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Metal-Ion Homeostasis in Amyotrophic Lateral Sclerosis and Motor Neuron Disease: A Narrative Review on Pathophysiology, Therapeutic Targets and Clinical Evidence

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ABSTRACT

Amyotrophic lateral sclerosis (ALS), within the broader motor neuron disease (MND) spectrum, is a progressive neurodegenerative disorder involving upper and lower motor neurons. Disturbances in metal-ion homeostasis may interact with excitotoxicity, mitochondrial dysfunction, oxidative stress, protein aggregation, neuroinflammation and regulated cell death. This review examines zinc (Zn), copper (Cu), magnesium (Mg), calcium (Ca), cobalt (Co), iron (Fe), manganese (Mn) and selenium (Se). These elements have dual biological roles: They are essential cofactors at physiological concentrations but can become harmful when deficient, redistributed, poorly sequestered or excessive. Calcium dysregulation is closely linked to excitotoxic motor-neuron injury; iron accumulation provides a mechanistic connection to oxidative stress and ferroptosis; and copper/zinc biology is particularly relevant to SOD1-associated ALS. Targeted copper delivery with CuATSM and iron chelation represent important experimental approaches, although neither is established therapy and chelation has worsened outcomes in other neurodegenerative diseases. Observational associations involving zinc and selenium remain insufficient to establish supplementation as disease-modifying therapy, and magnesium, manganese and cobalt have plausible biological roles but limited clinical treatment evidence. Overall, current evidence favors correction of documented nutritional deficiencies and avoidance of excessive exposure rather than empirical high-dose mineral supplementation. Future work should integrate metal speciation, imaging, metalloproteomics, genetic stratification and longitudinal clinical outcomes to identify patients in whom metal-directed interventions may be rational.

Key words: Amyotrophic lateral sclerosis; motor neuron disease; zinc; copper; magnesium; calcium; cobalt; iron; manganese; selenium; SOD1; oxidative stress; ferroptosis; metal homeostasis.

1. Introduction

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by degeneration of upper and lower motor neurons. Its biology is multifactorial and includes glutamatergic excitotoxicity, mitochondrial dysfunction, oxidative and nitrosative stress, impaired axonal transport, neuroinflammation and abnormal protein aggregation [1,2]. Metal ions are relevant because they act both as essential cofactors and as potential mediators of neuronal injury. Iron, copper, manganese and zinc participate in antioxidant enzymes and mitochondrial metabolism; calcium and magnesium regulate excitability and intracellular signaling; and selenium is incorporated into selenoproteins that control redox balance [3–5].

A key difficulty is that an abnormal metal concentration does not automatically mean that supplementation is indicated. ALS can alter nutritional status, metabolism, renal handling, body composition and inflammatory signaling. A metal abnormality may therefore represent a cause, consequence, biomarker or epiphenomenon. Prospectively collected samples help to address reverse causation, whereas measurements made after symptom onset cannot [6]. The present review evaluates the mechanistic and clinical evidence for Zn, Cu, Mg, Ca, Co, Fe, Mn and Se, with particular attention to therapeutic implications, and summarizes the quality of evidence for each element (Tables 1–5, Figures 1–6).

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2. Conceptual Framework: The "Goldilocks" Principle

Metal biology in ALS is best understood as a concentration- and compartment-dependent phenomenon. Deficiency may impair enzyme activity or protein stability, physiological concentrations support neuronal function, while excess labile metal can promote oxidative chemistry, mitochondrial injury, protein aggregation or regulated cell death [3–5]. Total tissue or blood concentration is therefore an imperfect readout: what matters is the labile, protein-bound and subcellular distribution of each metal.

This framework is especially important for SOD1 biology. Cu/Zn-SOD1 requires both metals for normal maturation, but disease-associated SOD1 variants can produce toxic gain-of-function effects that are not simply corrected by increasing copper or zinc [4,7].

Table 1. Biological and therapeutic significance of the eight metals

Metal	Major physiological role	ALS/MND-related mechanism	Therapeutic evidence
Zn	SOD1 structure; >300 enzymes; transcription factors; synaptic function	Zn-deficient SOD1 misfolding; aggregation; oxidative/nitrosative stress	Insufficient; high-dose supplementation may cause Cu deficiency
Cu	SOD1; cytochrome-c oxidase; ceruloplasmin	Redox stress; SOD1 maturation (CCS-dependent); mitochondrial dysfunction	CuATSM experimental; human benefit unproven
Mg	ATP-dependent reactions; ion channels; NMDA-receptor block	Altered excitability and Ca^{2+} homeostasis	No established disease-modifying evidence
Ca	Excitability; synaptic signaling; mitochondrial function	Ca^{2+} overload; excitotoxicity; mitochondrial injury	Pathway target; Ca supplementation not indicated
Co	Central atom of vitamin B12	Possible exposure/toxicity marker	No therapeutic evidence
Fe	Electron transport; heme; Fe–S enzymes	Fenton chemistry; ferroptosis; ferritin/MRI iron signal	Conservative chelation investigational
Mn	Mn-SOD (SOD2); glutamine synthetase; metabolism	Mitochondrial redox balance; excess neurotoxicity	No established ALS therapy
Se	Glutathione peroxidases (incl. GPX4); thioredoxin reductases	Antioxidant defense; ferroptosis protection	Plausible but clinically unproven

Abbreviations: CCS, copper chaperone for SOD1; GPX, glutathione peroxidase; SOD, superoxide dismutase.

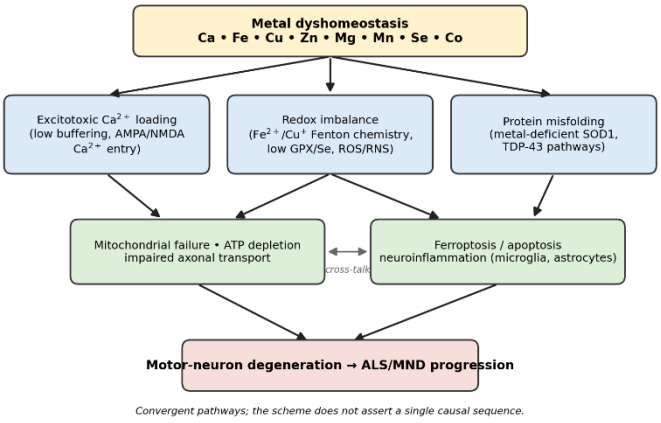


Figure 1. *Integrated model of metal-ion dysregulation in ALS/MND. Calcium, iron/copper redox chemistry and metal-dependent protein misfolding converge on mitochondrial failure, regulated cell death and neuro-inflammation. The scheme summarizes convergent pathways rather than asserting a single causal sequence.*

3. Zinc (Zn)

Zinc is required for hundreds of proteins, transcription factors, antioxidant systems and normal synaptic biology. It also contributes structurally to Cu/Zn-SOD1. Perturbed zinc binding can influence SOD1 stability and aggregation, and zinc-deficient SOD1 has been shown to induce nitric oxide-dependent

apoptosis in cultured motor neurons [7,8]. Zinc deficiency can also impair normal protein function more broadly [3,4].

Human observational studies have reported associations between zinc status and ALS. In a case-control study of US veterans, blood zinc and selenium were inversely associated with ALS, whereas copper was positively associated [9]. In a case-control study nested within the prospective EPIC cohort, higher erythrocyte zinc was associated with lower ALS risk (odds ratio 0.50; 95% CI 0.27–0.94, highest vs lowest tertile), whereas cadmium and lead were associated with higher risk (Figure 2) [6]. The lead estimate had a confidence interval that included 1. These findings are hypothesis-generating and do not demonstrate that zinc supplementation prevents or treats ALS.

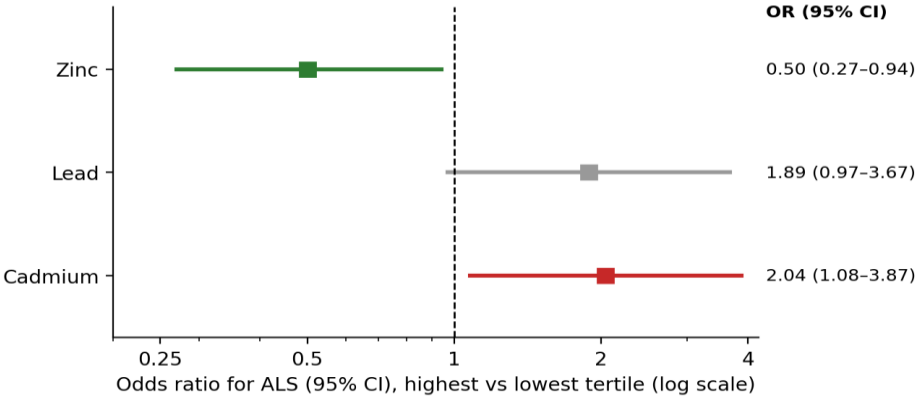


Figure 2. *Prospective blood-metal associations with ALS risk. Odds ratios (95% CI; highest vs lowest tertile) from a nested case-control study within the EPIC cohort (107 cases, 319 controls) [6]. Zinc was inversely associated and cadmium positively associated with ALS; the lead interval crosses 1. Association does not establish causation.*

A small pilot study of zinc plus copper in sporadic ALS reported a possible slowing of ALSFRS-R decline, but the study was very small and inadequately powered to establish efficacy [10]. Importantly, excessive zinc can induce copper deficiency. Empirical high-dose zinc supplementation is therefore not established therapy and may create a second nutritional problem [10]. The distinction between epidemiological association and therapeutic indication is central: any supplementation should be guided by documented deficiency and appropriate monitoring [6,9,10].

4. Copper (Cu)

Copper is required for Cu/Zn-SOD1, cytochrome-c oxidase and several other enzymes involved in mitochondrial respiration and redox regulation. Copper is therefore indispensable to neuronal metabolism, but poorly controlled redox-active copper can also contribute to oxidative injury [4,5]. In SOD1 maturation, the copper chaperone CCS inserts copper and promotes disulfide formation; failure of metalation leaves an immature, aggregation-prone enzyme (Figure 3) [7].

Reports of copper in human ALS samples are heterogeneous. Altered copper and other trace metals have been described in CSF and plasma [11], higher blood copper was associated with ALS in one case-control study [9], whereas a CSF study reported lower copper in ALS and spinal-onset patients than in controls [12]. A study of human spinal cord tissue also reported disrupted copper availability in sporadic ALS [13]. These discordant directions underline the importance of matrix, method and disease stage.

The most clinically interesting copper-directed strategy has been CuATSM, a brain-penetrant copper-containing compound designed to deliver copper selectively in pathological environments. SOD1 mouse studies reported neuroprotection and increased survival, including striking effects in mice co-expressing the copper chaperone [14–16]. Early human CuATSM studies were encouraging but lacked the evidentiary strength of randomized trials, and results of the randomized phase 2/3 study (NCT04082832) had not been formally published when this review was prepared. Subsequent post-

mortem analysis did not show significant preservation of motor-neuron density or reduction of TDP-43 pathology in treated patients compared with untreated patients [17]. CuATSM therefore remains an important experimental proof-of-concept rather than an established ALS treatment. It should not be confused with copper supplementation, which has no demonstrated benefit and can be toxic.

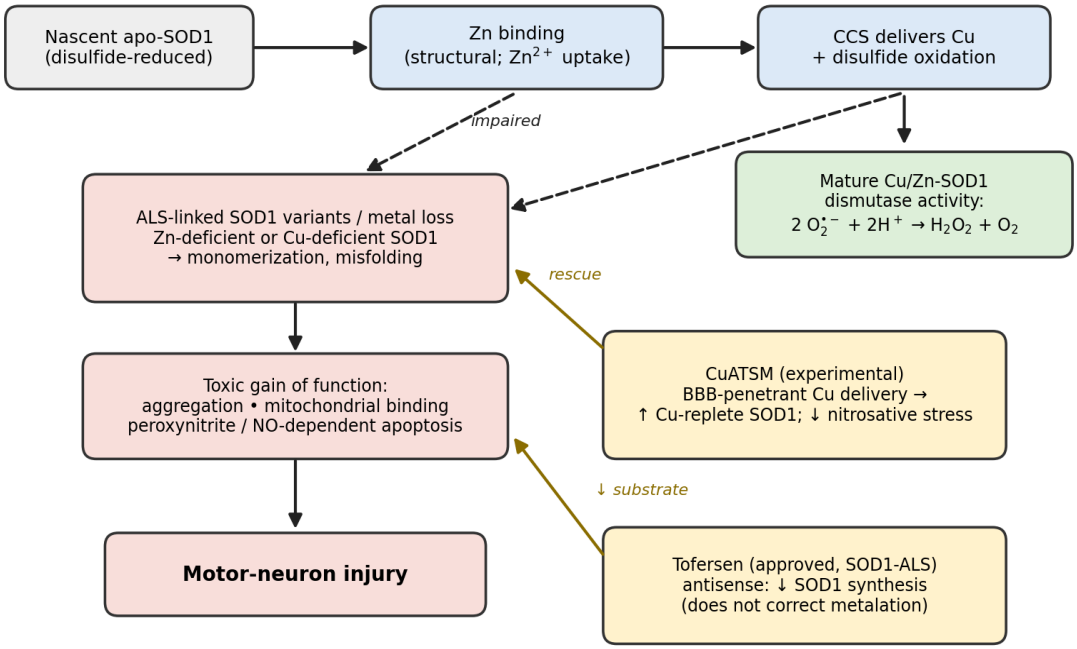


Figure 3. *Metalation of SOD1 and sites of therapeutic intervention. Zn binding and CCS-mediated Cu insertion generate mature Cu/Zn-SOD1; metal loss or variant-induced destabilization yields misfolded SOD1 with toxic gain of function* [7,8]. *CuATSM (experimental) delivers copper* [14–16], *whereas tofersen lowers SOD1 synthesis* [18].

5. Magnesium (Mg)

Magnesium is an essential intracellular cation involved in ATP-dependent reactions, mitochondrial metabolism, ion-channel regulation and NMDA-receptor physiology. Because extracellular Mg^{2+} blocks the NMDA-receptor channel in a voltage-dependent manner, magnesium influences calcium entry and is mechanistically relevant to excitotoxicity [3,19].

Multi-element CSF panels have been used to compare metal patterns across neurodegenerative diseases [20], and the relationship between dietary magnesium intake and ALS risk has been examined in large prospective cohorts [21]. These observations have not translated into convincing evidence that magnesium supplementation modifies disease progression. Correction of documented magnesium deficiency is clinically reasonable; high-dose supplementation as an ALS therapy is not evidence-based.

6. Calcium (Ca)

Calcium is central to the pathophysiology of motor-neuron excitotoxicity. Reduced astroglial glutamate transport has been documented in ALS tissue [22]. Vulnerable motor neurons express Ca^{2+}-permeable AMPA receptors and have relatively low calcium-buffering capacity; deficient RNA editing of the GluA2 subunit has been implicated in increased Ca^{2+} permeability [19,23,24]. CSF from ALS patients preferentially elevates intracellular calcium in motor neurons through AMPA/kainate receptors [25].

Excess intracellular Ca^{2+} promotes mitochondrial Ca^{2+} loading, respiratory-chain dysfunction, reactive oxygen species generation, ATP depletion and cell death (Figure 4). Mitochondrial Ca^{2+} capacity is impaired before symptom onset in $SOD1^{G93A}$ mice, and mutant SOD1 increases motor-neuron vulnerability to excitotoxicity through oxidative stress and perturbed calcium homeostasis [26,27].

Riluzole, which reduces glutamatergic transmission, remains a cornerstone of therapy [28]. The therapeutic target is therefore pathological intracellular calcium loading-not dietary calcium deficiency- and calcium supplementation should be based on conventional clinical indications rather than used as an ALS disease-modifying strategy.

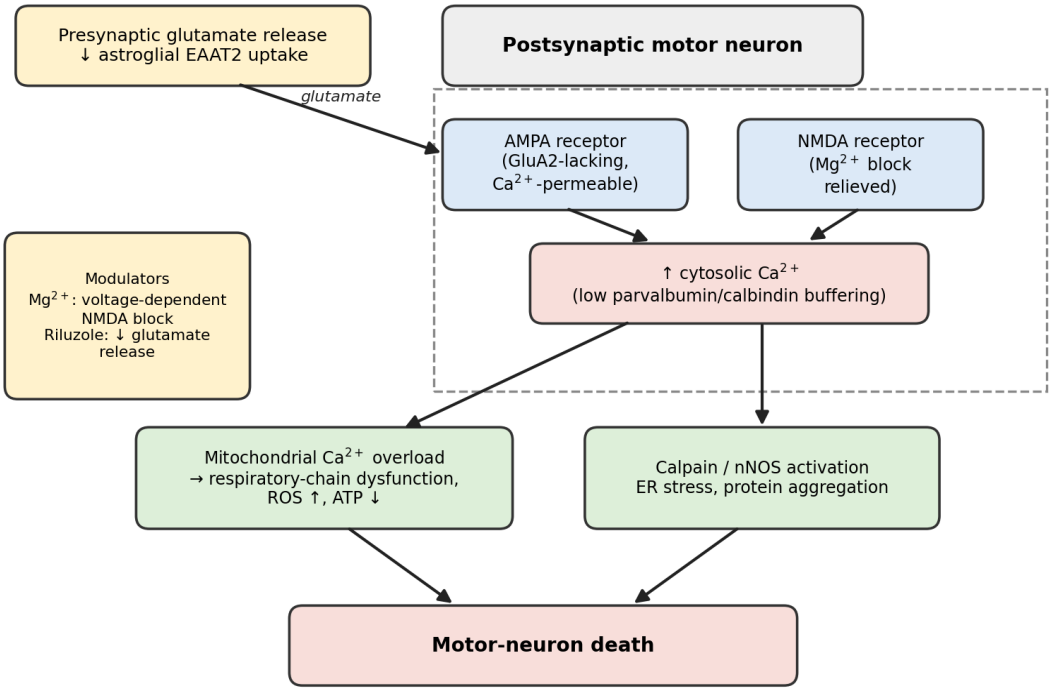


Figure 4. *Mechanism of calcium-mediated excitotoxicity in motor neurons. Impaired glutamate clearance, Ca^{2+}-permeable AMPA receptors and low Ca^{2+}-buffering capacity increase cytosolic Ca^{2+}, driving mitochondrial overload, protease/nNOS activation and cell death* [19,22,23,26].

7. Iron (Fe)

Iron is essential for mitochondrial electron transport, heme synthesis and numerous enzymes. In its labile form, however, Fe^{2+} participates in Fenton chemistry: $Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + OH^- + \bullet OH$. This chemistry can amplify oxidative damage [3,4].

MRI and neuropathological studies have identified increased iron-related signals and iron accumulation in the motor cortex of people with ALS [29,30], and higher serum ferritin has been associated with shorter survival [31]. These findings connect iron to oxidative stress and potentially to ferroptosis, a regulated cell-death pathway characterized by iron-dependent lipid peroxidation that is restrained by the selenoenzyme GPX4 [32,33] (Figure 5).

Iron chelation is therefore a rational experimental strategy. In an open-label pilot study of "conservative" chelation with deferiprone in 23 patients, treatment was well tolerated without anemia over 12 months, and declines in ALSFRS-R and body-mass index were smaller during the first three months of treatment than during an untreated run-in period; however, the study was small and uncontrolled [34]. A larger randomized placebo-controlled trial (FAIR-ALS II, NCT03293069) has completed recruitment, but I was unable to locate published efficacy results. Caution is warranted: randomized trials of deferiprone in Parkinson's disease and early Alzheimer's disease reported clinical worsening despite brain-iron lowering [35,36]. Iron deficiency itself is harmful; indiscriminate iron restriction is therefore inappropriate.

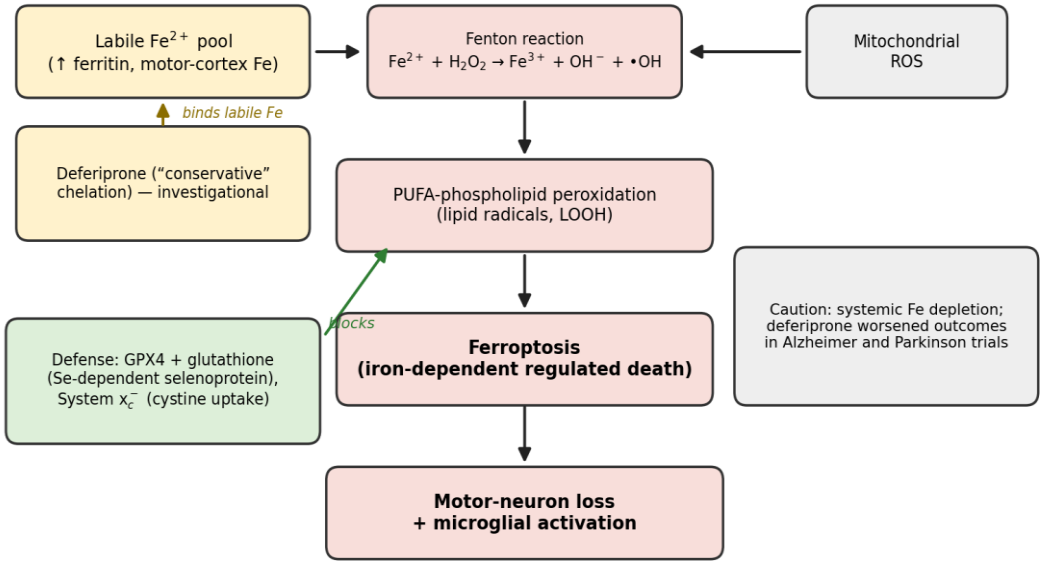


Figure 5. Iron, lipid peroxidation and ferroptosis in ALS. Labile Fe^{2+} drives Fenton chemistry and phospholipid peroxidation; GPX4 (selenium-dependent) and cystine uptake restrain ferroptosis [32,33]. Deferiprone is investigational in ALS [34] and was detrimental in Alzheimer's and Parkinson's disease trials [35,36].

8. Manganese (Mn)

Manganese is required for mitochondrial Mn-superoxide dismutase (SOD2) and several metabolic enzymes, including glutamine synthetase. Excessive manganese exposure, however, can be neurotoxic. An earlier study reported higher CSF manganese in ALS than controls [37]. More recent evidence is less consistent: a 2026 systematic review and meta-analysis of 12 studies found no statistically significant overall difference in manganese concentrations between ALS and controls and identified substantial heterogeneity [38]. This illustrates why single-study metal measurements should not be used to justify supplementation.

9. Selenium (Se)

Selenium is incorporated into glutathione peroxidases (including GPX4), thioredoxin reductases and other selenoproteins that regulate oxidative stress. Glutathione peroxidase catalyzes the reduction of hydrogen peroxide and lipid hydroperoxides, making selenium biologically relevant to ALS oxidative-stress pathways and to ferroptosis defense [4,33].

Human observational studies have reported inverse associations between selenium status and ALS risk or severity [9,39]. A small combination-treatment study (Alsamin; selenium with other antioxidants, amino acids and nimodipine) reported increased glutathione peroxidase activity and a possible slowing of progression, but only the combination produced the biochemical change, so the individual contribution of selenium cannot be determined [40]. A Cochrane review found no significant effect in the individual randomized studies, including a combination of methionine, vitamin E and selenium (Alsemet), and concluded that evidence for antioxidants in ALS is insufficient [41]. Selenium therefore remains mechanistically plausible but clinically unproven as an isolated ALS treatment.

10. Cobalt (Co)

Cobalt is physiologically important as the central atom of vitamin B12. Free or excessive cobalt exposure can have toxic effects. Cobalt has been included in some multi-element CSF and plasma panels [11,20], but no consistent, replicated ALS-specific pattern has emerged from them. There is currently no convincing evidence that cobalt deficiency causes ALS or that cobalt supplementation improves ALS/MND outcomes. Cobalt is therefore better regarded as a biomarker/exposure variable in ALS metallomics research than as a therapeutic target.

11. Integrated Mechanisms

Metal dyshomeostasis can converge on several major ALS pathways (Figure 1). Calcium excess promotes excitotoxicity; iron and copper can amplify oxidative chemistry; zinc and copper abnormalities can affect SOD1 structure and redox biology; manganese abnormalities can influence mitochondrial antioxidant capacity; magnesium affects excitability and calcium regulation; and selenium supports glutathione-dependent antioxidant defense [3–5,19,32]. These pathways converge on mitochondrial dysfunction, ATP depletion, oxidative injury, impaired axonal transport, neuroinflammation and regulated cell death. The interaction is therefore more accurately represented as a network than as a single-metal deficiency syndrome.

Table 2 summarizes the principal human studies discussed above, and Table 3 places metal-directed interventions alongside established therapies. Figure 6 gives a qualitative overview of the maturity of the evidence base for each element.

Table 2. Selected human studies of metals in ALS/MND

Study	Design / sample	Principal finding	Interpretation
Peters TL 2016 [9]	Case-control, US veterans; 163 ALS, 229 controls; blood ICP-MS	Se and Zn inversely, Cu positively associated with ALS	Post-onset sampling; reverse causation possible
Peters S 2021 [6]	Nested case-control in EPIC; 107 cases, 319 controls; erythrocyte metals	Zn OR 0.50 (0.27–0.94); Cd OR 2.04 (1.08–3.87); Pb OR 1.89 (0.97–3.67)	Prospective; hypothesis-generating
Oggiano 2018 [39]	Exploratory study of trace elements vs clinical severity	Se suggested protective; Pb suggested risk factor	Exploratory; small
Chen 2022 [12]	CSF ICP-MS; ALS (spinal/bulbar onset) vs controls	Cu lower in ALS and spinal onset; Ni higher in spinal onset	Single-centre; cross-sectional
Salehcheh 2026 [38]	Systematic review/meta-analysis; 12 studies of Mn	No significant overall Mn difference; substantial heterogeneity	Mn data inconsistent
Moreau 2018 [34]	Open-label pilot of deferiprone; 23 patients, 12 months	No anemia; smaller early ALSFRS-R and BMI decline vs run-in	Uncontrolled; not proof of efficacy
Yang 2023 [17]	Post-mortem comparison of CuATSM-treated vs untreated patients	No significant difference in neuron density or TDP-43 burden	Argues against pathological rescue

Abbreviations: ICP-MS, inductively coupled plasma mass spectrometry; OR, odds ratio (95% CI).

12. Interaction with Established ALS Treatment

Metal biology should be regarded as a complementary mechanistic field rather than a replacement for evidence-based ALS management. Riluzole and edaravone address glutamatergic and oxidative pathways, respectively [28,42], while tofersen is a genotype-specific therapy for SOD1-associated ALS. Tofersen reduces SOD1 protein production rather than attempting to normalize SOD1 metalation [18,43]. Metal-directed interventions may eventually complement these approaches, particularly if biomarkers can identify patients with specific pathological metal redistribution. At present, however,

no Zn, Cu, Mg, Ca, Co, Fe, Mn or Se supplementation regimen has been established as a stand-alone disease-modifying therapy for ALS/MND.

Table 3. Metal-related and established therapeutic approaches in ALS/MND

Approach	Target / mechanism	Evidence	Status / caveat
Riluzole [28]	Reduces glutamatergic excitotoxicity	Randomized controlled trial	Established therapy
Edaravone [42]	Free-radical scavenging	Randomized trial in selected patients	Approved in some jurisdictions
Tofersen [18,43]	SOD1 antisense; lowers SOD1 synthesis	Randomized phase 3 trial; regulatory approval	SOD1-ALS only; not metal-based
CuATSM [14–17]	Cu delivery to SOD1/mitochondria	Strong in mice; human pathology negative	Experimental
Deferiprone [34–36]	Conservative iron chelation	Open-label ALS pilot; worse outcomes in AD and PD trials	Investigational; caution
Zn ± Cu [10]	Nutritional supplementation	Very small pilot	Not recommended empirically
Se-containing antioxidant combinations [40,41]	Glutathione peroxidase support	Small studies; Cochrane: insufficient	Unproven

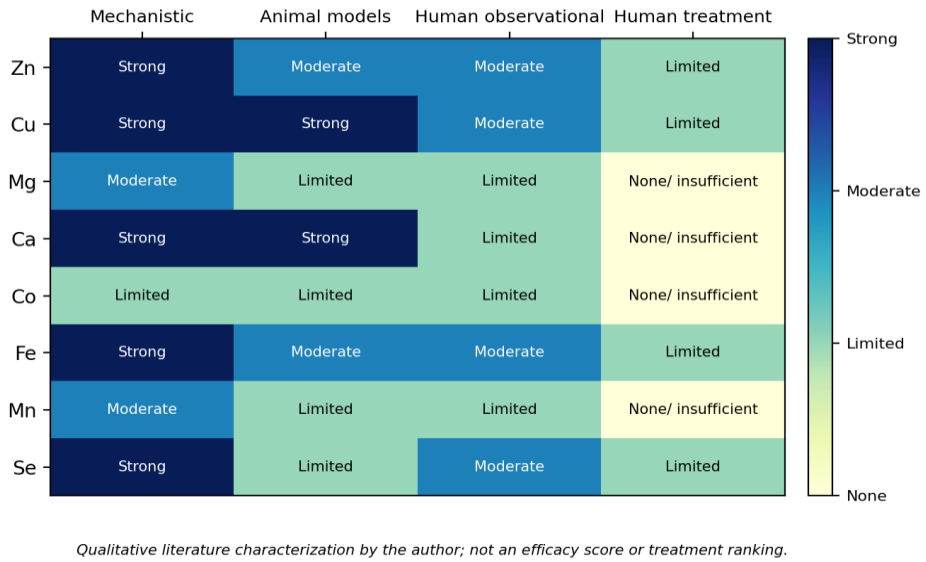


Figure 6. *Qualitative evidence map by element and evidence type. This figure is a literature characterization by the author, not a treatment ranking or efficacy score; it is consistent with Table 4.*

13. Clinical and Research Implications

The most defensible clinical approach is to identify genuine nutritional deficiencies, minimize excessive environmental or occupational exposure, and avoid high-dose empirical mineral supplementation. Future trials should measure not only total metal concentrations but also metal speciation, protein binding, cellular localization and longitudinal change. Precision metallomics could combine ICP-MS, metalloproteomics, quantitative susceptibility MRI, nutritional assessment, genetic stratification and longitudinal ALSFRS-R and respiratory outcomes [5]. This approach may distinguish pathological metal redistribution from secondary nutritional changes and could identify patients most likely to benefit from targeted metal manipulation. Study designs should favor prospective sampling, adequately

powered randomized trials and pharmacodynamic biomarkers such as imaging iron burden, SOD1 metalation state and neurofilament light chain.

Table 4. Evidence interpretation

Intervention	Mechanistic evidence	Animal evidence	Human treatment evidence	Current interpretation
Zinc	Strong	Moderate	Very limited	Investigational; avoid empirical high dose
CuATSM	Strong	Strong	Inconclusive	Experimental
Magnesium	Moderate	Limited	Insufficient	Correct documented deficiency
Calcium modulation	Strong	Strong	No proof for supplementation	Pathway target
Iron chelation	Strong	Moderate	Preliminary/inconclusive	Experimental; caution
Manganese manipulation	Moderate	Limited	None established	Avoid excess
Selenium	Strong	Limited/moderate	Insufficient	Correct deficiency; research target
Cobalt	Weak	Weak	None	Not a treatment target

Table 5. Practical interpretation for clinical research

Finding	Reasonable interpretation	What should not be inferred
Documented Zn deficiency	Correct deficiency using standard nutritional practice	That high-dose Zn treats ALS
Documented Cu deficiency	Investigate cause and correct appropriately	That Cu loading reverses SOD1 ALS
High CNS iron signal	Consider research/clinical context and differential diagnosis	That all ALS patients require chelation
Low Se status	Correct confirmed deficiency	That Se monotherapy is disease-modifying
Low Mg status	Correct deficiency	That Mg megadosing treats ALS
Abnormal Mn/Co exposure	Assess environmental/occupational exposure	That supplementation is therapeutic

14. Conclusions

Metal-ion homeostasis is an important component of ALS/MND biology and provides mechanistic links between excitotoxicity, oxidative stress, mitochondrial dysfunction, protein aggregation and regulated cell death. Calcium dysregulation and iron-associated oxidative injury are particularly important pathways, while copper/zinc biology is central to SOD1-associated ALS. Selenium and magnesium have plausible protective roles, whereas manganese and cobalt require careful interpretation because evidence is limited or inconsistent.

The present evidence does not justify routine high-dose mineral supplementation as an ALS treatment. Correction of documented deficiencies and avoidance of excessive exposure are more defensible. The future of metal-based ALS therapy is likely to depend on precision correction of pathological metal redistribution rather than nonspecific supplementation.

Declaration, Conflict of interest and funding

The content provided herein is developed using AI tools, and is meant to help Researchers who are working in the fields of neurological disorders.

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Data availability: No new datasets were generated or analyzed.

Author Note

This manuscript is a literature review and is not a treatment recommendation for an individual patient. Mineral supplementation or chelation should be undertaken only for a clinically justified indication and with appropriate medical monitoring.

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