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# Chelation Therapy for Off-Label Uses

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## Disclaimer

*Medical policies are a set of written guidelines that support current standards of practice. They are based on current generally accepted standards of and developed by nonprofit professional association(s) for the relevant clinical specialty, third-party entities that develop treatment criteria, or other federal or state governmental agencies. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and generally accepted standards of medical care. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.*

### Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

## Legislative Mandates

**EXCEPTION: For Illinois only:** Illinois Public Act 103-0458 [Insurance Code 215 ILCS 5/356z.61] (HB3809 Impaired Children) states all group or individual fully insured PPO, HMO, POS plans amended, delivered, issued, or renewed on or after January 1, 2025 shall provide coverage for therapy, diagnostic testing, and equipment necessary to increase quality of life for children who have been clinically or genetically diagnosed with any disease, syndrome, or disorder that includes low tone neuromuscular impairment, neurological impairment, or cognitive impairment.

## Coverage

Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the U.S. Food and Drug Administration) are considered **experimental, investigational and/or unproven**, including, but not limited to:

- Alzheimer disease;
- Atherosclerosis (e.g., coronary artery disease, secondary prevention in individuals with myocardial infarction, or peripheral vascular disease);
- Autism;
- Diabetes;
- Multiple sclerosis;
- Arthritis (includes rheumatoid arthritis).

## Policy Guidelines

A number of indications for chelation therapy have received U.S. Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care. These indications include:

- Extreme conditions of metal toxicity;
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia;
- Wilson disease (hepatolenticular degeneration);
- Lead poisoning;
- Control of ventricular arrhythmias or heart block associated with digitalis toxicity;
- Emergency treatment of hypercalcemia.

For the last 2 bullet points, most individuals should be treated with other modalities. Digitalis toxicity is currently treated in most individuals with Fab monoclonal antibodies. The FDA removed the approval for disodium-ethylenediaminetetraacetic acid (NaEDTA) as chelation therapy due to safety concerns and recommended that other chelators be used. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

## Description

Chelation therapy, an established treatment for heavy metal toxicities and transfusional hemosiderosis, has been investigated for a variety of off-label applications, such as treatment of atherosclerosis, Alzheimer disease, and autism. This medical policy does not address indications for chelation therapy approved by the U.S. Food and Drug Administration (FDA). Instead, it addresses off-label indications, including Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis.

### Chelation Therapy

Chelation therapy is an established treatment for the removal of metal toxins by converting them to a chemically inert form that can be excreted in the urine. Chelation therapy comprises intravenous or oral administration of chelating agents that remove metal ions such as lead,

aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body (see Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, deferoxamine is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning. Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia. (1)

Another class of chelating agents, called metal protein attenuating compounds (MPACs), is under investigation for the treatment of Alzheimer disease, which is associated with the disequilibrium of cerebral metals. Unlike traditional systemic chelators that bind and remove metals from tissues systemically, MPACs have subtle effects on metal homeostasis and abnormal metal interactions. In animal models of Alzheimer disease, MPACs promote the solubilization and clearance of β-amyloid by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. Therefore, MPACs interrupt 2 putative pathogenic processes of Alzheimer disease. However, no MPACs have received FDA approval for treating Alzheimer disease.

Chelation therapy also has been considered as a treatment for other indications, including atherosclerosis and autism spectrum disorder. For example, EDTA chelation therapy has been proposed in patients with atherosclerosis as a method of decreasing obstruction in the arteries.

Suggested toxic or normal levels of select heavy metals are listed in Table 1.

**Table 1. Toxic or Normal Concentrations of Heavy Metals**

| Metal | Toxic Levels (Normal Levels Where Indicated) |
|---|---|
| Arsenic | 24-h urine: ≥50 µg/L urine or 100 µg/g creatinine |
| Bismuth | No clear reference standard |
| Cadmium | Proteinuria and/or ≥15 µg/g creatinine |
| Chromium | No clear reference standard |
| Cobalt | Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine) |
| Copper | Normative excretion: 25 µg/24 h (urine) |
| Iron | • Nontoxic: <300 µg/dl<br>• Severe: >500 µg/dL |
| Lead | Pediatric<br>• Symptoms or blood lead level ≥45 µg/dL (blood)<br>• CDC level of concern: 3.5 µg/dL (41)<br>Adult<br>• Symptoms or blood lead level ≥70 µg/dL<br>• CDC level of concern: 10 µg/dL (42) |
| Manganese | No clear reference standard |
| Mercury | Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine) (43)[a] |

| | |
|---|---|
| Nickel | • Excessive exposure: ≥8 µg/L (blood)<br>• Severe poisoning: ≥500 µg/L (8-h urine) |
| Selenium | • Mild toxicity: >1 mg/L (serum)<br>• Serious toxicity: >2 mg/L |
| Silver | Asymptomatic workers have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine) |
| Thallium | 24-hour urine thallium >5 µg/L (44) |
| Zinc | Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells) |

Adapted from Adal (2018). (45)
CDC: Centers for Disease Control and Prevention.
[a] Hair analysis is useful to assess mercury exposure in epidemiologic studies. However, hair analysis in individual patients must be interpreted with consideration of the patient's history, signs, and symptoms, and possible alternative explanations. Measurement of blood and urine mercury levels can exclude exogenous contamination; therefore, blood or urine mercury levels may be more robust measures of exposure in individual patients. (46)

**Regulatory Status**

In 1953, EDTA (Versenate) was approved by the FDA for lowering blood lead levels among both pediatric and adult patients with lead poisoning. In 1991, succimer (Chemet) was approved by the FDA for the treatment of lead poisoning in pediatric patients only. The FDA approved disodium-EDTA for use in selected patients with hypercalcemia and use in patients with heart rhythm problems due to intoxication with digitalis. In 2008, the FDA withdrew approval of disodium-EDTA due to safety concerns and recommended that other forms of chelation therapy be used. (2)

Several iron-chelating agents are FDA approved:

- In 1968, deferoxamine (Desferal®; Novartis) was approved by the FDA for subcutaneous, intramuscular, or intravenous injections to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved by the FDA.
- In 2005, deferasirox (Exjade®; Novartis) was approved by the FDA, is available as a tablet for oral suspension, and is indicated for the treatment of chronic iron overload due to blood transfusions in patients age 2 years and older. Under the accelerated approval program, the FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia syndromes and specific liver iron concentration and serum ferritin levels. A generic version of deferasirox tablet for oral suspension has also been approved by the FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu®) was approved by the FDA. All formulations of deferasirox carry a boxed warning because it may cause serious and fatal renal toxicity and failure, hepatic toxicity and failure, and gastrointestinal hemorrhage. As a result, treatment with deferasirox requires close patient monitoring, including laboratory tests of renal and hepatic function.

- In 2011, the iron chelator deferiprone (Ferriprox®) was approved by the FDA for treatment of patients with transfusional overload due to thalassemia syndromes when another chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox® carries a boxed warning because it can cause agranulocytosis, which can lead to serious infections and death. As a result, absolute neutrophil count should be monitored before and during treatment.

In a June 2014 warning to consumers, the FDA advised that FDA-approved chelating agents would be available by prescription only. There are no FDA approved over-the-counter chelation products.

## Rationale

Medical policies assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life, and ability to function, including benefits and harms. Every clinical condition has specific outcomes that are important to patients and to managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent 1 or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The randomized controlled trial (RCT) is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. Randomized controlled trials are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice. The following is a summary of the key literature to date.

**Alzheimer Disease**

Clinical Context and Therapy Purpose

The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with Alzheimer disease.

The following PICO was used to select literature to inform this policy.

*Populations*

The population of interest is individuals with Alzheimer disease.

*Interventions*
The intervention of interest is chelation therapy.

*Comparators*
The comparator of interest is standard medical care without chelation therapy.

*Outcomes*
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Review
A Cochrane review (2008) evaluated metal protein attenuating compounds for treating Alzheimer disease. (3) Reviewers identified a placebo-controlled randomized trial. This study by Ritchie et al. (2003) assessed patients treated with PBT1, a metal protein attenuating compound also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier. (4) The U.S. Food and Drug Administration (FDA) withdrew clioquinol for oral use from the market in 1970 because of its association with subacute myelo-optic neuropathy. Ritchie et al. (2013) administered oral clioquinol to 16 patients with Alzheimer disease in doses increasing to 375 mg twice daily and compared this group with 16 matched controls who received placebo. At 36 weeks, there was no statistically significant between-group difference in cognition measured by the Alzheimer Disease Assessment Scale–Cognitive. One patient in the treatment group developed impaired visual acuity and color vision during weeks 31 to 36 of treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. Updates of this Cochrane review (2012 and 2014) included trials through January 2012. (5, 6) Only the Lannfelt et al. (2008) trial (discussed next) was identified. (5)

Further study of PBT1 was abandoned in favor of a successor compound, PBT2. Lannfelt et al. (2008) completed a double-blind, placebo-controlled randomized trial of 78 patients with Alzheimer disease who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29). (7) There was no statistically significant difference in Alzheimer Disease Assessment Scale-Cognitive or Mini-Mental Status Examination scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis, transient ischemic event) were reported in the placebo arm.

In 2025, Ayton and colleagues published the results of a phase 2, double-masked RCT of deferiprone 15 mg/kg twice daily versus placebo conducted in 9 sites across Australia. (8) Study participants were 54 years or older with amyloid-confirmed mild cognitive impairment or early Alzheimer disease with a Mini-Mental State Examination score of 20 or higher. Randomization was 2:1, with 53 assigned to deferiprone and 28 to placebo. The primary outcome measure was a composite cognitive measure assessed at baseline, 6 months, and 12 months. In an intention-to-treat analysis, the deferiprone group showed accelerated cognitive decline on the neuropsychological test battery (change in composite z score for deferiprone, -80.0 [95% confidence interval, -0.98 to -0.62]; for placebo, -0.30 [95% CI, -0.54 to -0.06]). The accelerated decline in the deferiprone group was driven by a decrease in executive function tests. Quantitative susceptibility mapping (QSM) magnetic resonance imaging (MRI) confirmed that use of deferiprone decreased iron concentrations in the hippocampus compared to placebo. The investigators concluded that these results suggest that iron chelation with deferiprone may be detrimental to patients with early Alzheimer disease.

Section Summary: Alzheimer Disease

There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published RCTs did not find that chelation was superior to placebo for improving health outcomes. One RCT, published in 2025, found that iron chelation with deferiprone accelerated the rate of cognitive decline in early Alzheimer disease.

**Cardiovascular Disease**

Clinical Context and Therapy Purpose

The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with cardiovascular disease.

The following PICO was used to select literature to inform this policy.

*Populations*

The population of interest is individuals with cardiovascular disease.

*Interventions*

The intervention of interest is chelation therapy.

*Comparators*

The comparator of interest is standard medical care without chelation therapy.

*Outcomes*

The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Systematic Review

Ravalli et al. (2022) published a systematic review and meta-analysis of 24 trials, including 4 RCTs, that evaluated the use of ethylenediaminetetraacetic acid (EDTA) in patients with cardiovascular disease. (9) Ankle-brachial index was the only outcome reported in at least 3 studies and included in meta-analysis (Table 2). Overall, 17 studies reported improved outcomes with EDTA, 5 reported no significant effect, and 2 reported no qualitative benefit. The studies included in this meta-analysis are limited by the lack of clinical outcomes, the variety of infusion methods, limited sample sizes, and minimal follow-up time.

Villarruz-Sulit et al. (2020) published a Cochrane review that evaluated EDTA chelation therapy for treating patients with atherosclerotic cardiovascular disease. (10) Five placebo-controlled trials were included (N=1993, range 10 to 1708); 3 studies included patients with peripheral vascular disease and 2 studies included patients with coronary artery disease, with 1 specifically recruiting patients with a previous myocardial infarction. One study had a high risk of bias, since investigators broke randomization partway through the trial, but all other trials were rated as moderate to low. A meta-analysis of included studies found no difference between chelation therapy and placebo with regard to all-cause mortality (n=1792, 2 studies; risk ratio [RR], 0.97; 95% confidence interval [CI], 0.73 to 1.28), cardiovascular death (n=1708, 1 study; RR, 1.02; 95% CI, 0.70 to 1.48), myocardial infarction (n=1792, 2 studies; RR, 0.81; 95% CI, 0.57 to 1.14), angina (n=1792, 2 studies; RR, 0.95; 95% CI, 0.55 to 1.67), or coronary revascularization (n=1792, 2 studies; RR, 0.46; 95% CI, 0.07 to 3.25). Cochrane reviewers found that the evidence was insufficient to support conclusions about the efficacy of chelation therapy for treating atherosclerosis. Additional RCTs reporting health outcomes like mortality and cerebrovascular events were suggested.

**Table 2. Comparison of Randomized Controlled Trials Included in Systematic Reviews and Meta-analyses**

| Study | Ravalli (2022) (9) | Villarruz-Sulit (2020) (10) |
|---|---|---|
| Lamas (2013) | ● | ● |
| Knudston (2002) | ● | ● |
| van Rij (1994) | ● | ● |
| Guldager (1992) | ● | ● |
| Olszewer (1990) | | ● |

**Table 3. Systematic Review and Meta-analysis Characteristics**

| Study | Dates | Trials | Participants | N (Range) | Design | Duration |
|---|---|---|---|---|---|---|
| Ravalli (2022) (9) | To October 2021 | 24 (4 RCTs, 15 prospective before/after trials, 5 retrospective studies) | Patients treated with EDTA for atherosclerotic cardiovascular disease | 5501 (4 to 2870) | RCT | NR |
| Villarruz-Sulit (2020) (10) | To August 2019 | 5 RCTs | Patients treated with EDTA for atherosclerotic cardiovascular disease | 1993 (10 to 1708) | RCT | 6 months to 5 years |

EDTA: ethylenediaminetetraacetic acid; N: number; NR: not reported; RCT: randomized controlled trial.

**Table 4. Systematic Review and Meta-analysis Results**

| Study | All-cause mortality | CHD Deaths | MI | Revascularization | Stroke | ABI |
|---|---|---|---|---|---|---|
| **Ravalli (2022) (9)** | | | | | | |
| Total N | 1792 | 1708 | 1792 | 1792 | 1867 | 181 |
| Risk ratio (95% CI) | 0.97 (0.73 to 1.28) | 1.02 (0.7 to 1.48) | 0.81 (0.07 to 3.25) | 0.46 (0.07 to 3.25) | 0.88 (0.40 to 1.92) | 0.02 (-0.03 to 0.06) |
| $I^2$ (p) | NA | NA | 0% (.85) | 56% (.13) | 0% (.43) | 0% (.59) |
| **Villarruz-Sulit (2020) (10)** | | | | | | |
| Total N | | | | | | 173 |
| Mean difference (95% CI) | | | | | | 0.08 (0.06 to 0.09) |
| $I^2$ (p) | | | | | | 94% (NR) |

ABI: ankle-brachial index; CHD: coronary heart disease; CI: confidence interval; MI: myocardial infarction; N: number; NA: not applicable; NR: not reported.

Randomized Controlled Trial

The largest RCT included in the meta-analyses is the multicenter, 2×2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT), which was published by Lamas et al. in 2013. (11) TACT included 1708 patients, age 50 years or older, who had a history of myocardial infarction at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to 40 intravenous infusions of disodium EDTA (n=839) or placebo (n=869). Patients also received oral high-dose vitamin plus mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. The primary endpoint was a composite outcome that included death from

any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years. The threshold for statistical significance was adjusted for multiple interim analyses to a p-value of .036. A total of 361 (43%) patients in the chelation group and 464 (57%) patients in the placebo group discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary endpoint was 33% (95% CI, 29% to 37%) in the chelation group and 39% (95% CI, 35% to 42%) in the control group, a statistically significant difference (p=.035). The most common individual clinical endpoint was coronary revascularization, which occurred in 130 (16%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=.08). The next most frequent endpoint was death, which occurred in 87 (10%) patients in the chelation group and 93 (11%) patients in the placebo group (p=.64). No individual component of the primary outcome differed statistically between groups; however, the trial was not powered to detect differences in individual components. Four severe adverse events definitely or possibly related to study therapy occurred, 2 each in the treatment and control groups, including 1 death in each. Quality of life outcomes (reported in 2014) did not differ between groups at 2-year follow-up. (12)

A 2014 follow-up publication reported results for the 4 treatment groups in the 2×2 factorial design (double-active group [disodium-EDTA infusions with oral high-dose vitamins; n=421 patients], active infusions with placebo vitamins [n=418 patients], placebo infusions with active vitamins [n=432 patients], or double placebo [n=437 patients]). (13) The proportion of patients who discontinued treatment, withdrew consent, or were lost to follow-up per treatment group were not reported. Five-year Kaplan-Meier estimates for the primary composite endpoint were 32%, 34%, 37%, and 40%, respectively. The reduction in primary endpoint by double-active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74; 95% CI, 0.57 to 0.95). In 633 patients with diabetes (»36% of each treatment group), the primary endpoint reduction in the double-active group compared with the double placebo group was more pronounced (HR , 0.49; 95% CI, 0.33 to 0.75). A post-hoc analysis showed that chelation was associated with a lower risk of the primary endpoint compared with placebo in patients with post anterior myocardial infarction (n=674; HR, 0.63; 95% CI, 0.47 to 0.86; p=.003); however, this effect was not seen in post non-anterior myocardial infarction. (14)

The trial was limited by the high number of withdrawals, with differential withdrawals between groups. The primary endpoint included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary endpoint barely met the significance threshold; if more patients had remained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the original (2013) publication, 60% of patients were enrolled at centers described as complementary and alternative medicine sites, and this may have resulted in the selection of a population not generalizable to that seen in general clinical care. (15) Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings. (16) This secondary analysis had the same limitations as the parent study previously described (i.e., high and differential withdrawal, heterogeneous composite endpoint). Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

The TACT2 study replicated the design of the original TACT study evaluating 40 weekly infusions of EDTA-based chelation in patients with prior myocardial infarction and diabetes. (17) Enrollment was complete in December 2020 and treatment was complete in December 2021. In August 2024, Lamas et al. published outcomes from TACT2 (N=1000). (18) TACT2 failed to replicate the findings from the original TACT trial. Primary composite outcome events were observed in 172 (35.6%) of participants receiving at least 1 active chelation infusion compared to 170 (35.7%) receiving at least 1 placebo infusion (adjusted HR, 0.93 [95% CI, 0.76 to 1.16]; p =.53). The Kaplan-Meier 5-year cumulative incidence estimates for the primary endpoint were 45.8% (95% CI, 39.9% - 51.5%) and 46.5% (95% CI, 39.7 - 53.0%) for chelation and placebo groups, respectively. There were no statistically significant differences in individual cardiovascular event components of the composite outcome. The adjusted HR for death from any cause was 0.96 (95% CI, 0.71-1.30). Blood lead levels dropped by 61% in participants receiving active chelation. All 40 infusions were received in 67% of participants assigned to active chelation and 67% assigned to placebo. Consent was withdrawn during follow-up for 60 (6%) participants (22 chelation and 38 placebo) and 62 (6%) participants were lost to follow-up (35 chelation and 27 placebo). Prespecified sensitivity analyses did not indicate impacts on primary endpoint effect size based on gaps in follow-up, loss to follow-up, or consent withdrawal.

Section Summary: Cardiovascular Disease

A Cochrane review of several RCTs of chelation therapy did not show sufficient evidence to draw conclusions about the efficacy of EDTA chelation therapy compared to placebo. A 2022 systematic review included similar RCTs and numerous observational trials but did not perform meta-analysis on clinical outcomes. The TACT RCT included in systematic reviews has significant limitations, including a high dropout rate with differential dropout between groups, but reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes and post-anterior myocardial infarction. In 2025, findings from the TACT2 RCT failed to replicate the findings from the original TACT study among individuals with diabetes and a previous myocardial infarction at least 6 months prior to recruitment.

Autism Spectrum Disorder

Based on symptom similarities between mercury poisoning and autism spectrum disorder, Bernard et al. (2001) hypothesized a link between environmental mercury and autism. (19) This theory was rejected by Nelson and Bauman (2003), who found that many characteristics of mercury poisoning, such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children. (20) A meta-analysis by Ng et al. (2007) concluded that there was no association between mercury poisoning and autism. (21)

Clinical Context and Therapy Purpose

The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with autism spectrum disorder.

The following PICO was used to select literature to inform this policy.

*Populations*
The population of interest is individuals with autism spectrum disorder.

*Interventions*
The intervention of interest is chelation therapy.

*Comparators*
The comparator of interest is standard medical care without chelation therapy.

*Outcomes*
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Observational Studies
Rossignol (2009) published a systematic review of novel and emerging treatments for autism and identified no controlled studies. (22) Rossignol (2009) stated that case series had suggested a potential role for chelation in treating some autistic people with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

Section Summary: Autism Spectrum Disorder
There is a lack of controlled studies on how chelation therapy affects health outcomes in patients with autism.

**Diabetes**
Clinical Context and Therapy Purpose
The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with diabetes.

The following PICO was used to select literature to inform this policy.

*Populations*

The population of interest is individuals with diabetes.

Interventions
The intervention of interest is chelation therapy.

*Comparators*
The comparator of interest is standard medical care without chelation therapy.

*Outcomes*
The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Study Selection Criteria
Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

Randomized Controlled Trials
*Cardiovascular Disease in Patients With Diabetes*
A trial by Cooper et al. (2009) in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes. (23) Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area in the active treatment group (-10.6 $g/m^2$) than in the placebo group (-0.1 $g/m^2$; p=.01). The trial was limited by small sample size and high dropout rate.

Escolar et al. (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. (24) In this trial (also discussed above), there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes. Among 538 (31% of the trial sample) self-reported diabetic patients, those randomized to EDTA had a 39% reduced risk of the primary composite outcome (i.e., death from any cause, reinfarction, stroke, coronary revascularization, or hospitalization for angina at 5 years) compared with placebo (HR, 0.61; 95% CI, 0.45 to 0.83; p=.02); among 1170 nondiabetic patients, risk of the primary outcome did not differ statistically between treatment groups (HR , 0.96; 95% CI, 0.77 to 1.20; p=.73). (11) For the subsequent subgroup analysis, the definition of diabetes was broadened to include self-reported diabetes, use of oral or insulin treatment for diabetes, or fasting blood glucose of 126 mg/dL or more at trial entry. Of 1708 patients in TACT, 633 (37%) had diabetes by this definition: 322 were randomized to EDTA and 311 to placebo. Compared with all other trial participants, this subgroup of diabetic patients had higher body mass index, fasting blood

glucose, and prevalence of heart failure, stroke, hypertension, peripheral artery disease, and hypercholesterolemia. Within this subgroup, baseline characteristics were similar between treatment groups. With approximately 5 years of follow-up, the primary composite endpoint occurred in 25% of the EDTA group and 38% of the placebo group (adjusted HR, 0.59; 99.4% CI, 0.39 to 0.88; p=.002). In adjusted analysis of the individual components of the primary endpoint, there were no statistically significant differences between treatment groups. Thirty-six adverse events attributable to the study drug led to trial withdrawal (16 in the EDTA group vs. 20 in the placebo group).

Several additional post-hoc analyses of TACT examined outcomes in patients with diabetes. Ujueta et al. (2020) reported outcomes in 162 post-myocardial infarction patients with diabetes mellitus and peripheral artery disease. (25) The analysis showed that chelation therapy was associated with a significant reduction in the composite primary endpoint compared with placebo (HR, 0.52; 95% CI, 0.30 to 0.92; p=.0069). Escolar et al. (2020) performed a sub-analysis of diabetes mellitus patients included in TACT (n=633) to determine the association between glucose lowering therapy and outcomes. (26) Chelation therapy was associated with a lower frequency of the primary outcome compared with placebo in patients on insulin (n=162; 26% vs. 48%; HR, 0.42; 95% CI, 0.25 to 0.74), but not in patients on oral glucose-lowering therapy or no glucose-lowering therapy.

The TACT2 RCT replicated the TACT study design but restricted enrollment to individuals with diabetes. (18) Results from the TACT2 RCT, summarized in the cardiovascular section above, failed to replicate the original TACT study findings.

*Diabetic Nephropathy*

Chen et al. (2012) conducted a single-blind RCT assessing the effects of chelation therapy on the progression of diabetic nephropathy in Chinese patients with high-normal lead levels. (27) Fifty patients with diabetes, high-normal body lead burden (80 to 6000 µg), and serum creatinine of 3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 µg/dL in the treatment group and 7.1 µg/dL in the control group; baseline mean body lead burden was 151 µg in the treatment group and 142 µg in the control group. According to the U.S. Occupational and Health Safety Administration, the maximum acceptable blood lead level in adults is 40 µg/dL. (28) Patients were randomized to 3 months of calcium disodium EDTA or to placebo. During 24 months of treatment follow-up, patients in the chelation group received additional chelation treatments as needed (i.e., for serum creatinine level above pretreatment levels or body lead burden >60 µg), and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate. Mean yearly rate of decrease in estimated glomerular filtration rate was 5.6 mL/min/1.73 $m^2$ in the chelation group and 9.2 mL/min/1.73 $m^2$ in the control group, a statistically significant difference (p=.04). The secondary endpoint was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) patients in the treatment group and 17 (68%) in the control group attained the secondary endpoint, a statistically significant difference (p=.02). There were no reported adverse events of chelation therapy during the trial.

Section Summary: Diabetes

Two small RCTs with limitations and the failed TACT2 RCT represent insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. One small, single-blind RCT is insufficient evidence that chelation therapy is effective for treating diabetic nephropathy in patients with high-normal lead levels. Additional RCTs with larger numbers of patients that report health outcomes (e.g., cardiovascular events, end-stage renal disease, mortality) are needed.

**Other Potential Indications: Multiple Sclerosis and Arthritis**

Clinical Context and Therapy Purpose

The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for individuals with multiple sclerosis (MS) or arthritis.

The following PICO was used to select literature to inform this policy.

*Populations*

The population of interest is individuals with MS or arthritis.

*Interventions*

The intervention of interest is chelation therapy.

*Comparators*

The comparator of interest is standard medical care without chelation therapy.

*Outcomes*

The outcomes of interest are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity.

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

- To assess efficacy outcomes, comparative controlled prospective trials were sought, with a preference for RCTs.
- In the absence of such trials, comparative observational studies were sought, with a preference for prospective studies.
- To assess long-term outcomes and adverse events, single-arm studies that capture longer periods of follow-up and/or larger populations were sought.
- Studies with duplicative or overlapping populations were excluded.

No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for MS or arthritis were identified.

Iron chelation therapy is being investigated for Parkinson disease (29, 30) and endotoxemia. (31) Devos et al. (2022) conducted a phase 2, randomized, double-blind, 36-week trial in 372

patients with newly diagnosed Parkinson disease. (32) Patients randomized to iron chelation with deferiprone had worse outcomes than those treated with placebo, with 22% of deferiprone-treated patients requiring initiation of dopaminergic therapy versus 2.7% of those treated with placebo. In addition, scores on the Unified Parkinson's Disease Rating Scale were worse with deferiprone, worsening by 15.6 points from baseline compared with 6.3 points in the placebo group (difference, 9.3 points; 95% CI, 6.3 to 12.2; p<.001).

**Summary of Evidence**

For individuals who have Alzheimer disease, or cardiovascular disease, or autism spectrum disorder, or diabetes, or multiple sclerosis, or arthritis who receive chelation therapy, the evidence includes a small number of randomized controlled trials (RCTs) and case series. Relevant outcomes are symptoms, change in disease status, morbid events, functional outcomes, health status measures, quality of life, and treatment-related morbidity. One RCT (the Trial to Assess Chelation Therapy [TACT]) reported that chelation therapy reduced cardiovascular events in patients with previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations (e.g., high dropout rates) and, therefore, conclusions are not definitive. Outcomes from the TACT2 RCT, which restricted enrollment to individuals with diabetes, were published in 2024 and failed to replicate the findings from the original TACT trial. For other conditions, the available RCTs did not report improvements in health outcomes with chelation therapy and, as evidence, case series are inadequate to determine efficacy. The evidence is insufficient to determine that the technology results in an improvement in the net health outcome.

**Practice Guidelines and Position Statements**

American Heart Association and American College of Cardiology

In 2016, the American College of Cardiology (ACC) and the American Heart Association (AHA) published a joint guideline on the management of patients with lower extremity peripheral artery disease, which stated that chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for the treatment of claudication. (33)

In 2014, the ACC and AHA published a focused update of the guideline for the management of stable ischemic heart disease, in conjunction with the American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. This update included a revised recommendation on chelation therapy stating that the “usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable IHD.” (34) Compared to the original publication of this guideline in 2012, the recommendation was upgraded from a class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies). (35) A 2023 guideline from these organizations on managing chronic coronary disease provided comments about chelation therapy but no formal recommendations. (36)

American Heart Association

In 2023, the AHA published a scientific statement about the cardiovascular risk of contaminant metals. (37) The authors cited the TACT trial findings of a reduced relative risk of cardiovascular events among patients who received chelation therapy, but also noted that TACT did not evaluate metal levels. Results of the TACT2 trial were not yet available at the time of publication.

American Academy of Pediatrics

In 2019, the American Academy of Pediatrics published guidance for the management of children with autism spectrum disorder. The guidance cautioned against the use of chelation therapy due to safety concerns and lack of supporting efficacy data. (38)

**Medicare National Coverage**

The Centers for Medicare & Medicare have issued 2 national coverage determinations on chelation therapy relevant to this medical policy. Section 20.21 states (39):

"The application of chelation therapy using ethylenediamine-tetra-acetic acid (EDTA) for the treatment and prevention of atherosclerosis is controversial. There is no widely accepted rationale to explain the beneficial effects attributed to this therapy. Its safety is questioned, and its clinical effectiveness has never been established by well designed, controlled clinical trials. It is not widely accepted and practiced by American physicians. EDTA chelation therapy for atherosclerosis is considered experimental. For these reasons, EDTA chelation therapy for the treatment or prevention of atherosclerosis is not covered.

Some practitioners refer to this therapy as chemoendarterectomy and may also show a diagnosis other than atherosclerosis, such as arteriosclerosis or calcinosis. Claims employing such variant terms should also be denied under this section."

Section 20.22 states (40):

"The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA [U.S. Food and Drug Administration] as an approved use is not covered. Any such use of EDTA is considered experimental."

These national coverage determinations are long-standing; effective dates of these versions have not been posted.

**Ongoing and Unpublished Clinical Trials**

Some currently unpublished trials that might influence this policy are listed in Table 5.

**Table 5. Summary of Key Trials**

| NCT Number | Trial Name | Planned Enrollment | Completion Date |
|---|---|---|---|

| | | | |
|---|---|---|---|
| NCT05111821 | Long-term Iron Chelation in the Prevention of Secondary Remote Degeneration After Stroke (CHEL-IC) | 100 | Dec 2024 (status unknown) |
| NCT03982693 | Trial to Assess Chelation Therapy in Critical Limb Ischemia (TACT3[a]) | 50 | Jul 2025 |
| NCT06763055 | The Fifth Intensive Preventing Secondary Injury in Acute Cerebral Haemorrhage Trial Within ACT-GLOBAL (INTERACT5) | 2000 | Jan 2029 |

NCT: national clinical trial.

[a] Denotes industry-sponsored or cosponsored trial.

## Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

| | |
|---|---|
| **CPT Codes** | 96365, 96366, 96374 |
| **HCPCS Codes** | J0470, J0600, J0895, J3520, M0300, S9355 |

*Current Procedural Terminology (CPT®) ©2024 American Medical Association: Chicago, IL.

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## Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been changed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

| Policy History/Revision | |
|---|---|
| **Date** | **Description of Change** |
| 09/01/2025 | Document updated with literature review. The following change was made to Coverage: Revised Coverage to focus only on the use of chelation therapy for various off-label applications. Added references 8 and 18. Title changed from “Chelation Therapy”. |
| 10/15/2024 | Document updated with literature review. Coverage unchanged. Added references 11, 14, 22, 32, 36, 40, 41; others updated, some removed. |
| 09/15/2023 | Reviewed. No changes. |
| 07/01/2022 | Document updated with literature review. The following change was made to Coverage: Removed hypoglycemia from the experimental, investigational and/or unproven statement in Coverage. Added references 17, 26, 27, 33, 36; others updated, some removed. |
| 9/15/2021 | Reviewed. No changes. |
| 10/01/2020 | Document updated with literature review. The following change was made to Coverage: Added note 2 which is specific to the first 2 medically necessary bullets in Coverage to state: “For control of ventricular arrhythmias or heart block associated with digitalis toxicity most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. The FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.” Added references 3, 13, 14, 16, 23, 26, 33, 37, 38, 39; some removed. |
| 10/15/2019 | Reviewed. No changes. |
| 08/15/2018 | Document updated with literature review. No coverage changes. References 36-40 added. |
| 12/01/2016 | Reviewed. No changes. |
| 02/01/2015 | Document updated with literature review. The following was added to the coverage section: 1) Chelation therapy may be considered medically necessary in the treatment of non-transfusion-dependent thalassemia (NTDT); 2) Other applications of chelation therapy are considered experimental, investigational and/or unproven including, but not limited to, secondary prevention in patients with myocardial infarction. |
| 07/15/2012 | Document updated with literature review. No coverage change. |
| 10/15/2010 | Document updated with literature review. The following was added to Coverage: Prior to the administration of any chelating agent, diagnosis of |

| | |
|---|---|
| | metal toxicity MUST be established through appropriate diagnostic testing; the administration of any chelating agents prior to diagnosis of metal toxicity is considered not medically necessary, and therefore will not be covered. Description updated and Rationale revised. CPT/HCPCS codes were updated. |
| 10/15/2007 | Routine update, policy no longer scheduled for routine literature review and update. |
| 08/15/2003 | Revised/updated entire document |
| 06/01/1998 | Revised/updated entire document |
| 05/01/1996 | Revised/updated entire document |
| 07/01/1995 | Revised/updated entire document |
| 04/01/1994 | Revised/updated entire document |
| 05/01/1990 | New Medical Document |