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Chelation therapy in lead poisoning: pharmacological mechanisms, clinical applications and emerging therapeutic approaches

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Abstract:

Background: Lead poisoning remains a significant global public health concern because of its widespread environmental distribution, occupational exposure and persistent toxic effects on multiple organ systems. Lead is a cumulative toxic metal that primarily affects the nervous, haematological, renal, cardiovascular and reproductive systems. Children are particularly vulnerable because of their developing nervous systems and greater gastrointestinal absorption of lead. Although prevention and elimination of exposure are the primary approaches to management, chelation therapy plays an important role in patients with significantly elevated blood lead concentrations or severe clinical manifestations. Objective: This review examines the pharmacological mechanisms of chelation therapy in lead poisoning, evaluates the clinical applications and limitations of currently available chelating agents, and discusses emerging therapeutic approaches and future research directions. Methods: A narrative literature review was developed using published scientific literature, clinical studies, toxicological reviews and international clinical guidelines. Particular emphasis was placed on the pharmacodynamics, pharmacokinetics, therapeutic efficacy, safety profiles and clinical applications of dimercaprol, calcium disodium EDTA, succimer and D-penicillamine. Results: Chelating agents reduce the biologically available lead burden by forming stable metal–ligand complexes that facilitate elimination, predominantly through renal excretion. Succimer is commonly used in selected patients with moderate lead poisoning, whereas calcium disodium EDTA and dimercaprol have important applications in severe poisoning and lead encephalopathy. However, clinical evidence indicates that reducing blood lead concentrations does not necessarily reverse established neurological injury. The Treatment of Lead-Exposed Children (TLC) trial demonstrated that succimer reduced blood lead concentrations in children with moderately elevated levels but did not improve long-term neuropsychological development. Emerging approaches include improved chelator design, targeted metal-binding molecules, antioxidant adjuncts, nanotechnology-based delivery systems and interventions directed towards oxidative stress and mitochondrial dysfunction. Conclusion: Chelation therapy remains an essential intervention for selected cases of lead poisoning, but its effectiveness depends on appropriate patient selection, removal of the exposure source, pharmacological characteristics of the chelating agent and careful clinical monitoring. Future research should focus on developing safer and more selective chelators capable of reducing tissue lead burden while minimizing essential mineral depletion and neurological complications.

Keywords:
Lead poisoning; chelation therapy; succimer; dimercaprol; calcium disodium EDTA; D-penicillamine; heavy metal toxicity; pharmacological mechanisms; neurotoxicity; emerging therapeutics.

1. Introduction:

Lead is a naturally occurring heavy metal that has historically been used in industrial manufacturing, construction materials, batteries, paints, ceramics, plumbing systems and various consumer products. Despite considerable international efforts to reduce lead exposure, lead poisoning continues to represent an important environmental and occupational health problem. Exposure can occur through inhalation of contaminated dust and fumes, ingestion of contaminated food and water, occupational activities and contact with lead-containing materials. Environmental contamination, informal recycling of lead-acid batteries, mining, industrial emissions and the use of contaminated traditional products remain important sources of exposure in several developing countries. Lead has no established beneficial physiological function in humans. Its accumulation in biological tissues can interfere with essential cellular processes, particularly those involving calcium signalling, haem synthesis, mitochondrial activity and oxidative balance. The developing nervous system is especially sensitive to lead exposure, and even relatively low concentrations have been associated with adverse neurodevelopmental outcomes. Lanphear et al. (2005) demonstrated an inverse association between childhood blood lead concentrations and intellectual performance, highlighting the importance of preventing exposure rather than relying exclusively on pharmacological treatment.

The clinical manifestations of lead poisoning depend on the concentration, duration and route of exposure, as well as individual susceptibility. Acute or severe exposure may produce abdominal pain, constipation, vomiting, anaemia, renal impairment, peripheral neuropathy and encephalopathy. Chronic exposure may result in impaired cognitive function, behavioural abnormalities, hypertension and progressive renal dysfunction. Kosnett et al. (2007) emphasized that adult lead exposure is also associated with important cardiovascular, renal and neurological consequences. The management of lead poisoning involves several complementary approaches, including identification and elimination of the exposure source, nutritional assessment, supportive treatment and pharmacological chelation when clinically indicated. Chelation therapy involves administering chemical compounds capable of binding lead ions and facilitating their elimination from the body. Commonly used chelating agents include succimer, calcium disodium EDTA, dimercaprol and D-penicillamine. Each agent possesses different chemical properties, pharmacokinetic characteristics, therapeutic indications and adverse-effect profiles.

Although chelation can substantially reduce circulating lead concentrations, it cannot reliably reverse established neurological injury. Rogan et al. (2001) [6] demonstrated that succimer treatment in children with moderately elevated blood lead concentrations did not produce measurable improvement in neuropsychological development. This finding illustrates the distinction between biochemical improvement and meaningful clinical recovery. The World Health Organization (WHO) published evidence-informed recommendations for the clinical management of lead exposure in 2021, emphasizing individualized treatment decisions, appropriate selection of chelating agents and reassessment after treatment (WHO, 2021). Therefore, understanding the pharmacological mechanisms, therapeutic applications and limitations of chelation therapy is essential for optimizing patient outcomes and identifying opportunities for the development of safer and more effective treatments.

2. Review methodology:

This article presents a narrative review of the scientific literature concerning chelation therapy in lead poisoning. Relevant publications were identified through literature searches of PubMed, biomedical reference databases, WHO publications, toxicological guidelines and clinical management recommendations. The literature search focused on the following concepts:

1. Lead toxicity and its molecular mechanisms.
2. Pharmacological properties of chelating agents.
3. Pharmacokinetics and pharmacodynamics of succimer, dimercaprol, calcium disodium EDTA and D-penicillamine.
4. Clinical efficacy and safety of chelation therapy.
5. Paediatric and adult lead poisoning.
6. Neurological and renal complications.

7. Emerging chelation strategies and therapeutic approaches.

Clinical trials, systematic reviews, narrative reviews, experimental investigations and international clinical guidelines were considered. Particular attention was given to the WHO guideline published in 2021 and landmark clinical research investigating succimer therapy. This is a narrative review rather than a systematic review or meta-analysis. Consequently, no pooled effect estimates or formal risk-of-bias assessments are presented.

3. Pathophysiology and pharmacological mechanisms of lead toxicity:

3.1. Absorption, distribution and accumulation:

Lead enters the human body primarily through inhalation and ingestion. Gastrointestinal absorption is influenced by age, nutritional status, chemical form of lead and the presence of dietary substances such as calcium and iron. Children generally absorb a greater proportion of ingested lead than adults, contributing to their increased vulnerability. Following absorption, lead enters the bloodstream and is transported predominantly within erythrocytes. A smaller proportion remains in plasma, where it can interact with tissues and biological molecules. Lead subsequently distributes into soft tissues, including the liver, kidneys and brain, before accumulating in mineralized tissues such as bones and teeth. Bone represents a major long-term reservoir of accumulated lead. Lead stored in skeletal tissue can be mobilized during pregnancy, lactation, ageing and increased bone turnover. Consequently, blood lead concentrations may increase even after the original environmental exposure has been reduced. The redistribution of lead between blood, soft tissues and bone is an important consideration during chelation therapy because the initial reduction in circulating lead may be followed by a rebound in blood lead concentration (WHO, 2021).

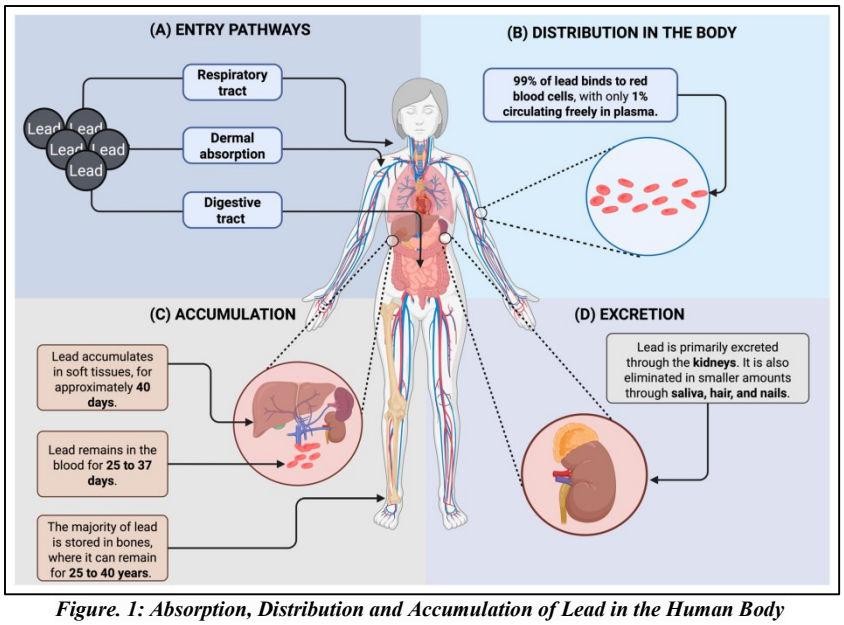


Figure. 1: Absorption, Distribution and Accumulation of Lead in the Human Body

3.2. Interference with calcium-dependent cellular processes:

One of the most important mechanisms of lead toxicity involves its ability to mimic or interfere with calcium ions. Calcium is essential for neurotransmitter release, intracellular signalling, muscle contraction and neuronal communication. Lead can interact with calcium-binding proteins and interfere with calcium-dependent signalling pathways. It may alter voltage-gated calcium channels, disturb intracellular calcium regulation and interfere with neurotransmitter release. These effects are particularly significant in the developing nervous system, where calcium-dependent processes contribute to neuronal differentiation, synaptic development and learning. Flora et al. (2012) described the importance of oxidative stress, altered cellular signalling and metal displacement in the pathophysiology of heavy-metal toxicity, including lead poisoning.

3.3. Oxidative stress and mitochondrial dysfunction:

Lead exposure promotes oxidative stress by increasing reactive oxygen species and weakening endogenous antioxidant defence mechanisms. It may interfere with glutathione metabolism and antioxidant enzymes, resulting in oxidative damage to proteins, lipids and nucleic acids. Mitochondria are particularly vulnerable

because they participate in energy production, calcium regulation and cellular redox balance. Lead-induced mitochondrial dysfunction can impair oxidative phosphorylation, reduce ATP production and contribute to cellular injury. In neuronal tissue, these alterations may interfere with synaptic function and contribute to neurodegeneration. In renal tissue, oxidative injury may affect tubular function and contribute to chronic nephrotoxicity.

3.4. Disruption of haem biosynthesis:

Lead interferes with several enzymes involved in haem synthesis. Two particularly important targets are delta-aminolevulinic acid dehydratase (ALAD) and ferrochelatase. ALAD catalyses the conversion of delta-aminolevulinic acid into porphobilinogen, whereas ferrochelatase facilitates the incorporation of iron into protoporphyrin IX during haem formation. Inhibition of these enzymes results in impaired haem production, accumulation of haem precursors and disruption of normal erythropoiesis. Clinically, these changes may contribute to anaemia and other haematological abnormalities. Heme synthesis disruption also provides a useful biochemical indication of lead exposure, although blood lead measurement remains the principal diagnostic investigation.

3.5. Renal, cardiovascular and neurological toxicity:

The kidneys are important targets of chronic lead exposure because of their role in filtration and elimination of circulating substances. Lead accumulation may produce proximal tubular dysfunction, oxidative damage and progressive interstitial injury. Cardiovascular effects include increased blood pressure and alterations in vascular function. Neurological effects may range from subtle cognitive and behavioural abnormalities to severe encephalopathy, seizures and coma. The developing brain is especially susceptible to lead-induced injury, and neurological consequences may persist despite successful chelation and reduction of blood lead concentrations (Lanphear et al., 2005).

4. Fundamental principles of chelation therapy:

Chelation therapy is based on the ability of selected chemical compounds to form coordination complexes with metal ions. Chelating molecules contain electron-donating functional groups that bind metal ions through coordinate covalent interactions. The resulting complexes may possess different chemical properties from the original free metal ions, including altered solubility, distribution and biological availability. In lead poisoning, the principal therapeutic objective is to bind biologically available lead and facilitate its elimination through urine or, depending on the compound, other excretory pathways.

4.1. Chemical basis of chelation:

Chelating agents generally contain functional groups such as:

1. Thiol groups (-SH).
2. Carboxyl groups (-COOH).
3. Amino groups (-NH_2).
4. Other oxygen- and nitrogen-containing donor groups.

The affinity of a chelator for lead depends on its molecular structure, ionization state, coordination geometry and stability of the resulting metal complex. Lead has a strong affinity for certain sulfur-containing ligands. This property explains the therapeutic importance of dithiol compounds such as dimercaprol and succimer.

4.2. Pharmacodynamic principles:

The pharmacodynamic activity of a chelating agent depends on several factors:

1. It’s binding affinity for lead.
2. Its ability to reach the relevant biological compartments.
3. The stability of the lead–chelator complex.
4. Its capacity to facilitate elimination.
5. Its selectivity relative to essential metals such as zinc, iron and copper.

An effective chelator should ideally remove toxic lead without significantly disturbing normal mineral metabolism. However, no currently established chelating agent achieves complete tissue lead removal or reliably reverses all established toxic effects.

4.3. Pharmacokinetic considerations:

The pharmacokinetic behaviour of chelating agents determines their clinical usefulness. Important considerations include absorption, distribution, metabolism, protein binding and elimination. Oral agents

offer practical advantages for selected patients who do not require emergency parenteral treatment. In contrast, intravenous or intramuscular preparations may be necessary in severe poisoning or when oral administration is not feasible. Renal function is particularly important because several lead–chelator complexes are eliminated through the kidneys. Patients with impaired renal function require specialist assessment and close monitoring.

5. Major chelating agents used in lead poisoning:

5.1. Succimer (DMSA):

Succimer, also known as meso-2,3-dimercaptosuccinic acid (DMSA), is an orally administered dithiol chelating agent used in selected cases of lead poisoning. Its molecular structure contains two sulfhydryl groups that facilitate binding to lead ions. Following administration, succimer forms complexes with lead that can be eliminated predominantly through urinary excretion.

5.2. Mechanism of action:

Succimer binds lead through its sulfur-containing functional groups, producing water-soluble complexes that facilitate elimination. It is relatively hydrophilic and is less likely than some older chelators to redistribute toxic metals into the central nervous system.

5.3. Pharmacokinetic characteristics:

Succimer is absorbed after oral administration, although absorption is incomplete. It undergoes extensive metabolism and forms disulfide derivatives with endogenous compounds. Renal elimination is important for the removal of its metabolites and associated metal complexes. Bradberry and Vale (2009) reviewed the pharmacokinetic and pharmacodynamic characteristics of succimer and highlighted its clinical effectiveness in reducing blood lead concentrations.

5.4. Clinical applications:

Succimer is commonly considered for children with confirmed blood lead concentrations of 45 µg/dL or higher, following appropriate clinical assessment and elimination of ongoing exposure. It is also used in selected adults under specialist supervision. The WHO recommends succimer or D-penicillamine as potential options for mild-to-moderate lead poisoning, depending on clinical circumstances and drug availability (WHO, 2021).

5.5. Adverse effects:

Reported adverse effects include:

1. Nausea and vomiting.
2. Diarrhoea.
3. Abdominal discomfort.
4. Skin rashes.
5. Elevated hepatic transaminases.
6. Rare haematological abnormalities.

Monitoring of hepatic function and blood counts may be required during treatment.

Limitations: Although succimer effectively reduces circulating lead, it does not reliably remove the entire skeletal lead burden. Its ability to improve long-term neurological outcomes is also limited.

Calcium disodium EDTA: Calcium disodium ethylenediaminetetraacetic acid ($CaNa_2EDTA$) is an important parenteral chelating agent used in severe lead poisoning. It is structurally related to EDTA, a polyaminocarboxylic acid capable of binding several metal ions.

Mechanism of action: Calcium disodium EDTA forms stable complexes with lead ions. The compound exchanges its calcium component for lead, producing a lead–EDTA complex that is eliminated predominantly through the kidneys. An important pharmacological distinction is that calcium disodium EDTA should not be confused with disodium EDTA. Administration of the incorrect formulation can produce severe hypocalcaemia.

Pharmacokinetic characteristics: Calcium disodium EDTA is poorly absorbed through the gastrointestinal tract and is therefore administered parenterally. It distributes mainly within extracellular fluid and undergoes

limited metabolism. The resulting metal complex is eliminated through renal filtration. Adequate renal function and appropriate fluid management are important during treatment.

Clinical applications: $CaNa_2EDTA$ is used in severe lead poisoning, particularly when substantial elevation of blood lead concentration or neurological manifestations require hospital-based treatment. In patients with severe poisoning, it may be used alone or in combination with other chelating agents, depending on the clinical situation and specialist recommendations.

Adverse effects: Potential adverse effects include:

1. Nephrotoxicity.
2. Proteinuria.
3. Haematuria.
4. Electrolyte disturbances.
5. Zinc depletion.
6. Local reactions following administration.

Renal function, urinalysis and relevant biochemical parameters require monitoring.

Dimercaprol (British anti-lewisite): Dimercaprol, also known as British Anti-Lewisite (BAL), is an older dithiol chelating agent originally developed as an antidote for arsenical chemical warfare agents. It remains an important component of selected treatment regimens for severe lead poisoning, particularly lead encephalopathy.

Mechanism of action: Dimercaprol contains two sulfhydryl groups that bind lead and other heavy metals. These groups form coordination complexes with metal ions, facilitating their elimination. Its lipophilic properties allow distribution into tissues, although its pharmacological limitations include toxicity and the potential for undesirable metal redistribution.

Pharmacokinetic characteristics: Dimercaprol is administered by intramuscular injection because oral administration is unsuitable. It undergoes rapid metabolism and requires repeated administration in clinical protocols.

Clinical applications: Dimercaprol may be used in combination with calcium disodium EDTA in patients with severe lead poisoning and neurological manifestations. The selection and sequence of treatment require specialist toxicological supervision.

Adverse effects: Important adverse reactions include:

1. Hypertension.
2. Tachycardia.
3. Nausea and vomiting.
4. Pain at the injection site.
5. Fever.
6. Excessive salivation and lacrimation.
7. Neurological adverse effects.

Its relatively narrow therapeutic margin and administration difficulties limit its routine use.

5.4. D-Penicillamine:

D-Penicillamine is an orally administered thiol-containing compound with metal-binding properties. Although it is primarily recognized for its applications in other metal-related disorders, it has also been used as an alternative chelating agent in lead poisoning.

Mechanism of action: The sulfhydryl group of D-penicillamine interacts with metal ions, producing complexes that can undergo renal elimination. Its ability to bind metals is influenced by chemical affinity and the surrounding biological environment.

Clinical applications: D-Penicillamine has historically been used in selected patients with mild-to-moderate lead poisoning. The WHO includes it as a possible therapeutic option where appropriate, although its use must be balanced against adverse effects and the availability of alternative chelators (WHO, 2021).

Adverse effects: Potential adverse reactions include:

1. Skin eruptions.
2. Gastrointestinal disturbances.
3. Proteinuria.
4. Nephrotic syndrome.
5. Bone marrow suppression.
6. Hypersensitivity reactions.

Because of these complications, it is not generally considered the preferred first-line chelator when safer and more established alternatives are available.

5.5. Comparative pharmacological characteristics:

Table. 1: Comparative Pharmacological Characteristics of Chelating Agents Used In Lead Poisoning

Characteristic	Succimer	$CaNa_2EDTA$	Dimercaprol	D-Penicillamine
Administration	Oral	Parenteral	Intramuscular	Oral
Main binding groups	Thiol	Carboxylate and amino	Thiol	Thiol
Major elimination	Renal	Renal	Metabolism and renal elimination of metabolites	Renal
Main application	Selected moderate poisoning	Severe poisoning	Severe poisoning with encephalopathy	Selected alternative cases
Important adverse effects	GI effects, rash, liver enzyme elevation	Nephrotoxicity, zinc depletion	Hypertension, tachycardia, injection pain	Proteinuria, cytopenias
Main limitation	Does not reverse established neurodevelopmental injury	Renal toxicity	Poor tolerability	Significant adverse-effect potential

The comparative characteristics demonstrate that the selection of a chelator should be based on poisoning severity, clinical presentation, renal function, patient age, availability and treatment setting rather than on binding affinity alone.

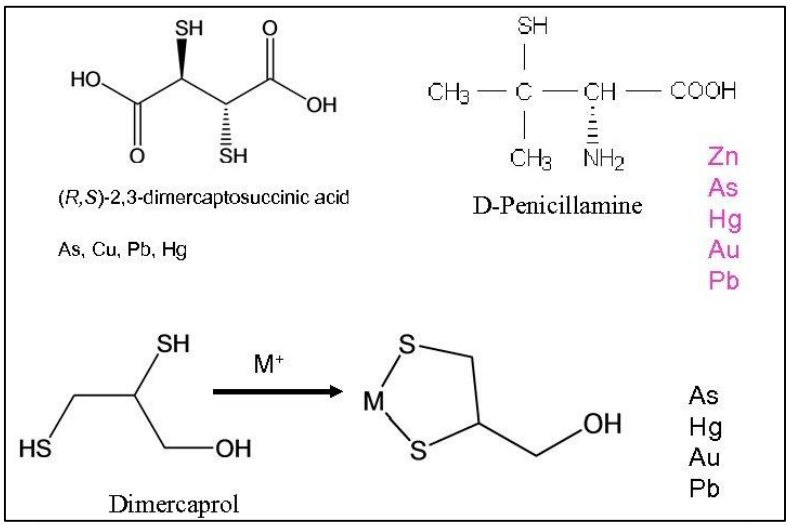


Figure. 2: Pharmacological Mechanism of Chelation Therapy in Lead Poisoning

6. Clinical applications of chelation therapy:

6.1. Diagnosis and patient assessment:

The diagnosis of lead poisoning is primarily based on measurement of blood lead concentration using a venous blood sample. Blood lead concentration provides an indication of recent and ongoing exposure, although it does not fully represent the total lead burden stored in the skeleton.

Clinical assessment should include:

1. Detailed exposure history.
2. Neurological examination.
3. Assessment of gastrointestinal symptoms.
4. Complete blood count.
5. Renal function assessment.
6. Hepatic function assessment when indicated.
7. Evaluation of nutritional status.
8. Investigation of the environmental or occupational exposure source.

Abdominal radiography may be useful in selected patients with suspected ingestion of lead-containing foreign material.

6.2. Paediatric lead poisoning:

Children are especially vulnerable to lead toxicity because of increased gastrointestinal absorption, hand-to-mouth behaviour and the susceptibility of the developing nervous system. Clinical manifestations may include developmental delay, impaired attention, behavioural changes, abdominal pain, anaemia and, in severe cases, encephalopathy. Chelation is generally considered when venous blood lead concentrations reach clinically significant levels, particularly 45 μg/dL or higher, according to relevant clinical guidance. The Treatment of Lead-Exposed Children trial investigated succimer in children with blood lead concentrations between 20 and 44 μg/dL. Rogan et al. (2001) found that although succimer reduced blood lead concentrations temporarily, it did not improve cognitive or behavioural outcomes compared with placebo. The findings support the principle that chelation should not be used simply to lower modestly elevated blood lead concentrations in the expectation of reversing developmental injury.

6.3. Severe lead poisoning and encephalopathy:

Severe lead poisoning represents a medical emergency. Neurological manifestations may include confusion, irritability, drowsiness, ataxia, seizures and coma. Patients with suspected lead encephalopathy require urgent hospital assessment and specialist management. The WHO recommends urgent parenteral chelation for patients with significant neurological features of lead toxicity, irrespective of whether the blood lead concentration alone adequately reflects the severity of the clinical presentation (WHO, 2021). Dimercaprol and calcium disodium EDTA are established components of treatment approaches for severe cases. Succimer may also be considered where clinically appropriate and oral administration is feasible.

6.4. Lead poisoning in adults:

Adults may experience occupational exposure through battery manufacturing, mining, metal processing, construction, recycling and other industrial activities. Chronic exposure may result in hypertension, renal dysfunction, peripheral neuropathy and reproductive abnormalities. Kosnett et al. (2007) emphasized that adult lead exposure requires clinical evaluation even in the absence of dramatic symptoms. Chelation is generally reserved for patients with substantial blood lead elevation or significant clinical manifestations. Exposure cessation is essential before or alongside chelation because continued exposure may undermine treatment effectiveness.

6.5. Lead poisoning during pregnancy:

Pregnancy presents additional challenges because lead stored in maternal bone can be mobilized and cross the placenta. Foetal exposure may interfere with neurological development and may contribute to adverse pregnancy outcomes. Chelation decisions during pregnancy require individualized risk–benefit assessment because both lead exposure and chelating agents may have potential consequences for the developing foetus. The WHO guideline recommends urgent treatment of lead encephalopathy during pregnancy. For pregnant women with blood lead concentrations of 45 μg/dL or higher without encephalopathy, recommendations differ according to trimester. In particular, evidence is insufficient to establish a recommendation for chelation during the first trimester, whereas treatment is recommended in the second and third trimesters after clinical assessment (WHO, 2021).

6.6. Post-chelation management:

Following chelation, blood lead concentrations should be reassessed after an appropriate period of redistribution. A rebound may occur because lead stored in soft tissues and bone can re-enter circulation after chelator administration has stopped. The WHO suggests reassessment approximately 2–4 weeks after treatment, with the shorter interval considered for patients with higher initial concentrations (WHO, 2021). Long-term management should include environmental remediation, nutritional support and continued clinical follow-up.

7. Clinical efficacy and limitations of chelation therapy:

The principal demonstrated benefit of chelation therapy is the reduction of circulating lead concentrations and acceleration of lead elimination. However, biochemical efficacy should not be interpreted as equivalent to neurological recovery or complete elimination of tissue lead. The TLC trial remains one of the most important clinical investigations in this area. Rogan et al. (2001) demonstrated that succimer treatment did

not improve neuropsychological development in children with moderate lead exposure. This result has important clinical implications. Chelation should not be considered a substitute for environmental prevention, and it should not be routinely used in patients with low-level exposure without appropriate indications. Similarly, the evidence supporting specific chelator combinations in severe poisoning is limited. The WHO systematic evidence review identified substantial uncertainty in comparative treatment efficacy, emphasizing the need for individualized clinical decision-making (WHO, 2021).

7.1. Major limitations:

The principal limitations of current chelation therapy include:

1. Incomplete removal of lead stored in bone.
2. Potential redistribution of lead between tissue compartments.
3. Adverse effects associated with individual chelating agents.
4. Loss of essential trace elements.
5. Dependence on renal elimination.
6. Lack of strong evidence for improvement in long-term neurological outcomes in several clinical settings.
7. Possibility of rebound elevation in blood lead concentrations.

These limitations highlight the importance of combining chelation with environmental intervention and long-term follow-up.

8. Adverse effects, drug interactions and safety considerations:

Chelating agents are pharmacologically active compounds that may bind essential metals in addition to lead. Consequently, treatment may disturb normal mineral balance and produce clinically important adverse effects.

8.1. Essential mineral depletion:

Zinc, copper, iron and calcium are necessary for normal cellular activity. Some chelators may bind these elements, resulting in depletion or altered mineral metabolism. Excessive or inappropriate chelation can therefore create additional nutritional and physiological complications.

8.2. Renal toxicity:

Renal elimination is an important pathway for several chelator–lead complexes. Patients with impaired renal function may have reduced capacity to eliminate these complexes. $CaNa_2EDTA$ is particularly associated with renal toxicity, making renal monitoring an essential component of treatment.

8.3. Hepatic and haematological complications:

Succimer may cause increases in hepatic transaminases, while D-penicillamine can produce haematological abnormalities and renal complications. Appropriate monitoring depends on the agent used and the patient's clinical condition.

8.4. Avoidance of inappropriate chelation:

Chelation should never be undertaken as a general wellness treatment or as a preventive intervention in individuals without a clinically established indication. It should not be administered during continuing uncontrolled exposure as a replacement for source elimination. Unsupervised chelation may produce serious adverse effects and should be avoided.

9. Emerging therapeutic approaches:

Despite the availability of established chelating agents, limitations involving toxicity, incomplete tissue penetration and inadequate reversal of established neurological injury have stimulated research into alternative therapeutic approaches. These emerging strategies aim to improve metal-binding selectivity, reduce oxidative injury, improve drug delivery and target tissue-specific pathological mechanisms.

9.1. Development of novel chelating molecules:

One important research direction involves designing compounds with improved affinity and selectivity for lead. Traditional chelators may interact with essential metals, potentially causing mineral depletion. New compounds are being investigated to achieve improved selectivity while maintaining sufficient stability of

metal–ligand complexes. Bjørklund et al. (2018) discussed the pharmacological and toxicological characteristics of metal chelators and highlighted the importance of selecting appropriate ligands for different metal-related disorders. Future lead-specific compounds may be designed to improve distribution into relevant tissue compartments without increasing toxicity.

9.2. Antioxidant-based adjunctive treatment:

Oxidative stress is an important contributor to lead-induced cellular damage.
Antioxidant compounds have therefore been investigated as possible adjuncts to conventional treatment. Examples include:

1. N-acetylcysteine.
2. Vitamin C.
3. Vitamin E.
4. Glutathione-related compounds.
5. Selected polyphenolic compounds.

These substances may influence oxidative stress pathways and endogenous antioxidant defence mechanisms. However, evidence supporting their routine use as treatments for lead poisoning remains insufficient. They should not replace established exposure control or indicated chelation therapy.

9.3. Nanotechnology-based chelation systems:

Nanotechnology offers potential opportunities for improving the delivery and targeting of metal-binding compounds. Nanoparticles can be engineered to carry therapeutic molecules, alter drug-release characteristics and potentially improve tissue distribution. In experimental settings, nanomaterial-based approaches have been investigated for adsorption, sequestration and delivery-related applications involving toxic metals. Nevertheless, important safety concerns remain, including nanoparticle accumulation, long-term toxicity, immune reactions and uncertain elimination pathways. Consequently, nanotechnology-based chelation remains an experimental research area rather than an established clinical treatment for lead poisoning.

9.4. Targeting mitochondrial dysfunction:

Because mitochondria are important targets of lead-induced toxicity, mitochondrial protection represents another potential therapeutic direction. Experimental approaches include compounds intended to reduce mitochondrial oxidative stress, preserve membrane integrity and improve cellular energy metabolism. Such interventions could theoretically protect vulnerable neuronal and renal tissues. However, further preclinical and clinical investigations are required to establish whether mitochondrial-targeted treatments provide meaningful clinical benefits.

9.5. Nutritional interventions:

Nutritional status influences lead absorption and toxicity. Calcium and iron deficiencies may increase gastrointestinal lead absorption, while adequate dietary intake of essential nutrients supports normal physiological function. WHO (2021) recognizes the importance of assessing and correcting nutritional deficiencies in individuals exposed to lead. Nutritional interventions should therefore be considered an important supportive component of management, although they cannot independently remove an established toxic lead burden.

9.6. Metal transport and cellular detoxification pathways:

Another developing area of research involves investigating cellular metal transporters and endogenous detoxification mechanisms. Lead interacts with proteins involved in metal homeostasis, including pathways associated with divalent metal transport and intracellular metal sequestration. A better understanding of these mechanisms may help identify therapeutic targets that reduce lead uptake into vulnerable cells or improve intracellular detoxification. At present, these approaches remain predominantly experimental and require substantial translational research.

10. Role of clinical guidelines and evidence-based practice:

International clinical guidelines provide an important framework for selecting appropriate treatment strategies. The WHO guideline published in 2021 recommends that clinical decisions incorporate blood lead concentrations, clinical manifestations, patient age, pregnancy status and the nature of exposure. For mild-to-moderate poisoning, succimer or D-penicillamine may be considered, whereas severe poisoning may require

calcium disodium EDTA alone or in combination with succimer or dimercaprol (WHO, 2021). The Centers for Disease Control and Prevention (CDC) also emphasizes clinical evaluation and appropriate specialist involvement in children with elevated blood lead concentrations. Current recommendations should be interpreted within the patient's clinical context rather than applied as isolated numerical treatment thresholds. In particular, blood lead concentrations should not be used as the sole determinant of neurological severity.

11. Future research perspectives:

Future research should focus on several important areas.

Improved chelator selectivity: New compounds should demonstrate strong lead-binding capacity while minimizing interactions with essential minerals.

Better tissue distribution: Research should investigate whether therapeutic agents can safely access relevant tissue compartments, particularly the central nervous system, without increasing toxic redistribution.

Long-term clinical outcomes: Future randomized clinical studies should evaluate neurological, cognitive, renal and cardiovascular outcomes rather than relying exclusively on changes in blood lead concentrations.

Biomarker development: Improved biomarkers may help distinguish recent exposure from cumulative body burden and identify patients who are most likely to benefit from chelation.

Safer combination therapies: Research into combinations of chelators and supportive antioxidant approaches may identify strategies that improve efficacy while reducing toxicity. Such combinations require controlled evaluation before clinical adoption.

Translational nanomedicine: Nanotechnology-based delivery systems require further investigation regarding pharmacokinetics, tissue targeting, immunological safety and long-term elimination.

Greater representation of developing countries: More clinical research is required in regions with substantial occupational and environmental exposure, particularly where diagnostic resources and access to established chelating agents are limited.

12. Conclusion:

Chelation therapy remains an important pharmacological intervention in the management of selected patients with lead poisoning. Its principal mechanism involves the formation of stable metal–ligand complexes that facilitate the elimination of lead from the body. Succimer, calcium disodium EDTA, dimercaprol and D-penicillamine represent the major established pharmacological options. Their selection depends on poisoning severity, clinical manifestations, patient characteristics, renal function and treatment availability. Although chelation can reduce circulating lead concentrations and improve certain acute manifestations, it cannot reliably reverse established neurological damage or completely eliminate lead stored in skeletal tissue. Evidence from the TLC trial demonstrates that biochemical improvement does not necessarily translate into improved long-term neuropsychological outcomes.

Therefore, the optimal management of lead poisoning requires a comprehensive approach incorporating exposure elimination, appropriate chelation, nutritional assessment, supportive care and long-term monitoring. Emerging approaches involving selective chelators, antioxidant adjuncts, nanotechnology and mitochondrial protection may provide opportunities for improving future treatment outcomes. However, these strategies require further experimental and clinical validation. Ultimately, the most effective strategy for reducing the global burden of lead poisoning remains prevention of exposure, supported by evidence-based clinical management and the development of safer pharmacological interventions.

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