
Medical Policy



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***Current Policy Effective Date: 5/1/24**
(See policy history boxes for previous effective dates)

Title: Chelation Therapy, Including Off-Label Uses

Description/Background

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. 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, they promote the solubilization and clearance of A β -amyloid protein by binding its metal-ion complex and inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt two putative pathogenic processes of Alzheimer disease. However, no MPACs have received U.S. Food and Drug Administration (FDA) approval for the treatment of Alzheimer disease.

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

Regulatory Status:

FDA approved calcium-EDTA (Versenate) for lowering blood lead levels among both pediatric and adult patients with lead poisoning. Succimer is approved for the treatment of lead poisoning in pediatric patients only. FDA approved disodium-EDTA for use in selected patients with hypercalcemia and for use in patients with heart rhythm problems due to intoxication with the drug, 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:

- Deferoxamine for subcutaneous, intramuscular, or intravenous injections was approved for treating acute iron intoxication and chronic iron overload due to transfusion-dependent anemia.
- Deferasirox, approved in 2005, is available as a tablet for oral suspension and is indicated for the treatment of chronic iron overload due to blood transfusions in patients aged 2 years and older. Under the accelerated approval program, FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 10 years and older with chronic iron overload due to nontransfusion-dependent thalassemia (NTDT).

In 2011, the FDA approved the iron chelator, deferiprone (Ferriprox®), for the treatment of patients with transfusional overload due to thalassemia syndromes when other chelation therapy is inadequate. Deferiprone is available in tablet form for oral use.

In a June 2014 warning to consumers, FDA advised that FDA-approved chelating agents are available by prescription only.³ There are no FDA-approved over-the-counter chelation products.

Medical Policy Statement

The safety and effectiveness of chelation therapy for specified conditions have been established. It is a useful therapeutic option for patients meeting patient selection guidelines.

Inclusionary and Exclusionary Guidelines

Inclusions (must have one of the following diagnoses):

- Aluminum overload in persons with end-stage renal failure
- Biliary cirrhosis
- Treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)
- Control of ventricular arrhythmias or heart block associated with digitalis toxicity**
- Cooley's anemia (thalassemia major)
- Cystinuria
- Emergency treatment of hypercalcemia**

- Extreme conditions of metal toxicity (heavy metal poisoning) Note: heavy metals include antimony, arsenic, bismuth, cadmium, cerium, chromium, cobalt, copper, gallium, gold, iron, lead, manganese, mercury, nickel, platinum, silver, tellurium, thallium, tin, uranium, vanadium and zinc. Toxic levels should be confirmed with blood levels where appropriate.
- Hemochromatosis: Clinical symptoms of chronic iron toxicity should correlate with an elevated serum ferritin. Parenteral chelation therapy is not medically necessary in genetic or hereditary hemochromatosis. Subcutaneous infusion of deferoxamine via a portable pump may be considered medically necessary for acquired hemochromatosis complicating a chronic hemolytic anemia such as thalassemia or sideroblastic anemia or when hypoproteinemia precludes phlebotomy as treatment.
- Hemochromatosis
- Lead poisoning
- Sickle cell anemia
- Wilson disease (hepatolenticular degeneration)

**For these two bullet points, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients with Fab monoclonal antibodies. FDA removed the approval for NaEDTA as chelation therapy due to safety concerns and recommended that other chelators be used. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

Informational item/Guidelines: Suggested toxic or normal levels of select heavy metals are listed in Table 1. Reference standards for bismuth, chromium, and manganese were not identified and are not included in Table 1.

Table 1. Toxic or Normal Concentrations of Heavy Metals⁴⁰

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24h urine: $\geq 50 \mu\text{g/L}$ urine or $100 \mu\text{g/g}$ creatinine
Cadmium	Proteinuria and/or $\geq 15 \mu\text{g/L}$ (serum)
Cobalt	Normative excretion: $0.1\text{-}1.2 \mu\text{g/L}$ (serum), $0.1\text{-}2.2 \mu\text{g/L}$ (urine)
Copper	Normative excretion: $25 \mu\text{g}/24 \text{ j}$ (urine)
Iron	Nontoxic: $< 300 \mu\text{g/dL}$ Severe: $> 500 \mu\text{g/dL}$
Lead	Pediatric <ul style="list-style-type: none"> • Symptoms or blood lead level $\geq 45 \mu\text{g/dL}$ (blood) • CDC level of concern: $5 \mu\text{g/dL}$⁴ Adult <ul style="list-style-type: none"> • Symptoms or blood lead level $\geq 40 \mu\text{g/dL}$ (blood) • CEC level of concern: $10 \mu\text{g/dL}$⁵
Mercury	Background exposure normative limits: $1\text{-}8 \mu\text{g/L}$ (whole blood); $4\text{-}5 \mu\text{g/L}$ (urine) ^{48,a}
Nickel	Excessive exposure: $\geq 8 \mu\text{g/L}$ (blood) Severe poisoning: $\geq 500 \mu\text{g/L}$ (8h urine)
Selenium	Mild toxicity: $> 1 \text{ mg/L}$ (serum) Serious toxicity: $> 2 \text{ mg/L}$
Silver	Asymptomatic worker have mean levels of $11 \mu\text{g/L}$ (serum) and $2.6 \mu\text{g/L}$ (spot urine)
Thallium	24-hour urine thallium $> 5 \mu\text{g/L}$ ⁷
Zinc	Normative range: $0.6\text{-}1.1 \text{ mg/L}$ (plasma), $10\text{-}14 \text{ mg/L}$ (red cells)

CDC: centers for disease control and prevention.

^aHair 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.⁴⁵

Exclusions

Off-label applications of chelation therapy are considered experimental/investigational, including, but not limited to:

- Alzheimer disease
 - Arthritis
 - Atherosclerosis (i.e., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
 - Autism
 - Cadmium exposure
 - Chronic fatigue syndrome secondary to dental amalgam therapy;
 - Diabetes
 - Multiple sclerosis
 - Parkinson’s disease
 - Rheumatoid arthritis
 - All other conditions not mentioned in “inclusions”
-

CPT/HCPCS Level II Codes *(Note: The inclusion of a code in this list is not a guarantee of coverage. Please refer to the medical policy statement to determine the status of a given procedure)*

Established codes: (established for specific diagnoses only)

J0470	J0600	J0895	J3520	96365	96366
96374	S9355				

Other codes (investigational, not medically necessary, etc.):

M0300

Rationale

Evidence reviews assess the clinical evidence to determine whether the use of a technology improves the net health outcome. Broadly defined, health outcomes are 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 a technology, 2 domains are examined: the relevance and the quality and credibility. To be relevant, studies must represent one 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. RCTs 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.

ALZHEIMER DISEASE

Clinical Context and Therapy Purpose

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 evidence review does not address indications for chelation therapy approved by the U.S. Food and Drug Administration (FDA). The question addressed in this evidence review is: Does chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, MS, and arthritis, improve the net health outcome?

The following **PICO** was used to select literature to inform this review.

Populations

The population of interest includes patients with Alzheimer disease.

Interventions

The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

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, QOL.

Review of Evidence

A 2008 Cochrane Review evaluated metal protein attenuating compounds (MPAC) for treating Alzheimer disease.⁴ The review identified one placebo-controlled RCT. This study, by Richie et al, was published in 2003. Patients were treated patients with PBT1, an MPAC also known as clioquinol, an anti-fungal medication that crosses the blood-brain barrier.⁵ FDA withdrew Clioquinol for oral use in 1970 because of its association with subacute myelo-optic neuropathy. Richie et al administered oral clioquinol to 16 Alzheimer disease patients 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's Disease Assessment Scale – Cognitive (ADAS-Cog scale). One patient in the treatment group developed impaired visual acuity and color vision during weeks 31 to 36 during treatment with clioquinol 375 mg twice daily. Her symptoms resolved on treatment cessation. A 2012 update of this review included trials through December 2011.⁶ Only the Lannfelt et al trial discussed next was identified.

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt et al completed a double-blind, placebo-controlled RCT in which 78 Alzheimer's disease patients were treated for 12 weeks with 50 mg PBT2 (n=20), 250 mg PBT2 (n=29), or placebo (n=29).⁷ There was no statistically significant difference in ADAS-Cog scale 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 and transient ischemic event) were reported, both by patients receiving placebo.

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 the treatment was superior to placebo for improving health outcomes.

CARDIOVASCULAR DISEASE

Clinical Context and Therapy Purpose

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 evidence review does not address indications for chelation therapy approved by the FDA.

The following **PICO** was used to select literature to inform this review.

Populations

The population of interest includes individuals with cardiovascular disease.

Interventions

The intervention of interest is chelation therapy, which is an established treatment for heavy metal toxicities and transfusional hemosiderosis but has also been investigated for a variety of off-label applications not approved by the FDA.

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, QOL.

Review of Evidence

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.⁷ Ankle-brachial index was the only outcome reported in at least 3 studies and included in meta-analysis (Table 3). 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 ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease.⁸ 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 part way 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 1. Comparison of Randomized Controlled Trials Included in Systematic Reviews and Meta-analyses

Study	Ravalli (2022) ⁷ ,	Villarruz-Sulit (2020) ⁸ ,
Lamas (2013)	●	●
Knudston (2002)	●	●
van Rij (1994)	●	●
Guldager (1992)	●	●
Olszewer (1990)		●

Table 3. Systematic Review and Meta-analysis Results

Study	All-cause mortality	CHD Deaths	MI	Revascularization	Stroke	ABI
Ravalli (2022) ⁷ ,						
Total N	1792	1708	1792	1792	1867	181
Risk ratio (95% CI)	0.97 (0.73 to 1.28)	1.02 (0.70 to 1.48)	0.81 (0.57 to 1.14)	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) ⁸ ,						
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; NA: not applicable; NR: not reported.

¹If the M-A includes a quantitative synthesis then include numbers analyzed, measures of effect (absolute or relative) with CI and measure of heterogeneity. If the M-A includes only a qualitative synthesis then include the ranges of N and effects.

Randomized Controlled Trial

The largest RCT included in meta-analyses is the multicenter, 2x2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT), which was published by Lamas et al in 2013.⁹ 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.¹⁰

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]).¹¹ 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 (HR, 0.74; 95% CI, 0.57 to 0.95). In 633 patients with diabetes ($\approx 36\%$ 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.¹²

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.¹³ Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings.¹⁴ 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.¹⁵ Enrollment was complete in December 2020 and treatment was complete in December 2021. Subjects are now being followed for up to 5 years for a composite primary endpoint of all-cause mortality, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina. Results are anticipated in 2024.

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. Additional RCTs reporting health outcomes would be needed to establish treatment efficacy. The largest of these RCTs 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. However, this trial was not of high-quality and, therefore, results might have been biased.

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.¹⁶ 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.¹⁷ A meta-analysis by Ng et al (2007) concluded that there was no association between mercury poisoning and autism.¹⁸

Clinical Context and Test Purpose

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

The following **PICO** was used to select literature to inform this review.

Populations

The population of interest includes individuals with autism spectrum disorder 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, QOL, and treatment-related morbidity.

Observational Studies

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and identified no controlled studies.¹⁹ The author stated the case series suggested a potential role for chelation in 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 the effect of chelation therapy on 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 patients with diabetes.

The following **PICO** was used to select literature to inform this review.

Populations

The population of interest includes 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, QOL, and treatment-related morbidity.

Review of Evidence

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.²⁰ 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/m²) than in the placebo group (-0.1 g/m²; 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.²¹ 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).⁹ 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 versus 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.²² 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.²³ 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. As previously mentioned, the TACT2 is further examining EDTA in this patient population.¹⁵

Diabetic Nephropathy

Chen et al (2012) in China conducted a single-blind RCT of chelation therapy effects on the progression of diabetic nephropathy in patients with high-normal lead levels.²⁴ Fifty patients with diabetes, high-normal body lead burden (80-6000 µg), and serum creatinine 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, and baseline mean body lead burden was 151 mcg in the treatment group and 142 µg in the control group. According to the U.S. Occupational and Health Safety Administration, maximum acceptable blood lead level in adults is 40 µg/dL.²⁵ Patients were randomized to 3 months of calcium disodium EDTA or placebo. During 24 months of treatment, 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 mcg), 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 (eGFR). Mean (SD) yearly rate of decrease in eGFR was 5.6 mL/min/1.73 m² (5.0) in the chelation group and 9.2 mL/min/1.73 m² (3.6) in the control group, a statistically significant difference (p=0.04). Secondary end point was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine patients (36%) in the treatment group and 17 (68%) in the control group attained the secondary end

point, a statistically significant difference ($p=0.02$). There were no reported adverse effects of chelation therapy during the 27-month trial period.

Section Summary: Diabetes

Two small RCTs with limitations 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 such as cardiovascular events, end-stage renal disease, and 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 patients with multiple sclerosis (MS) or arthritis.

The following **PICO** was used to select literature to inform this review.

Populations

The population of interest includes 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, QOL, and treatment-related morbidity.

Review of Evidence

No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for other conditions (e.g., MS, arthritis) MS or arthritis were identified.

Iron chelation therapy is being investigated for Parkinson disease^{26,27} and endotoxemia.²⁸ Devos et al (2022) conducted a phase 2, randomized, double-blind, 36-week trial in 372 patients with newly diagnosed Parkinson's disease.²⁹ 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 in 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, cardiovascular disease, autism spectrum disorder, diabetes, 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 a previous myocardial infarction and that the benefit was greater in diabetic patients compared with nondiabetic patients. However, this trial had significant limitations, including high dropout rates, and therefore conclusions are not definitive. For other conditions, the available RCTs do not report improvements in health outcomes with chelation therapy and the case series are not adequate evidence to determine efficacy. The evidence is insufficient to determine the effect of the technology on health outcomes.

ONGOING AND UNPUBLISHED CLINICAL TRIALS

Some currently unpublished trials that might influence this policy are listed in Table 4.

Table 4: Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02733185	Trial to assess chelation therapy 2 (TACT2)	1000	Dec 2023
NCT05111821	Long term iron chelation in the prevention of secondary remote degeneration after stroke	100	Jun 2024
Unpublished			
NCT02728843 ^a	Study of Parkinson's early stage with deferiprone(SKY)	140	Sep 2019 (completed)

NCT: national clinical trial.

^a Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

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 recommended that chelation therapy (e.g., ethylenediaminetetraacetic acid) is not beneficial for the treatment of claudication.³⁰

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.”³¹ Compared to the original publication of this guideline in 2012, the recommendation was upgraded from a class

III (no benefit) to class IIb (benefit \geq 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).³²

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.³³

U.S. Preventive Services Task Force Recommendations

Not applicable.

Government Regulations

National:

National Coverage Determination (NCD) for Chelation Therapy for Treatment of Atherosclerosis (20.21)³⁴

Indications and Limitations of Coverage

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.

National Coverage Determination (NCD) for Ethylenediamine-Tetra-Acetic (EDTA) Chelation Therapy for Treatment of Atherosclerosis (20.22)³⁵

Indications and Limitations of Coverage

The use of EDTA as a chelating agent to treat atherosclerosis, arteriosclerosis, calcinosis, or similar generalized condition not listed by the FDA as an approved use is not covered. Any such use of EDTA is considered experimental.

Local:

There is no local coverage determination.

(The above Medicare information is current as of the review date for this policy. However, the coverage issues and policies maintained by the Centers for Medicare & Medicare Services [CMS, formerly HCFA] are updated and/or revised periodically. Therefore, the most current CMS information may not be contained in this document. For the most current information, the reader should contact an official Medicare source.)

Related Policies

N/A

References

1. Centers for Disease Control and Prevention (CDC). Deaths associated with hypocalcemia from chelation therapy--Texas, Pennsylvania, and Oregon, 2003-2005. *MMWR Morb Mortal Wkly Rep.* Mar 03 2006; 55(8): 204-7. PMID 16511441
2. Food and Drug Administration. Hospira, Inc., et al.; Withdrawal of Approval of One New Drug Application and Two Abbreviated New Drug Application. *Federal Register.* 2008;73(113):33440-33441.
3. Sampson E, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's disease. *Cochrane Database Syst Rev.* Jan 23 2008; (1): CD005380. PMID 18254079
4. Ritchie CW, Bush AI, Mackinnon A, et al. Metal-protein attenuation with iodochlorhydroxyquin (clioquinol) targeting Abeta amyloid deposition and toxicity in Alzheimer disease: a pilot phase 2 clinical trial. *Arch Neurol.* Dec 2003; 60(12): 1685-91. PMID 14676042
5. Sampson EL, Jenagaratnam L, McShane R. Metal protein attenuating compounds for the treatment of Alzheimer's dementia. *Cochrane Database Syst Rev.* May 16 2012; (5): CD005380. PMID 22592705
6. Lannfelt L, Blennow K, Zetterberg H, et al. Safety, efficacy, and biomarker findings of PBT2 in targeting Abeta as a modifying therapy for Alzheimer's disease: a phase IIa, double-blind, randomised, placebo-controlled trial. *Lancet Neurol.* Sep 2008; 7(9): 779-86. PMID 18672400
7. Ravalli F, Vela Parada X, Ujueta F, et al. Chelation Therapy in Patients With Cardiovascular Disease: A Systematic Review. *J Am Heart Assoc.* Mar 15 2022; 11(6): e024648. PMID 35229619
8. Villarruz-Sulit MV, Forster R, Dans AL, et al. Chelation therapy for atherosclerotic cardiovascular disease. *Cochrane Database Syst Rev.* May 05 2020; 5: CD002785. PMID 32367513
9. Lamas GA, Goertz C, Boineau R, et al. Effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction: the TACT randomized trial. *JAMA.* Mar 27 2013; 309(12): 1241-50. PMID 23532240
10. Mark DB, Anstrom KJ, Clapp-Channing NE, et al. Quality-of-life outcomes with a disodium EDTA chelation regimen for coronary disease: results from the trial to assess chelation therapy randomized trial. *Circ Cardiovasc Qual Outcomes.* Jul 2014; 7(4): 508-16. PMID 24987051
11. Lamas GA, Boineau R, Goertz C, et al. EDTA chelation therapy alone and in combination with oral high-dose multivitamins and minerals for coronary disease: The factorial group results of the Trial to Assess Chelation Therapy. *Am Heart J.* Jul 2014; 168(1): 37-44.e5. PMID 24952858
12. Lewis EF, Ujueta F, Lamas GA, et al. Differential Outcomes With Edetate Disodium-Based Treatment Among Stable Post Anterior vs. Non-Anterior Myocardial Infarction Patients. *Cardiovasc Revasc Med.* Nov 2020; 21(11): 1389-1395. PMID 32303436

13. Nissen SE. Concerns about reliability in the Trial to Assess Chelation Therapy (TACT). *JAMA*. Mar 27 2013; 309(12): 1293-4. PMID 23532246
14. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: When evidence conflicts with beliefs. *Am Heart J*. Jul 2014; 168(1): 4-5. PMID 24952853
15. Lamas GA, Anstrom KJ, Navas-Acien A, et al. The trial to assess chelation therapy 2 (TACT2): Rationale and design. *AmHeart J*. Oct 2022; 252: 1-11. PMID 35598636
16. Bernard S, Enayati A, Redwood L, et al. Autism: a novel form of mercury poisoning. *Med Hypotheses*. Apr 2001; 56(4): 462-71. PMID 11339848
17. Nelson KB, Bauman ML. Thimerosal and autism?. *Pediatrics*. Mar 2003; 111(3): 674-9. PMID 12612255
18. Ng DK, Chan CH, Soo MT, et al. Low-level chronic mercury exposure in children and adolescents: meta-analysis. *Pediatr Int*. Feb 2007; 49(1): 80-7. PMID 17250511
19. Rossignol DA. Novel and emerging treatments for autism spectrum disorders: a systematic review. *Ann Clin Psychiatry*. Oct-Dec 2009; 21(4): 213-36. PMID 19917212
20. Cooper GJ, Young AA, Gamble GD, et al. A copper(II)-selective chelator ameliorates left-ventricular hypertrophy in type 2 diabetic patients: a randomised placebo-controlled study. *Diabetologia*. Apr 2009; 52(4): 715-22. PMID 19172243
21. Escolar E, Lamas GA, Mark DB, et al. The effect of an EDTA-based chelation regimen on patients with diabetes mellitus and prior myocardial infarction in the Trial to Assess Chelation Therapy (TACT). *Circ Cardiovasc Qual Outcomes*. Jan 2014; 7(1): 15-24. PMID 24254885
22. Ujueta F, Arenas IA, Escolar E, et al. The effect of EDTA-based chelation on patients with diabetes and peripheral artery disease in the Trial to Assess Chelation Therapy (TACT). *J Diabetes Complications*. Jul 2019; 33(7): 490-494. PMID 31101487
23. Escolar E, Ujueta F, Kim H, et al. Possible differential benefits of edetate disodium in post-myocardial infarction patients with diabetes treated with different hypoglycemic strategies in the Trial to Assess Chelation Therapy (TACT). *J Diabetes Complications*. Aug 2020; 34(8): 107616. PMID 32446881
24. Chen KH, Lin JL, Lin-Tan DT, et al. Effect of chelation therapy on progressive diabetic nephropathy in patients with type 2 diabetes and high-normal body lead burdens. *Am J Kidney Dis*. Oct 2012; 60(4): 530-8. PMID 22721929
25. U.S. Department of Labor, Occupational Health and Safety Administration. Safety and Health Regulations for Construction: Substance Data Sheet for Occupational Exposure to Lead. 1993; http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10642. Accessed December 23, 2019.
26. Weinreb O, Mandel S, Youdim MBH, et al. Targeting dysregulation of brain iron homeostasis in Parkinson's disease by iron chelators. *Free Radic Biol Med*. Sep 2013; 62: 52-64. PMID 23376471
27. Grolez G, Moreau C, Sablonniere B, et al. Ceruloplasmin activity and iron chelation treatment of patients with Parkinson's disease. *BMC Neurol*. May 06 2015; 15: 74. PMID 25943368
28. van Eijk LT, Heemskerk S, van der Pluijm RW, et al. The effect of iron loading and iron chelation on the innate immune response and subclinical organ injury during human endotoxemia: a randomized trial. *Haematologica*. Mar 2014; 99(3): 579-87. PMID 24241495
29. Devos D, Labreuche J, Rascol O, et al. Trial of Deferiprone in Parkinson's Disease. *N Engl J Med*. Dec 01 2022; 387(22):2045-2055. PMID 36449420

30. Gerhard-Herman MD, Gornik HL, Barrett C, et al. 2016 AHA/ACC Guideline on the Management of Patients With Lower Extremity Peripheral Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation*. Mar 21 2017; 135(12): e726-e779. PMID 27840333
31. Fihn SD, Blankenship JC, Alexander KP, et al. 2014 ACC/AHA/AATS/PCNA/SCAI/STS focused update of the guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines, and the American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. *J Am Coll Cardiol*. Nov 04 2014; 64(18): 1929-49. PMID 25077860
32. Qaseem A, Fihn SD, Dallas P, et al. Management of stable ischemic heart disease: summary of a clinical practice guideline from the American College of Physicians/American College of Cardiology Foundation/American Heart Association/American Association for Thoracic Surgery/Preventive Cardiovascular Nurses Association/Society of Thoracic Surgeons. *Ann Intern Med*. Nov 20 2012; 157(10): 735-43. PMID 23165665
33. Hyman SL, Levy SE, Myers SM, et al. Identification, Evaluation, and Management of Children With Autism Spectrum Disorder. *Pediatrics*. Jan 2020; 145(1). PMID 31843864
34. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for CHELATION THERAPY for Treatment of Atherosclerosis (20.21). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=86>. Accessed January 2024.
35. Centers for Medicare & Medicaid Services (CMS). National Coverage Determination (NCD) for Ethylenediamine- Tetra-Acetic (EDTA) CHELATION THERAPY for Treatment of Atherosclerosis (20.22). n.d.; <https://www.cms.gov/medicare-coverage-database/details/ncd-details.aspx?NCDId=146&ncdver=1&bc=AAAAQAAAAAAA&>. Accessed January 2024.
36. Centers for Disease Control and Prevention (CDC). What Do Parents Need to Know to Protect Their Children? 2017, May 17; http://www.cdc.gov/nceh/lead/ACCLPP/blood_lead_levels.htm. Accessed January 2024.
37. Centers for Disease Control and Prevention (CDC). Very high blood lead levels among adults - United States, 2002-2011. *MMWR Morb Mortal Wkly Rep*. Nov 29 2013; 62(47): 967-71. PMID 24280917
38. Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury. 1999 March; <https://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf>. Accessed January 23, 2024.
39. Centers for Disease Control and Prevention (CDC). Emergency preparedness and response. Case definition: thallium. 2015 November 18; <https://emergency.cdc.gov/agent/thallium/casedef.asp>. Accessed January 2024.
40. Adal A. Medscape. Heavy metal toxicity. 2018; <http://emedicine.medscape.com/article/814960-overview>. Accessed December 18, 2019.
41. Kempson IM, Lombi E. Hair analysis as a biomonitor for toxicology, disease and health status. *Chem Soc Rev*. Jul 2011; 40(7): 3915-40. PMID 21468435
39. Blue Cross Blue Shield Association. Chelation Therapy for Off-Label Uses. Medical Policy Reference Manual, MPRM: issue: 2.2017. Last reviewed March 2023.

The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2024, the date the research was completed.

Joint BCBSM/BCN Medical Policy History

Policy Effective Date	BCBSM Signature Date	BCN Signature Date	Comments
6/25/02	6/25/02	6/25/02	Joint medical policy established
9/7/04	9/7/04	9/28/04	Routine maintenance
1/1/07	11/1/06	11/19/06	Routine maintenance
1/1/09	10/13/08	12/30/08	Routine maintenance
1/1/12	10/11/11	11/9/11	Routine update; references updated, policy reformatted to mirror BCBSA
9/1/13	6/19/13	6/26/13	Routine maintenance. Policy updated to mirror BCBSA.
5/1/15	2/17/15	2/27/15	Title changed to "Chelation Therapy Including Off-Label Uses." Policy status unchanged. Rationale and references updated.
5/1/16	2/16/16	2/16/16	Routine maintenance Added J0895
5/1/17	2/21/17	2/21/17	Removed hypoglycemia from exclusions as this indication is not reviewed in the policy. Added J0895 to policy. Routine policy maintenance.
5/1/18	2/20/18	2/20/18	Updated rationale section, removed reference 8, added references 38, 39 and 46.
5/1/19	2/19/19		Routine policy maintenance. No change in policy status.
5/1/20	2/18/20		Routine policy maintenance. No change in policy status.
5/1/21	2/16/21		Routine policy maintenance. No change in policy status.
5/1/22	2/15/22		Routine policy maintenance, no change in policy status.
5/1/23	2/21/23		Routine policy maintenance. No change in policy status. (ds)
5/1/24	2/20/24		Routine policy maintenance, references added. No change in policy status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2025

Pre-Consolidation Medical Policy History

Original Policy Date	Comments
BCN: 4/1/99	Revised: 6/28/01
BCBSM: N/A	Revised: N/A

BLUE CARE NETWORK BENEFIT COVERAGE
POLICY: CHELATION THERAPY, INCLUDING OFF-LABEL USES

I. Coverage Determination:

Commercial HMO (includes Self-Funded groups unless otherwise specified)	Covered for FDA approved indications; criteria apply. Not covered for off-label uses.
BCNA (Medicare Advantage)	See government section
BCN65 (Medicare Complementary)	Coinsurance covered if primary Medicare covers the service.

II. Administrative Guidelines:

- The member's contract must be active at the time the service is rendered.
- Coverage is based on each member's certificate and is not guaranteed. Please consult the individual member's certificate for details. Additional information regarding coverage or benefits may also be obtained through customer or provider inquiry services at BCN.
- The service must be authorized by the member's PCP except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Services must be performed by a BCN-contracted provider, if available, except for Self-Referral Option (SRO) members seeking Tier 2 coverage.
- Payment is based on BCN payment rules, individual certificate and certificate riders.
- Appropriate copayments will apply. Refer to certificate and applicable riders for detailed information.
- CPT - HCPCS codes are used for descriptive purposes only and are not a guarantee of coverage.