Conflict of interest

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

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