

RESEARCH MONOGRAPH . COMPOUND PROFILE

Magnesium

An essential mineral element required as a cofactor in over 600 enzymatic reactions, distinguished by its voltage-dependent block of the NMDA receptor ion channel, its role in cellular energy metabolism through ATP chelation, and its broad clinical evidence base spanning cardiovascular, neurological, musculoskeletal, and metabolic indications.

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ABSTRACT

Magnesium (Mg^{2+}) is the second most abundant intracellular cation, the fourth most abundant cation in the human body, and an essential cofactor in more than 600 enzymatic reactions encompassing DNA and RNA synthesis, protein synthesis, cellular energy metabolism, ion channel regulation, and neuromuscular function. Total body magnesium in the adult human is approximately 24 to 29 grams, of which approximately 60 percent resides in bone mineral, 39 percent in intracellular soft tissue compartments, and less than 1 percent in extracellular fluid and plasma. Serum magnesium concentration in healthy adults is maintained within a narrow physiological range of 0.75 to 0.95 millimoles per liter through coordinated intestinal absorption, renal reabsorption, and osseous exchange, with the transient receptor potential melastatin channels TRPM6 and TRPM7 serving as the principal apical magnesium entry pathways in intestinal and renal epithelial cells. The molecular pharmacology of magnesium is anchored by its voltage-dependent block of the N-methyl-D-aspartate (NMDA) receptor ion channel, a mechanism through which extracellular Mg^{2+} occupies a binding site within the channel pore at resting membrane potential and is expelled upon postsynaptic depolarization, thereby gating calcium influx and serving as a coincidence detector for synaptic plasticity. This NMDA receptor interaction, together with magnesium's roles as a physiological calcium antagonist, a modulator of potassium and sodium channel conductance, and a required cofactor for ATP-dependent kinase and phosphatase reactions, underlies the broad clinical pharmacology of the element across neurological, cardiovascular, musculoskeletal, and metabolic systems.

Subclinical magnesium deficiency is increasingly recognized as a prevalent and underdiagnosed condition, with epidemiological surveys indicating that approximately 50 to 80 percent of adults in industrialized nations consume less than the estimated average requirement. The clinical consequences of chronic marginal magnesium status include increased risk of hypertension, type 2 diabetes mellitus, metabolic syndrome, coronary artery disease, stroke, migraine, depression, and osteoporosis. The tolerable upper intake level for supplemental magnesium from nonfood sources is set at 350 milligrams per day for adults by the United States Institute of Medicine, though this threshold is under active re-evaluation in light of accumulating evidence that higher supplemental intakes are well tolerated in individuals with normal renal function. Magnesium is available in numerous supplemental salt forms that differ substantially in elemental magnesium content, solubility, bioavailability, and tissue distribution. Organic salts (citrate, glycinate, taurate, malate, threonate) demonstrate superior bioavailability compared to inorganic forms (oxide, hydroxide, carbonate, sulfate) in human pharmacokinetic studies. Magnesium L-threonate has attracted particular research interest for its capacity to elevate brain magnesium concentrations through blood-brain barrier penetration via glucose transporters, with randomized controlled trials demonstrating significant improvements in cognitive performance and working memory. This monograph documents the chemical identity, discovery history, molecular pharmacology, pharmacokinetics across supplemental forms, preclinical and clinical evidence base, sourcing and quality verification, reconstitution and handling, stack interactions, adverse event profile, and a comparative assessment of five magnesium salt forms against five competency standards. The compound is generally recognized as safe at

recommended supplemental doses in individuals with normal renal function; dose adjustment or avoidance is indicated in moderate to severe renal impairment.

1. Compound Identification

1.1 Names, synonyms, and registry identifiers

Element name: Magnesium.

Symbol: Mg.

Atomic number: 12.

Ionic form of biological relevance: Magnesium ion, Mg^{2+} (divalent cation).

Chemical Abstracts Service registry numbers: 7439-95-4 (elemental magnesium), 7786-30-3 (magnesium chloride), 3344-18-1 (magnesium citrate), 14783-68-7 (magnesium glycinate, also designated magnesium bisglycinate), 1309-48-4 (magnesium oxide), 7487-88-9 (magnesium sulfate, Epsom salt), 778571-57-6 (magnesium L-threonate), 334824-43-0 (magnesium taurate).

International Union of Pure and Applied Chemistry name: Magnesium (element); the supplemental forms are named as the magnesium salt of the corresponding acid or amino acid chelate.

Common supplemental designations: Magnesium citrate, magnesium bisglycinate (magnesium glycinate), magnesium oxide, magnesium chloride, magnesium sulfate, magnesium L-threonate (Magtein), magnesium taurate, magnesium malate, magnesium orotate, magnesium carbonate, magnesium hydroxide (milk of magnesia).

1.2 Structural class and chemistry

Magnesium is an alkaline earth metal (Group 2) with the electron configuration $[\text{Ne}]3s^2$. In biological systems, it exists exclusively as the divalent cation Mg^{2+} with an ionic radius of 0.72 angstroms, substantially smaller than calcium (1.00 angstroms), and with a correspondingly higher charge density and a tightly bound first hydration shell of six water molecules [1]. The hydrated radius of Mg^{2+} (approximately 4.28 angstroms) is considerably larger than that of Ca^{2+} , a property

that dictates much of the differential biology of the two divalent cations, including the selectivity of ion channel permeation and the kinetics of ligand exchange at enzyme active sites.

Atomic mass: 24.305 daltons.

Physical properties (elemental): Silver-white metal, density 1.738 grams per cubic centimeter, melting point 650 degrees Celsius, boiling point 1091 degrees Celsius. Reacts with water and readily oxidizes in air. The elemental form is not biologically relevant; the divalent cation in aqueous solution is the species of physiological and pharmacological interest.

Coordination chemistry: Mg^{2+} in biological systems adopts octahedral coordination with six ligands, typically water molecules, phosphate oxygens (as in ATP and nucleic acids), carboxylate oxygens (as in citrate, aspartate, and glutamate residues), and nitrogen donors (as in chlorophyll and some enzyme active sites). The slow ligand exchange rate of the Mg^{2+} aqua ion (approximately 10^5 per second, compared to 10^8 per second for Ca^{2+}) contributes to the high kinetic stability of Mg-ATP and Mg-enzyme complexes and is a fundamental determinant of the distinct biological roles of magnesium relative to calcium [2].

1.3 Synthesis and production of supplemental forms

Magnesium supplemental salts are produced by reaction of magnesium oxide, magnesium hydroxide, or magnesium carbonate with the corresponding acid. Magnesium citrate is prepared by reaction of magnesium oxide with citric acid in aqueous solution followed by crystallization or spray-drying. Magnesium bisglycinate is produced by chelation of magnesium with two equivalents of glycine under controlled pH and temperature, forming a stable amino acid chelate with a defined 1:2 metal-to-ligand stoichiometry [3]. Magnesium L-threonate is synthesized by reaction of magnesium hydroxide with L-threonic acid (a metabolite of ascorbic acid) under aqueous conditions. Magnesium oxide is produced by calcination of magnesium carbonate or magnesium hydroxide at high temperature. Pharmaceutical-grade magnesium sulfate (Epsom salt) is produced by reaction of magnesium oxide with sulfuric acid followed by crystallization as the heptahydrate. Quality verification of supplemental magnesium products requires confirmation of elemental magnesium content, counterion identity, and absence of heavy metal contaminants (lead, arsenic, cadmium, mercury) at levels below United States Pharmacopeia limits.

2. Abstract

Magnesium is an essential mineral nutrient and divalent cation required for the catalytic activity of more than 600 enzymes in the human metabolome, including all enzymes utilizing or producing adenosine triphosphate (ATP), all kinases and phosphatases, and the enzymes of DNA replication, RNA transcription, and protein synthesis [4]. The element is the second most abundant intracellular cation after potassium and the fourth most abundant cation in the body after calcium, potassium, and sodium.

The principal molecular pharmacology of supplemental magnesium centers on three mechanisms: voltage-dependent block of the NMDA receptor ion channel, physiological antagonism of calcium at multiple cellular targets, and restoration of enzymatic cofactor availability in states of deficiency. At the NMDA receptor, extracellular Mg^{2+} occupies a binding site within the channel pore at resting membrane potential, preventing ion flux; depolarization of the postsynaptic membrane expels the Mg^{2+} block and permits calcium and sodium influx, a mechanism that serves as the coincidence detector underlying long-term potentiation and synaptic plasticity [5, 6]. Magnesium additionally modulates voltage-gated calcium channels, ATP-sensitive potassium channels, and transient receptor potential channels throughout the cardiovascular, neurological, and musculoskeletal systems.

Subclinical magnesium deficiency is a condition of considerable public health significance. Population surveys consistently demonstrate that 50 to 80 percent of adults in the United States and Europe consume dietary magnesium below the recommended dietary allowance (RDA) of 310 to 420 milligrams per day, depending on age and sex [7, 8]. Chronic marginal magnesium status has been associated with increased risk of hypertension, type 2 diabetes, metabolic syndrome, coronary artery disease, atrial fibrillation, stroke, migraine headache, major depressive disorder, and osteoporosis in large prospective cohort studies and meta-analyses [9, 10].

The clinical evidence base for magnesium supplementation spans multiple indications. In migraine prophylaxis, meta-analyses of randomized controlled trials support oral magnesium supplementation (400 to 600 milligrams per day as elemental magnesium) for reduction of migraine frequency and severity [11]. In cardiovascular medicine, intravenous magnesium sulfate is standard of care for

eclampsia and pre-eclampsia, for torsade de pointes ventricular tachycardia, and for acute severe asthma; oral supplementation has demonstrated modest but significant reductions in blood pressure in meta-analyses of hypertensive populations [12, 13]. In mental health, meta-analyses of randomized trials report significant reduction in depression scores with magnesium supplementation [14]. Magnesium L-threonate, a form designed to enhance central nervous system magnesium delivery via glucose transporter-mediated blood-brain barrier penetration, has produced significant improvements in cognitive performance, working memory, and estimated brain cognitive age in randomized controlled trials [15, 16].

Magnesium supplementation is generally well tolerated. The principal dose-limiting adverse effect is osmotic diarrhea, which occurs at supplemental doses exceeding approximately 350 to 500 milligrams of elemental magnesium depending on the salt form, with magnesium oxide and magnesium citrate producing the highest incidence and magnesium bisglycinate the lowest. Serious toxicity (hypermagnesemia with neuromuscular depression, hypotension, and cardiac arrest) occurs almost exclusively in the setting of renal impairment or iatrogenic overdose of intravenous magnesium sulfate.

3. Discovery and Development History

3.1 Ancient and early modern recognition

Magnesium compounds have been recognized for therapeutic properties since antiquity. The name derives from the Greek district of Magnesia in Thessaly, where *magnesia alba* (magnesium carbonate) and *magnesia nigra* (manganese dioxide) were both mined, leading to centuries of taxonomic confusion between the two substances [17]. The medicinal use of magnesium-containing mineral waters was documented in classical Greek and Roman texts, and the laxative properties of magnesium salts were empirically recognized long before the element was identified.

3.2 Epsom salts and early chemistry

In 1618, Henry Wicker, a farmer in Epsom, Surrey, England, discovered a spring whose water cattle refused to drink owing to its bitter taste but which appeared to promote wound healing. Evaporation of the spring water yielded magnesium sulfate heptahydrate, subsequently marketed as Epsom salt and used as a laxative and bathing compound for over 400 years [17]. In 1695, Nehemiah Grew first isolated and described the salt from Epsom spring water as a distinct chemical species.

3.3 Elemental identification

In 1755, Joseph Black at the University of Edinburgh demonstrated through careful quantitative experiments that *magnesia alba* (magnesium carbonate) was a distinct earth from *calx* (calcium oxide), establishing magnesium as a separate element on chemical grounds [18]. Black showed that *magnesia alba* released a fixed air (carbon dioxide) on heating and that the calcined product (*magnesia usta*, magnesium oxide) differed from quicklime in its chemical behavior. In 1808, Sir Humphry Davy isolated metallic magnesium by electrolysis of a mixture of *magnesia* and mercuric oxide, confirming its elemental identity. Antoine Bussy produced larger quantities of the pure metal in 1831 by reduction of magnesium chloride with potassium.

3.4 Recognition of biological essentiality

The essential role of magnesium in plant biology was established through agricultural chemistry in the nineteenth century, with magnesium identified as the central atom of chlorophyll by Richard Willstatter in 1906 [19]. Mammalian essentiality was demonstrated in the early twentieth century through animal depletion experiments showing that magnesium-deficient diets produced neuromuscular hyperexcitability, seizures, and death. The McCollum laboratory at Johns Hopkins University characterized the magnesium deficiency syndrome in rats in the 1930s. Wacker and Parisi published the landmark 1968 review in the *New England Journal of Medicine* establishing the clinical significance of magnesium in human medicine and documenting the association between hypomagnesemia and cardiac arrhythmia, neuromuscular dysfunction, and metabolic derangement [20].

3.5 Modern supplementation and research expansion

The modern era of magnesium research was catalyzed by three developments: the recognition of widespread subclinical deficiency in industrialized populations (Marier 1986, Seelig 1994), the characterization of TRPM6 and TRPM7 as the molecular gatekeepers of epithelial magnesium transport (Schlingmann et al. 2002, Walder et al. 2002), and the development of magnesium L-threonate by Bhatt, Bhatt, and colleagues at the Massachusetts Institute of Technology (Bhatt et al. 2011, published as Slutsky et al. 2010), which demonstrated for the first time that a specific magnesium compound could selectively elevate brain magnesium concentrations and enhance synaptic plasticity in rodent models [15, 21]. These advances transformed magnesium from a nutritional commodity into a pharmacologically differentiated research compound with form-specific therapeutic implications.

4. Mechanism of Action

4.1 NMDA receptor voltage-dependent block

The NMDA receptor is a heterotetrameric ligand-gated ion channel of the ionotropic glutamate receptor family, composed of obligate GluN1 subunits and variable GluN2 (A through D) or GluN3 subunits. It is expressed at high density on postsynaptic membranes throughout the hippocampus, cortex, amygdala, and spinal cord and is the principal molecular substrate for long-term potentiation, long-term depression, and experience-dependent synaptic plasticity [5].

Extracellular Mg^{2+} blocks the NMDA receptor channel pore in a voltage-dependent manner. At resting membrane potential (approximately negative 70 millivolts), Mg^{2+} occupies a deep binding site within the channel formed by asparagine residues in the M2 segment of the GluN1 and GluN2 subunits (the "N+1 site"). The binding is of moderate affinity (IC_{50} approximately 10 to 30 micromolar at negative 70 millivolts in physiological extracellular Mg^{2+} concentrations of 0.8 to 1.0 millimolar) and is steeply voltage-dependent: depolarization of the postsynaptic membrane to approximately negative 30 to negative 20 millivolts relieves the block by electrostatic expulsion of the Mg^{2+} ion from the pore [5, 6]. Recent structural studies using cryo-electron microscopy have revealed that Mg^{2+} remains hydrated when bound to the channel pore, in contrast to permeant Ca^{2+} ions which undergo partial dehydration at multiple binding sites within the selectivity filter; this hydration state difference is the molecular basis for the blocking versus permeation distinction [22].

The functional consequence is that the NMDA receptor serves as a coincidence detector: calcium influx through the channel occurs only when glutamate is released from the presynaptic terminal (opening the channel) and the postsynaptic membrane is simultaneously depolarized (relieving the Mg^{2+} block). This mechanism is the molecular foundation of Hebbian synaptic plasticity and is essential for learning, memory consolidation, and adaptive neural circuit refinement. Reduction of extracellular Mg^{2+} concentration, as occurs in hypomagnesemia, shifts the voltage dependence of the block, permitting inappropriate NMDA receptor activation

at more negative potentials and contributing to neuronal hyperexcitability, excitotoxicity, cortical spreading depression (the electrophysiological substrate of migraine aura), and enhanced nociceptive transmission [11, 23].

4.2 Calcium antagonism

Magnesium functions as a physiological calcium antagonist at multiple cellular targets. At voltage-gated calcium channels (L-type, T-type, and N-type), Mg^{2+} competes with Ca^{2+} for permeation and reduces calcium influx in a concentration-dependent manner. The L-type calcium channel antagonism in vascular smooth muscle contributes to the vasodilatory and antihypertensive effects of magnesium; the T-type channel modulation in cardiac pacemaker cells contributes to heart rate regulation [24]. In the sarcoplasmic reticulum, Mg^{2+} inhibits the ryanodine receptor calcium release channel, reducing cytoplasmic calcium transients and opposing the contractile effects of calcium in both cardiac and skeletal muscle. At the mitochondrial level, Mg^{2+} modulates the mitochondrial calcium uniporter and influences the permeability transition pore, with implications for mitochondrial bioenergetics and apoptotic signaling.

4.3 ATP chelation and enzymatic cofactor function

Approximately 90 percent of intracellular magnesium is bound to organic molecules, with the Mg-ATP complex representing the predominant species [2]. All kinases (over 500 in the human kinome) require Mg-ATP as substrate rather than free ATP; the magnesium coordinates the beta and gamma phosphate groups and positions the ATP molecule for nucleophilic attack by the kinase substrate hydroxyl. Similarly, all ATPases (Na^{+}/K^{+} -ATPase, Ca^{2+} -ATPase, myosin ATPase), DNA and RNA polymerases, and the ribosomal translation machinery require Mg^{2+} as cofactor. The consequence is that intracellular magnesium depletion produces a global reduction in phosphorylation-dependent signaling, energy metabolism, and macromolecular synthesis, manifesting clinically as fatigue, weakness, and impaired cellular repair.

4.4 Potassium channel regulation and membrane potential

Magnesium is required for the function of inward-rectifier potassium channels (Kir), which are blocked by intracellular Mg^{2+} in a voltage-dependent manner analogous to the extracellular Mg^{2+} block of the NMDA receptor. Mg^{2+} depletion im-

pairs Kir channel function and produces secondary potassium wasting, the mechanism underlying the well-documented clinical observation that refractory hypokalemia frequently requires magnesium repletion before potassium correction is effective [25]. Magnesium also modulates the activity of ATP-sensitive potassium channels (KATP) in pancreatic beta cells, cardiac myocytes, and vascular smooth muscle, influencing insulin secretion, cardiac action potential duration, and vascular tone.

4.5 Anti-inflammatory and antioxidant mechanisms

Magnesium deficiency activates the nuclear factor kappa-B (NF-kappaB) inflammatory signaling pathway and increases circulating concentrations of interleukin-6, tumor necrosis factor alpha, and C-reactive protein in both animal models and human observational studies [26]. Supplementation reduces these inflammatory markers in meta-analyses of randomized trials. The anti-inflammatory mechanism is mediated in part through magnesium's inhibition of NMDA receptor-dependent calcium signaling in immune cells and in part through modulation of toll-like receptor signaling. Magnesium additionally functions as an antioxidant cofactor through its role in glutathione synthesis (as a cofactor for gamma-glutamylcysteine synthetase) and through stabilization of mitochondrial electron transport chain complexes, reducing superoxide generation [27].

5. Pharmacokinetics

5.1 Absorption

Magnesium absorption occurs primarily in the distal jejunum and ileum through two parallel pathways: a saturable, active transcellular pathway mediated by the TRPM6 channel on the apical membrane of enterocytes, and a passive, nonsaturable paracellular pathway driven by electrochemical gradients through tight junction claudin proteins (principally claudin 16 and claudin 19) [21, 28]. At physiological dietary intakes (approximately 300 to 400 milligrams per day), the paracellular pathway accounts for approximately 80 to 90 percent of absorbed magnesium; at low intakes, the transcellular TRPM6 pathway is upregulated to maintain absorption efficiency. Overall fractional absorption from dietary sources is approximately 30 to 50 percent and is inversely related to intake, declining to approximately 15 to 25 percent at high supplemental doses [7].

Absorption kinetics from supplemental forms show detectable increases in serum magnesium within approximately 1 hour of oral ingestion, with peak absorption occurring at 2 to 2.5 hours and approximately 80 percent of total absorption complete by 6 hours. Food does not substantially affect total magnesium absorption but may slow the rate of absorption. Phytate, oxalate, and high-dose calcium or zinc supplementation can reduce magnesium absorption through formation of insoluble complexes or competition for paracellular transport [7].

5.2 Bioavailability by supplemental form

Bioavailability varies substantially across magnesium salt forms and is a principal determinant of clinical efficacy:

Magnesium citrate: High aqueous solubility across the physiological pH range. Bioavailability approximately 25 to 30 percent of elemental magnesium. A pharmacokinetic comparison by Lindberg et al. (1990) demonstrated significantly greater absorption from magnesium citrate than from magnesium oxide, measured by 24-hour urinary magnesium excretion [29].

Magnesium bisglycinate (glycinate): Absorbed in part through the dipeptide transporter pathway (PepT1) in addition to paracellular magnesium flux, conferring absorption that is partially independent of conventional magnesium transport. Bioavailability is comparable to magnesium citrate, with lower incidence of gastrointestinal adverse effects in controlled comparisons [3, 30].

Magnesium oxide: Contains the highest elemental magnesium fraction (60 percent by weight) but has poor aqueous solubility (virtually insoluble in water, only 43 percent soluble in simulated peak gastric acid). Bioavailability is approximately 4 to 5 percent in pharmacokinetic studies, substantially lower than organic forms [29]. Primarily functions as an osmotic laxative at supplemental doses.

Magnesium L-threonate: Moderate elemental magnesium content (approximately 8 percent by weight). Distinguished by capacity to elevate cerebrospinal fluid and brain magnesium concentrations through blood-brain barrier penetration via glucose transporters (GLUT family). The threonic acid moiety (a vitamin C metabolite) serves as a carrier molecule facilitating central nervous system delivery [15].

Magnesium sulfate (Epsom salt): Moderate bioavailability when administered orally; well characterized pharmacokinetics for intravenous administration. Peak serum concentrations after intravenous bolus are immediate; after oral administration, absorption is limited by the osmotic effect which draws water into the intestinal lumen and accelerates transit.

Magnesium taurate: Chelated with taurine, an amino sulfonic acid with independent cardiovascular and neurological activity. Limited pharmacokinetic data in humans; theoretical advantage for cardiovascular applications owing to the additive effects of taurine on cardiac electrophysiology and vascular function.

5.3 Distribution

Total body magnesium in adults is approximately 24 to 29 grams (approximately 1000 to 1200 millimoles). Distribution is approximately 60 percent in bone (as surface-adsorbed Mg^{2+} on hydroxyapatite crystals, serving as an exchangeable reservoir), 39 percent in intracellular soft tissue compartments (primarily skeletal muscle, liver, and cardiac tissue), and less than 1 percent in extracellular fluid [1, 7]. Serum magnesium (0.75 to 0.95 millimoles per liter) comprises approximately 55 percent free ionized Mg^{2+} , 30 percent albumin-bound, and 15 percent complexed

with anions (citrate, phosphate, bicarbonate). Because less than 1 percent of total body magnesium is in plasma, serum magnesium is a poor biomarker for total body magnesium status; the red blood cell magnesium, 24-hour urinary magnesium, and the magnesium loading test (parenteral magnesium with measurement of urinary retention) are more sensitive indicators of deficiency [8].

5.4 Renal handling

The kidney is the principal regulator of magnesium homeostasis. Of the approximately 2400 milligrams of magnesium filtered daily by the glomeruli, approximately 95 to 97 percent is reabsorbed. Reabsorption occurs in the proximal tubule (approximately 15 to 25 percent, paracellular), the thick ascending limb of Henle (approximately 60 to 70 percent, paracellular via claudin 16 and claudin 19), and the distal convoluted tubule (approximately 5 to 10 percent, transcellular via TRPM6) [21, 28]. The distal convoluted tubule is the site of fine regulation; TRPM6 expression and activity are modulated by epidermal growth factor, insulin, aldosterone, and intracellular magnesium concentration through a negative feedback mechanism.

Loop diuretics (furosemide, bumetanide) inhibit the Na-K-2Cl cotransporter in the thick ascending limb and abolish the lumen-positive transepithelial voltage that drives paracellular magnesium reabsorption, producing obligate renal magnesium wasting. Thiazide diuretics produce a more modest magnesium-wasting effect. Proton pump inhibitors reduce intestinal TRPM6 expression and can produce clinically significant hypomagnesemia with chronic use exceeding one year [31].

5.5 Elimination

Renal excretion is the principal elimination pathway, with urinary magnesium excretion of approximately 50 to 150 milligrams per day in magnesium-replete individuals on normal dietary intake. Fractional excretion of magnesium can decrease to less than 0.5 percent in states of deficiency and increase to greater than 15 percent in states of excess, providing substantial adaptive capacity. Fecal magnesium excretion of unabsorbed dietary and supplemental magnesium accounts for the remainder. There is no identified hepatic metabolism of the magnesium ion; elimination is entirely renal and fecal.

6. Preclinical Pharmacology

6.1 Neuroprotection and synaptic plasticity

The landmark preclinical study by Bhatt, Bhatt, and colleagues (Slutsky et al. 2010, published in *Neuron*) demonstrated that elevation of extracellular magnesium concentration in hippocampal slice cultures enhanced synaptic plasticity by increasing the density of functional presynaptic release sites, increasing the NR2B-containing NMDA receptor fraction, and enhancing the long-term potentiation to long-term depression ratio [15]. Subsequent in vivo studies demonstrated that oral magnesium L-threonate (but not magnesium chloride or magnesium gluconate at equimolar elemental magnesium doses) produced sustained elevation of cerebrospinal fluid magnesium and improved spatial and working memory in both young and aged rats, with effect sizes comparable to environmental enrichment.

6.2 Cardiovascular preclinical models

Magnesium deficiency in rodent models produces vascular inflammation, endothelial dysfunction, increased arterial stiffness, and enhanced atherogenesis. Supplementation reverses these effects. In isolated cardiac preparations, Mg^{2+} suppresses early afterdepolarizations and delayed afterdepolarizations through L-type calcium channel antagonism and stabilization of the resting membrane potential, the mechanistic basis for the antiarrhythmic activity observed clinically [24].

6.3 Pain and nociception models

NMDA receptor antagonism by magnesium reduces central sensitization in rodent inflammatory and neuropathic pain models. Intrathecal magnesium sulfate produces dose-dependent antinociception in the formalin test, the chronic constriction injury model, and the spinal nerve ligation model. Systemic magnesium supplementation reduces mechanical allodynia and thermal hyperalgesia in these models at clinically translatable doses [23].

6.4 Metabolic models

Magnesium deficiency in rodents produces insulin resistance through impaired insulin receptor tyrosine kinase activity (which requires Mg-ATP as substrate), reduced GLUT4 translocation, and increased inflammatory cytokine signaling. Supplementation restores insulin sensitivity in magnesium-depleted models and improves glucose tolerance in diet-induced obesity models [32].

7. Clinical Evidence Base

7.1 Migraine prophylaxis

The clinical evidence for magnesium in migraine is supported by multiple randomized controlled trials and meta-analyses. A meta-analysis by Chiu et al. (2016) of randomized controlled trials of intravenous and oral magnesium for migraine reported significant reduction in acute migraine pain with intravenous magnesium sulfate (1 to 2 grams) and significant reduction in migraine frequency with oral magnesium supplementation (400 to 600 milligrams per day) over prophylactic periods of 8 to 12 weeks [11]. The American Academy of Neurology and the American Headache Society include magnesium (400 to 600 milligrams daily) in their Level B recommendations for migraine prophylaxis. A 2025 comprehensive review in *Nutrients* confirmed the effectiveness of magnesium supplementation in alleviating migraine through mechanisms including reduction of cortical spreading depression, modulation of serotonin receptor signaling, inhibition of platelet aggregation, and reduction of neurogenic inflammation [33].

7.2 Cardiovascular indications

Hypertension: A meta-analysis of 34 randomized controlled trials (2028 participants) by Zhang et al. (2016) reported that magnesium supplementation at median doses of 368 milligrams per day for a median duration of 3 months produced significant reductions in systolic blood pressure (mean reduction 2.00 mmHg) and diastolic blood pressure (mean reduction 1.78 mmHg), with greater effects in magnesium-deficient populations and at doses exceeding 300 milligrams per day [12]. A 2025 meta-analysis confirmed significant reductions in diastolic blood pressure with supplementation.

Eclampsia and pre-eclampsia: Intravenous magnesium sulfate is the established standard of care for prevention and treatment of eclamptic seizures, supported by the Magpie Trial (2002), a randomized controlled trial in 10,141 women with pre-eclampsia that demonstrated a 58 percent reduction in eclampsia risk with magnesium sulfate versus placebo [34].

Cardiac arrhythmia: Intravenous magnesium sulfate (1 to 2 grams) is first-line therapy for torsade de pointes ventricular tachycardia and is included in advanced cardiac life support algorithms. A meta-analysis of magnesium for atrial fibrillation rate control and rhythm conversion reported significant benefit for postoperative atrial fibrillation prophylaxis [35].

Heart failure: Prospective cohort studies (the Atherosclerosis Risk in Communities study, the Framingham Heart Study) have reported inverse associations between serum magnesium concentration and incident heart failure, with the lowest quintile of serum magnesium associated with approximately 70 percent increased risk [10].

7.3 Type 2 diabetes and metabolic syndrome

A meta-analysis of prospective cohort studies by Fang et al. (2016) reported that each 100 milligram per day increment in dietary magnesium intake was associated with an 8 to 13 percent reduction in type 2 diabetes risk [36]. Randomized controlled trials of magnesium supplementation in type 2 diabetes patients have demonstrated improvements in fasting glucose, HbA1c, and insulin sensitivity, with the most pronounced effects in magnesium-deficient populations. The prevalence of hypomagnesemia in type 2 diabetes populations ranges from 14 to 48 percent, substantially higher than the 2.5 to 15 percent prevalence in the general population [8].

7.4 Depression

A meta-analysis of randomized controlled trials by Boyle et al. (2017) and a subsequent 2024 meta-analysis reported that magnesium supplementation produced significant reductions in depression symptom scores across studies, with effect sizes comparable to those of mild antidepressant interventions [14]. A randomized equivalence trial by Tarleton et al. (2017) reported that 248 milligrams of elemental magnesium daily (as magnesium chloride) for 6 weeks produced clinically meaningful improvement in depression and anxiety scores equivalent to baseline improvement with standard antidepressant therapy [37].

7.5 Cognitive function

Magnesium L-threonate has been evaluated in three published randomized controlled trials for cognitive endpoints. A 2022 trial in 109 healthy Chinese adults (ages 18 to 65) demonstrated that a Magtein-based formulation produced significant improvements in all five subcategories of cognitive testing and overall memory quotient scores compared to control [16]. A 2025 randomized, double-blind, placebo-controlled trial in 100 adults (ages 18 to 45) reported that 2 grams of magnesium L-threonate daily for 6 weeks significantly improved overall cognitive performance on the NIH Total Cognition Composite, with a 7.5-year improvement in estimated brain cognitive age and significant enhancement of working memory, episodic memory, and reaction time compared to placebo [38].

7.6 Musculoskeletal applications

The evidence for magnesium supplementation in muscle cramps is mixed. A Cochrane review reported insufficient evidence to support magnesium for idiopathic leg cramps in older adults, though individual trials have shown benefit in pregnancy-associated leg cramps [39]. Magnesium is included in osteoporosis management guidelines as a cofactor for vitamin D metabolism and bone mineralization, with observational studies reporting positive associations between magnesium intake and bone mineral density.

7.7 Asthma

Intravenous magnesium sulfate (2 grams in adults, 25 to 50 milligrams per kilogram in children) is included in acute severe asthma management guidelines as adjunctive therapy, supported by a meta-analysis demonstrating significant reduction in hospital admission rates when administered in the emergency department alongside standard bronchodilator therapy [40].

8. Sourcing and Quality Verification

Magnesium supplements are available from pharmaceutical manufacturers, nutraceutical companies, and chemical research suppliers in a wide range of forms and purity grades. United States Pharmacopeia (USP) grade material meets defined standards for identity, purity, potency, and heavy metal limits. National Sanitation Foundation (NSF) International certification and Good Manufacturing Practice (GMP) compliance provide additional quality assurance for consumer supplements.

Investigators and consumers should verify:

- Elemental magnesium content per dose (which varies substantially by salt form: magnesium oxide contains approximately 60 percent elemental Mg, magnesium citrate approximately 16 percent, magnesium bisglycinate approximately 14 percent, magnesium L-threonate approximately 8 percent)
- Heavy metal testing for lead (less than 0.5 micrograms per daily serving), arsenic, cadmium, and mercury
- Third-party certificate of analysis from an independent laboratory (ConsumerLab, NSF International, USP Verified)
- For chelated forms (bisglycinate, taurate), confirmation of chelation integrity (that the product contains the true amino acid chelate rather than a physical mixture of magnesium oxide and free amino acid)

Research-grade magnesium salts are available from Sigma-Aldrich, Thermo Fisher Scientific, and specialty chemical suppliers at greater than 99 percent purity for in vitro and in vivo research applications. Magnesium L-threonate is available as the branded Magtein ingredient from AIDP (now part of the JOST Chemical ecosystem) and from multiple research chemical suppliers.

9. Reconstitution and Handling

9.1 Oral supplemental forms

Magnesium supplements are supplied as tablets, capsules, powders, and liquid solutions. No reconstitution is required for standard oral dosage forms. Powder forms (commonly magnesium citrate, magnesium bisglycinate, or magnesium glycinate) are dissolved in water or beverage for consumption. Magnesium citrate powder is freely soluble in water; magnesium bisglycinate powder is soluble but may require stirring. Magnesium oxide powder is poorly soluble and forms a suspension rather than a true solution.

9.2 Parenteral forms

Magnesium sulfate for intravenous or intramuscular administration is supplied as a sterile aqueous solution (typically 20 percent or 50 percent weight-per-volume, corresponding to 200 milligrams per milliliter or 500 milligrams per milliliter of magnesium sulfate). Intravenous administration requires dilution in 0.9 percent sodium chloride or 5 percent dextrose in water; typical concentrations for infusion are 10 to 20 milligrams per milliliter. Rapid intravenous push of undiluted magnesium sulfate can produce hypotension, bradycardia, and respiratory depression and is contraindicated except in cardiac arrest protocols.

9.3 Storage

Solid magnesium supplements should be stored at room temperature (15 to 30 degrees Celsius) in a dry environment protected from moisture. Magnesium oxide is hygroscopic and should be stored in airtight containers. Solution forms should be protected from freezing. Magnesium sulfate solution for injection is stable at room temperature and does not require refrigeration; the solution should be inspected for particulate matter and discoloration before use.

9.4 Research applications

For in vitro research, magnesium chloride hexahydrate is the standard source for preparation of magnesium-containing buffers and cell culture media. Stock solutions are prepared at 1 molar concentration in ultrapure water and sterilized by filtration (0.22 micrometer). For in vivo research, magnesium L-threonate is dissolved in drinking water at concentrations of 604 milligrams per liter (providing approximately 50 milligrams per kilogram per day of elemental magnesium in mice with ad libitum water consumption), following the protocol established by Bhatt et al. [15].

10. Stack Interactions and Combinations

10.1 Synergistic combinations

Vitamin D: Magnesium is a required cofactor for 25-hydroxylase and 1-alpha-hydroxylase, the hepatic and renal enzymes responsible for vitamin D activation. Magnesium deficiency impairs vitamin D metabolism and can produce functional vitamin D deficiency even when 25-hydroxyvitamin D levels are nominally adequate. Concurrent supplementation is recommended by multiple clinical guidelines [41].

Vitamin B6 (pyridoxine): Enhances intestinal magnesium absorption. The MAGNESIUM-B6 combination is a registered pharmaceutical product in several European jurisdictions. A 2018 randomized trial (MAGNUM) demonstrated that the combination of magnesium and vitamin B6 produced greater reduction in severe stress scores than magnesium alone [42].

Potassium: Magnesium and potassium depletion frequently coexist, and refractory hypokalemia requires magnesium correction before potassium repletion is effective. The combination is standard in electrolyte management protocols [25].

Taurine: When administered as magnesium taurate, the taurine moiety provides additive cardiovascular benefit through independent modulation of calcium homeostasis, inhibition of the renin-angiotensin system, and antioxidant activity.

Zinc: Commonly co-supplemented (as in the ZMA formulation: zinc monomethionine aspartate, magnesium aspartate, and vitamin B6). The combination supports testosterone synthesis, immune function, and sleep quality, though the clinical evidence for the specific ZMA combination is limited.

10.2 Antagonistic interactions and timing considerations

Calcium: High-dose calcium supplementation (greater than 500 milligrams per dose) can reduce magnesium absorption through competition for paracellular transport. Separation of doses by 2 hours is recommended when high-dose calcium

is required [7].

Iron: Magnesium can reduce iron absorption and vice versa. Separation of doses by 2 hours is recommended.

Zinc: At high supplemental doses (greater than 50 milligrams per day), zinc can reduce magnesium absorption. Standard supplemental doses (15 to 30 milligrams) do not produce clinically significant interaction.

10.3 Drug interactions

Proton pump inhibitors: Chronic PPI use (greater than 1 year) reduces intestinal TRPM6 expression and can produce clinically significant hypomagnesemia. The FDA issued a safety communication in 2011 regarding this interaction. Magnesium monitoring is recommended in patients on chronic PPI therapy [31].

Loop and thiazide diuretics: Increase renal magnesium wasting. Magnesium supplementation is commonly required in patients on chronic diuretic therapy.

Tetracycline and fluoroquinolone antibiotics: Magnesium forms insoluble chelation complexes with these antibiotics, reducing their absorption by 50 to 90 percent. Administration should be separated by at least 2 hours before or 4 to 6 hours after the magnesium dose [43].

Bisphosphonates: Magnesium reduces oral bisphosphonate absorption. Separation by at least 2 hours is required.

Digoxin: Hypomagnesemia increases digoxin toxicity risk through enhanced binding of digoxin to the Na⁺/K⁺-ATPase. Magnesium repletion is essential in patients receiving digoxin therapy.

Potassium-sparing diuretics (amiloride, triamterene, spironolactone): Reduce renal magnesium excretion and can produce hypermagnesemia when combined with high-dose magnesium supplementation, particularly in renal impairment.

11. Adverse Events and Safety

11.1 Common adverse events

The principal dose-limiting adverse effect of oral magnesium supplementation is osmotic diarrhea, reflecting the osmotic activity of unabsorbed magnesium salts in the intestinal lumen. Incidence and severity vary by salt form:

- Magnesium oxide: highest incidence of diarrhea owing to poor absorption and high osmotic effect (10 to 30 percent at supplemental doses of 400 milligrams elemental magnesium)
- Magnesium citrate: moderate incidence (5 to 15 percent); used therapeutically as an osmotic laxative at higher doses
- Magnesium bisglycinate: lowest incidence among common forms (less than 5 percent at equivalent elemental magnesium doses), owing to amino acid chelate absorption pathway that reduces luminal osmotic load [30]
- Magnesium L-threonate: low incidence of gastrointestinal effects; headache and drowsiness reported at low frequency in clinical trials

Additional common adverse effects at supplemental doses include nausea (2 to 5 percent), abdominal cramping (2 to 5 percent), and bloating (1 to 3 percent).

11.2 Tolerable upper intake level

The United States Institute of Medicine set the tolerable upper intake level (UL) for supplemental magnesium from nonfood sources at 350 milligrams per day for adults, based on the lowest observed adverse effect level for osmotic diarrhea [7]. This UL applies only to supplemental magnesium; there is no UL for dietary (food-sourced) magnesium, as no adverse effects from dietary intake have been documented. The European Food Safety Authority has set a similar UL of 250 milligrams per day for supplemental magnesium, though this is considered conservative by contemporary reviewers.

A 2023 perspective published in *Advances in Nutrition* called for re-evaluation of the magnesium UL, noting that the original evidence base was limited, that more recent comprehensive data on diarrhea incidence support a higher threshold, and

that many clinical trials have safely administered supplemental doses of 400 to 600 milligrams per day without clinically significant adverse effects in participants with normal renal function [44].

11.3 Hypermagnesemia and serious toxicity

Clinically significant hypermagnesemia (serum magnesium greater than 1.1 millimoles per liter) is rare in individuals with normal renal function and occurs almost exclusively in three settings: renal impairment with concurrent magnesium supplementation or magnesium-containing medication (antacids, laxatives), iatrogenic overdose of intravenous magnesium sulfate, and massive oral ingestion.

The clinical manifestations of hypermagnesemia are dose-dependent:

- 1.5 to 2.5 millimoles per liter: nausea, flushing, headache, lethargy, diminished deep tendon reflexes
- 2.5 to 5.0 millimoles per liter: somnolence, hypocalcemia, absent deep tendon reflexes, hypotension, bradycardia, ECG changes (prolonged PR interval, widened QRS)
- Greater than 5.0 millimoles per liter: respiratory depression, complete heart block, cardiac arrest

Treatment of severe hypermagnesemia includes intravenous calcium gluconate (which directly antagonizes the neuromuscular and cardiac effects of magnesium), saline diuresis, and hemodialysis in renal failure [45].

11.4 Special populations

Renal impairment: Magnesium supplementation is contraindicated or requires dose reduction and monitoring in patients with estimated glomerular filtration rate less than 30 milliliters per minute per 1.73 square meters. Even moderate renal impairment (eGFR 30 to 60) warrants caution with high-dose supplementation.

Pregnancy: Magnesium supplementation at standard doses is generally considered safe and is commonly recommended for pregnancy-associated leg cramps and pre-eclampsia prophylaxis. Intravenous magnesium sulfate for eclampsia management is Level A evidence. Excessive magnesium supplementation near term can produce neonatal respiratory depression.

Pediatric populations: Magnesium requirements and ULs are age-adjusted. Supplementation is generally safe at age-appropriate doses.

12. Comparative Assessment

This section presents a structured comparative assessment of five magnesium supplemental salt forms evaluated against five competency standards: bioavailability, clinical evidence depth, tolerability, application specificity, and overall validation. The five forms were selected as the principal magnesium preparations with substantive clinical pharmacology data and distinct therapeutic positioning.

12.1 Magnesium Citrate

Composition and elemental content: Magnesium salt of citric acid; approximately 16 percent elemental magnesium by weight.

Bioavailability: High. Freely soluble across the physiological pH range. Pharmacokinetic studies demonstrate approximately 25 to 30 percent fractional absorption, significantly greater than magnesium oxide [29]. The citrate anion enhances solubility in the relatively alkaline environment of the distal small intestine where absorption is maximal.

Clinical evidence depth: Substantial. Magnesium citrate is among the most studied supplemental forms, with inclusion in numerous randomized trials for hypertension, migraine, and general magnesium repletion. It is the most commonly recommended oral form in clinical practice guidelines.

Tolerability: Moderate. The high solubility and osmotic activity produce a dose-dependent laxative effect that limits tolerability at high doses (greater than 400 milligrams elemental magnesium). The laxative effect is therapeutically useful in some contexts (constipation management) but dose-limiting in others.

Application specificity: General-purpose magnesium repletion and mild laxative effect. No organ-specific targeting beyond general systemic bioavailability.

Overall validation: High. The combination of established bioavailability, extensive clinical trial inclusion, wide availability, and moderate cost positions magnesium citrate as the general-purpose reference standard for oral magnesium supplementation.

12.2 Magnesium Bisglycinate (Glycinate)

Composition and elemental content: Chelate of magnesium with two glycine molecules; approximately 14 percent elemental magnesium by weight.

Bioavailability: High. Absorbed in part through the intestinal dipeptide transporter (PepT1), providing an absorption pathway independent of conventional magnesium transport and partially resistant to inhibition by phytate, calcium, and other competitive factors [3, 30].

Clinical evidence depth: Moderate. Growing body of randomized controlled trial data, though smaller than the citrate literature. Studies in sleep quality, anxiety, and general magnesium repletion have reported positive outcomes. A 2021 systematic review reported superior gastrointestinal tolerability compared to other forms at equivalent elemental magnesium doses.

Tolerability: High. The amino acid chelate absorption pathway reduces luminal magnesium concentration and osmotic load, producing significantly lower rates of diarrhea compared to magnesium citrate and magnesium oxide. This is the principal clinical advantage of the bisglycinate form and the basis for its recommendation in patients requiring high-dose supplementation.

Application specificity: Preferred form for high-dose magnesium repletion in patients with gastrointestinal sensitivity. The glycine moiety has independent inhibitory neurotransmitter activity (glycine is a co-agonist at the NMDA receptor and an agonist at the strychnine-sensitive glycine receptor), conferring theoretical calming and sleep-promoting effects, though the clinical significance of the glycine contribution at supplemental doses has not been definitively established.

Overall validation: Moderate to high. The superior tolerability profile and growing clinical evidence base support magnesium bisglycinate as a preferred form for chronic supplementation, though the total clinical evidence depth is less than that of magnesium citrate.

12.3 Magnesium L-Threonate

Composition and elemental content: Magnesium salt of L-threonic acid (a metabolite of vitamin C); approximately 8 percent elemental magnesium by weight.

Bioavailability: Moderate for systemic magnesium; uniquely high for central nervous system delivery. The L-threonate ligand facilitates blood-brain barrier penetration via glucose transporters, producing sustained elevation of cerebrospinal fluid magnesium concentrations that is not achieved by equimolar doses of other magnesium forms in preclinical studies [15].

Clinical evidence depth: Moderate and growing. Three published randomized controlled trials demonstrate significant cognitive enhancement in healthy adults, with particularly strong effects on working memory, episodic memory, and estimated brain cognitive age [16, 38]. No published trials for the standard cardiovascular or metabolic indications of magnesium supplementation, limiting evidence breadth.

Tolerability: High. Clinical trials report low incidence of gastrointestinal adverse effects. The low elemental magnesium content per dose (approximately 144 milligrams per 2-gram dose) reduces osmotic effects.

Application specificity: High. The brain-penetrant pharmacokinetic profile and the cognitive trial evidence base position magnesium L-threonate specifically for cognitive applications, sleep quality, and neurological indications. It is not a practical source of systemic magnesium repletion owing to the low elemental magnesium content per dose.

Overall validation: Moderate. The cognitive trial evidence is compelling but limited in scope and population diversity. The mechanism (enhanced brain magnesium delivery) is well characterized preclinically but the clinical evidence base is narrower than that of citrate or bisglycinate for general magnesium applications.

12.4 Magnesium Oxide

Composition and elemental content: Simple oxide; approximately 60 percent elemental magnesium by weight, the highest of any supplemental form.

Bioavailability: Low. Virtually insoluble in water and only partially soluble in gastric acid. Pharmacokinetic studies demonstrate approximately 4 to 5 percent fractional absorption, approximately one-fifth to one-sixth that of magnesium citrate at equivalent elemental doses [29].

Clinical evidence depth: Substantial by volume of studies (owing to historical availability and low cost), but clinical relevance is limited by poor bioavailability. Many older randomized trials used magnesium oxide and may have underestimated the clinical effect of magnesium supplementation as a result.

Tolerability: Low. The large fraction of unabsorbed magnesium produces dose-dependent osmotic diarrhea, limiting tolerability at the doses required to achieve clinically meaningful systemic absorption.

Application specificity: Principal application is as an antacid and osmotic laxative. Not recommended as a primary form for systemic magnesium repletion or for any specific pharmacological target.

Overall validation: Low for systemic supplementation. The combination of poor bioavailability, high gastrointestinal adverse event rate, and availability of superior alternatives makes magnesium oxide an inferior choice for therapeutic magnesium supplementation, despite its high elemental magnesium content and low cost.

12.5 Magnesium Taurate

Composition and elemental content: Chelate of magnesium with taurine (2-aminoethanesulfonic acid); approximately 9 percent elemental magnesium by weight.

Bioavailability: Moderate. Limited human pharmacokinetic data. Absorption is expected to be comparable to other organic magnesium salts on the basis of solubility and molecular weight.

Clinical evidence depth: Low. Small number of published clinical studies. The theoretical basis for cardiovascular application is well argued (taurine independently modulates calcium homeostasis, reduces blood pressure, and has antiarrhythmic activity), but large randomized controlled trials specifically evaluating magnesium taurate against other magnesium forms are absent.

Tolerability: Expected to be high based on the organic chelate structure and the low elemental magnesium content per dose. Clinical tolerability data are limited.

Application specificity: Positioned for cardiovascular applications on the basis of the additive magnesium-aurine pharmacology. Taurine independently reduces blood pressure (meta-analyses of taurine supplementation report reductions of ap-

proximately 3 to 4 mmHg systolic), stabilizes cardiac membrane potential, and has antioxidant activity. The combination is theoretically rational for hypertension and cardiac arrhythmia management.

Overall validation: Low. The mechanistic rationale is sound, but the clinical evidence specifically for the magnesium taurate salt (as opposed to separate magnesium and taurine supplementation) is insufficient to support evidence-based recommendation over better-studied forms.

12.6 Comparator summary

The five magnesium salt forms occupy distinct positions in the supplementation landscape. **Magnesium citrate** is the general-purpose reference standard with the deepest clinical evidence base and high bioavailability, limited by moderate gastrointestinal tolerability at high doses. **Magnesium bisglycinate** offers comparable bioavailability with superior tolerability and is the preferred form for high-dose chronic supplementation. **Magnesium L-threonate** is uniquely positioned for cognitive and neurological applications through its brain-penetrant pharmacokinetic profile, supported by growing randomized trial evidence, but is not suitable as a sole source of systemic magnesium repletion. **Magnesium oxide** has poor bioavailability and high gastrointestinal adverse event rates and is not recommended for therapeutic supplementation despite its high elemental magnesium content. **Magnesium taurate** has a sound mechanistic rationale for cardiovascular applications but insufficient clinical evidence to support recommendation over established forms.

For research applications requiring systemic magnesium repletion, magnesium citrate or magnesium bisglycinate is recommended. For cognitive research, magnesium L-threonate is the form of choice. For cardiovascular research requiring maximal evidence-based support, magnesium citrate is preferred, with magnesium taurate as a mechanistically rational but less validated alternative. Form selection should be guided by the specific research question, the target tissue, the required dose of elemental magnesium, and the tolerability requirements of the study population.

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