Medical Policy

Blue Cross Blue Shield Blue Care Network of Michigan

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***Current Policy Effective Date: 5/1/25**
(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 Aβ-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 considered 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

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.
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- 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 Metals[40]

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24h urine: ≥ 50 µg/L urine or 100 µg/g creatinine
Cadmium	Proteinuria and/or ≥ 15 µg/L (serum)
Cobalt	Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)
Copper	Normative excretion: 25 µg24 j (urine)
Iron	Nontoxic: < 300 µg/dL Severe: > 500 µg/dL
Lead	**Pediatric** • Symptoms or blood lead level ≥ 45 µg/dL (blood) • CDC level of concern: 5 µg/dL[4]
	Adult • Symptoms or blood lead level ≥ 40 µg/dL (blood) • CEC level of concern: 10 µg/dL[5]
Mercury	Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[48,a]
Nickel	Excessive exposure: ≥ 8µg/L (blood) Severe poisoning: ≥ 500 µg/L (8h urine)
Selenium	Mild toxicity: > 1 mg/L (serum) Serious toxicity: > 2 mg/L
Silver	Asymptomatic worker have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)
Thallium	24-hour urine thallium > 5 µg/L[7]
Zinc	Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

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

Populations
The population of interest includes 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, QOL.

Review of Evidence
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 (discussednext) was identified.[5]

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 patients with Alzheimer disease 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.

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.

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.[8] 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.[9] 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)	Villarruz-Sulit (2020)
Lamas (2013)		

in 2013.[10] TACT included 1708patients, 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.[11]

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]).[12] 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 (»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.[13]

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.[14] Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings.[15] 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 inpatients with prior myocardial infarction and diabetes.[16] 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.

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

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 individuals 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.[20] 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 individuals 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.[21] Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12months, 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.[22] 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.[23] 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.[24] 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.[16]

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.[25] 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.[26] 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/173 m^2 (5.0) in the chelation group and 9.2 mL/min/173 m^2 (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 individuals 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[27,28] and endotoxemia.[29] Devos et al (2022) conducted a phase 2, randomized, double-blind, 36-week trial in 372 patients with newly diagnosed Parkinson disease.[30] 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			
NCT06568926	Adherence of beta thalassemia patients to oral chelation therapy	200	Jul 2026
Unpublished			
NCT02728843[a]	Study of Parkinson's early stage with deferiprone(SKY)	140	Sep 2019 (completed)
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

NCT: national clinical trial.
[a] Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointlyby, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

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.[31]

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."[32] 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).[33]

American Heart Association

In 2023, the AHA published a scientific statement about the cardiovascular risk of contaminant metals.[35] 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 (which finished in 2023), are awaited to provide objective data on the metal level lowering effects of chelation therapy.

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.[36]

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)[37]

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)[38]

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

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The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through January 2025, 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)

5/1/25	2/18/25		Minor edits in MPS and inclusion section. No change in status. Vendor managed: N/A (ds)

Next Review Date: 1st Qtr. 2026

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 according to policy criteria
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.