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, desferroxamine 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 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 (Clinically based guidelines that may support individual consideration and pre-authorization decisions)

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 Metals

<table>
<thead>
<tr>
<th>Metal</th>
<th>Toxic Levels (Normal Levels Where Indicated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic</td>
<td>24h urine: ≥ 50 µg/L urine or 100 µg/g creatinine</td>
</tr>
<tr>
<td>Cadmium</td>
<td>Proteinuria and/or ≥ 15 µg/L (serum)</td>
</tr>
<tr>
<td>Cobalt</td>
<td>Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)</td>
</tr>
<tr>
<td>Copper</td>
<td>Normative excretion: 25 µg24 j (urine)</td>
</tr>
<tr>
<td>Iron</td>
<td>Nontoxic: &lt; 300 µg/dL</td>
</tr>
<tr>
<td></td>
<td>Severe: &gt; 500 µg/dL</td>
</tr>
<tr>
<td></td>
<td>Pediatric</td>
</tr>
<tr>
<td>Lead</td>
<td>Symptoms or blood lead level ≥ 45 µg/dL (blood)</td>
</tr>
<tr>
<td></td>
<td>CDC level of concern: 5 µg/dL4</td>
</tr>
<tr>
<td>Adult</td>
<td>Symptoms or blood lead level ≥ 40 µg/dL (blood)</td>
</tr>
<tr>
<td></td>
<td>CEC level of concern: 10 µg/dL5</td>
</tr>
<tr>
<td>Mercury</td>
<td>Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)48,a</td>
</tr>
<tr>
<td>Nickel</td>
<td>Excessive exposure: ≥ 8µg/L (blood)</td>
</tr>
<tr>
<td></td>
<td>Severe poisoning: ≥ 500 µg/L (8h urine)</td>
</tr>
<tr>
<td>Selenium</td>
<td>Mild toxicity: &gt; 1 mg/L (serum)</td>
</tr>
<tr>
<td></td>
<td>Serious toxicity: &gt; 2 mg/L</td>
</tr>
<tr>
<td>Silver</td>
<td>Asymptomatic worker have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)</td>
</tr>
<tr>
<td>Thallium</td>
<td>24-hour urinary thallium &gt; 5 µg/L7</td>
</tr>
<tr>
<td>Zinc</td>
<td>Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)</td>
</tr>
</tbody>
</table>

CDC: centers for disease control and prevention.

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)**

<table>
<thead>
<tr>
<th>Code 1</th>
<th>Code 2</th>
<th>Code 3</th>
<th>Code 4</th>
<th>Code 5</th>
<th>Code 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>J0470</td>
<td>J0600</td>
<td>J0895</td>
<td>J3520</td>
<td>96365</td>
<td>96366</td>
</tr>
<tr>
<td>96374</td>
<td>S9355</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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.

Chelation therapy is an established treatment for the indications listed here, particularly for the treatment of metal toxicity and transfusional hemosiderosis. Thus, literature searches have focused on the use of chelation therapy for other conditions including, but not limited to, atherosclerosis, autism, Alzheimer disease, diabetes, and other conditions such as multiple sclerosis.

ALZHEIMER DISEASE

Clinical Context and Test 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.

Patients
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.

A 2008 Cochrane Review evaluated metal protein attenuating compounds (MPAC) for treating Alzheimer disease. 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. 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. 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). 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 Test 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 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.

Patients
The population of interest includes patients 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.

Atherosclerosis
In 2002, Villarruz et al published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with
atherosclerotic cardiovascular disease.\(^8\) Five randomized placebo-controlled trials were identified, none of which reported mortality, nonfatal events, and cerebrovascular vascular events. Four of the five studies (total n=250) found no significant benefit of EDTA chelation therapy on outcomes reported including direct or indirect measurement of disease severity and subjective measures of improvement. The fifth study, which included only 10 patients, was apparently stopped early due to benefit, but relevant outcome data were unavailable. The Cochrane reviewers concluded that there was insufficient evidence to draw conclusions of the efficacy of chelation therapy for treating atherosclerosis; additional RCTs that report health outcomes including mortality and cerebrovascular events were suggested.

Among published RCTs, Knudtson et al (2002) randomized 84 patients with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo.\(^9\) Treatment was administered for 3 hours twice weekly for 15 weeks, and monthly for 3 months. Outcome measures included change in time to ischemia, functional reserve for exercise, and quality of life. There was no significant difference between the two groups. Another double-blind, placebo-controlled RCT of EDTA chelation showed no change in short- or long-term improvement in vasomotor response.\(^10\) Two small RCTs from the 1990s also reported no benefit of chelation therapy as a treatment of peripheral arterial disease.\(^11,12\)

**Section Summary: Atherosclerosis**

Several RCTs of chelation therapy for treating atherosclerosis generally have reported intermediate outcomes and have not found EDTA chelation therapy to be more effective than placebo. Additional RCTs that report health outcomes are needed to establish the efficacy of this treatment.

**Myocardial Infarction**

In 2013, Lamas et al published results of the multicenter 2x2 factorial, randomized, double-blind Trial to Assess Chelation Therapy (TACT).\(^13\) The trial included 1708 patients, age 50 years or older, who had a history of myocardial infarction (MI) at least 6 weeks before enrollment and a serum creatinine level of 2.0 mg/dL or less. Patients were randomized to receive 40 infusions of disodium EDTA (n=839) or placebo (n=869). Patients also received either oral high-dose vitamin and mineral therapy or placebo. The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. Primary end point 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 0.036. A total of 361 patients in the chelation group (43%) and 464 patients in the placebo group (57%) discontinued treatment, withdrew consent, or were lost to follow-up. Kaplan-Meier 5-year estimates for the primary end point were 33% (95% confidence interval [CI], 29 to 37) in the chelation group and 39% (95% CI, 35 to 42) in the control group, a statistically significant difference (log-rank test, p=0.035). The most common individual clinical end point was coronary revascularization, which occurred in 130 (15%) of 839 patients in the chelation group and 157 (18%) of 869 patients in the control group (p=0.08). The next most frequent end point was death, which occurred in 87 patients (10%) in the chelation group and 93 patients (11%) in the placebo group (p=0.64). No individual component of the primary outcome differed statistically between groups; however, the study was not powered to detect differences in individual components. Four severe adverse events that were definitely or possibly related to study therapy occurred. There were two events each in the treatment and control groups, including one death in each group. Quality-of-life outcomes (reported in 2014)
did not differ between groups with 2 years of follow-up.\textsuperscript{14}

A subsequent publication in 2014 reported results of the 4 treatment groups in the 2x2 factorial design (double active group [disodium EDTA infusions with oral high-dose vitamins; n=421 patients randomized], active infusions with placebo vitamins [n=418], placebo infusions with active vitamins [n=432], and double placebo [n=437]).\textsuperscript{15} The proportion of patients who discontinued treatment, withdrew consent, or were lost to follow-up per treatment group was not reported. Five-year Kaplan-Meier estimates for the primary composite end point were 32%, 34%, 37%, and 40%, respectively. The reduction in primary end point by double active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74 [95% CI, 0.57 to 0.95]). In 633 patients with diabetes (≈36% of each treatment group), the primary end point reduction of double active compared with double placebo was more pronounced (HR=0.49 [95% CI, 0.33 to 0.75]).

The study is limited by the high number of withdrawals, with differential withdrawals between groups. The primary end point included components of varying clinical significance, and the largest difference between groups was for revascularization events. The primary end point 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 a population that is not generalizable to that seen in general clinical care.\textsuperscript{16} Editorialists commenting on the subsequent (2014) publication suggested that further research is warranted to replicate the findings.\textsuperscript{17}

Section Summary: Myocardial Infarction
One RCT with limitations, including high dropout with differential dropout between groups, reported that cardiovascular events were reduced in patients treated with chelation therapy. This effect was greater among patients with diabetes mellitus. However, this was not a high-quality trial and therefore results may be biased. Further trials of high quality are needed to corroborate whether chelation therapy improves outcomes in patients with prior MI.

AUTISM SPECTRUM DISORDER

Clinical Context and Test 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 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.

Patients
The population of interest includes patients with autism spectrum disorder 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.S. Food andDrug Administration.

**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.

Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard et al (2001) hypothesized a link between environmental mercury and autism.18 This theory was rejected by Nelson and Bauman (2003), who found that many of the characteristics of mercury poisoning such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and thrombocytopenia, are never seen in autistic children.19 A 2007 systematic review by Ng et al concluded that there was no association between mercury poisoning and autism.20

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and identified no controlled studies.21 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 Test 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 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.

**Patients**
The population of interest includes patients with diabetes.
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, and treatment-related morbidity.

Cardiovascular Disease in Patients With Diabetes
A 2009 trial by Cooper et al in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes. 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 compared with the placebo group (-10.6 g/m² vs. -0.1 g/m², p=0.01). The study was limited by the small sample size and high dropout rate.

Escolar et al (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. In TACT, 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 compared with placebo (HR=0.61; 95% CI, 0.45 to 0.83; log rank test, p=0.02); 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; log rank test, p=0.73). For the subsequent subgroup analysis, the definition of diabetes mellitus 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 mellitus 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 end point occurred in 25% of the EDTA group and 38% of the placebo group (HR=0.59; 99.4% CI, 0.39 to 0.88 [adjusted for multiple subgroups]; log-rank test, p=0.002). In adjusted analysis of the individual components of the primary end point, there were no statistically significant differences between treatment groups. Thirty-six adverse events attributable to study drug that led to trial withdrawal, 16 in the EDTA group and 20 in the placebo group.

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. 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 m² (5.0) in the chelation group and 9.2 mL/min/173 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 Test 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 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.

Patients
The population of interest includes patients with MS or arthritis.

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, and treatment-related morbidity.

No RCTs or other controlled studies that evaluated the safety and efficacy of chelation therapy for other conditions such as multiple sclerosis or arthritis, were identified. Iron chelation therapy is being investigated for Parkinson disease\textsuperscript{26,27} and endotoxemia.\textsuperscript{28}

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 2.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02728843\textsuperscript{a}</td>
<td>Study of Parkinson's early stage with deferiprone(SKY)</td>
<td>140</td>
<td>Sep 2019 (completed)</td>
</tr>
<tr>
<td>NCT02175225</td>
<td>Study of deferoxamine mesylate in intracerebral hemorrhage</td>
<td>294</td>
<td>May 2018 (completed)</td>
</tr>
<tr>
<td>NCT02655315</td>
<td>Conservative iron chelation as a disease-modifying strategy in Parkinson's disease (FAIRPARKII)</td>
<td>338</td>
<td>Feb 2021</td>
</tr>
<tr>
<td>NCT02733185</td>
<td>Trial to assess chelation therapy 2 (TACT2)</td>
<td>1200</td>
<td>Dec 2022</td>
</tr>
<tr>
<td>Unpublished</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NCT02367248</td>
<td>Safety and effectiveness study of deferoxamine and Xingnaojing injection in intracerebral hemorrhage</td>
<td>180</td>
<td>Dec 2016 (unknown)</td>
</tr>
</tbody>
</table>

NCT: national clinical trial.
\textsuperscript{a} Denotes industry-sponsored or cosponsored trial.

SUPPLEMENTAL INFORMATION

PRACTICE GUIDELINES AND POSITION STATEMENTS

American College of Physicians et al
In 2012, the American College of Physicians (ACP), American College of Cardiology Foundation (ACCF), American Heart Association (AHA), American Association for Thoracic
Surgery, Preventive Cardiovascular Nurses Association, and Society of Thoracic Surgeons published a clinical practice guideline on management of stable ischemic heart disease (IHD). The guidelines recommended that “chelation therapy should not be used with the intent of improving symptoms or reducing cardiovascular risk in patients with stable IHD. (Grade: strong recommendation; low-quality evidence)” However, citing the Trial to Assess Chelation Therapy, a 2014 focused update of this guideline 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.” The recommendation was upgraded from 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).

American College of Cardiology
In 2005, the American College of Cardiology stated that chelation “is not indicated for treatment of intermittent claudication and may have harmful adverse effects. (Level of Evidence A: Data derived from multiple randomized clinical trials or meta-analyses.)” In 2013, ACCF and AHA compiled previous ACC/AHA and ACCF/AHA recommendations issued in 2005 and 2011 on the management of peripheral artery disease. The recommendation against chelation therapy remained unchanged.

Canadian Cardiovascular Society
Evidence-based, consensus guidelines from the Canadian Cardiovascular Society in 2014 included a conditional recommendation (based on moderate quality evidence) that chelation therapy should not be used to attempt to improve angina or exercise tolerance in patients with stable ischemic heart disease.

National Institute for Health and Care Excellence
The National Institute for Health and Care Excellence issued clinical guidance on autism in children and young people in 2013 and autism in adults, which was updated in 2016. Both documents specifically recommend against the use of chelation therapy for the management of autism.

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)

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)39

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


17. Maron DJ, Hlatky MA. Trial to Assess Chelation Therapy (TACT) and equipoise: When evidence conflicts with beliefs [editorial]. Am Heart J. Jul 2014;168(1):4-5. PMID 24952853


The articles reviewed in this research include those obtained in an Internet based literature search for relevant medical references through December 2020, the date the research was completed.
### Joint BCBSM/BCN Medical Policy History

<table>
<thead>
<tr>
<th>Policy Effective Date</th>
<th>BCBSM Signature Date</th>
<th>BCN Signature Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>6/25/02</td>
<td>6/25/02</td>
<td>6/25/02</td>
<td>Joint medical policy established</td>
</tr>
<tr>
<td>9/7/04</td>
<td>9/7/04</td>
<td>9/28/04</td>
<td>Routine maintenance</td>
</tr>
<tr>
<td>1/1/07</td>
<td>11/1/06</td>
<td>11/19/06</td>
<td>Routine maintenance</td>
</tr>
<tr>
<td>1/1/09</td>
<td>10/13/08</td>
<td>12/30/08</td>
<td>Routine maintenance</td>
</tr>
<tr>
<td>1/1/12</td>
<td>10/11/11</td>
<td>11/9/11</td>
<td>Routine update; references updated, policy reformatted to mirror BCBSA</td>
</tr>
<tr>
<td>9/1/13</td>
<td>6/19/13</td>
<td>6/26/13</td>
<td>Routine maintenance. Policy updated to mirror BCBSA.</td>
</tr>
<tr>
<td>5/1/16</td>
<td>2/16/16</td>
<td>2/16/16</td>
<td>Routine maintenance. Added J0895</td>
</tr>
<tr>
<td>5/1/17</td>
<td>2/21/17</td>
<td>2/21/17</td>
<td>Removed hypoglycemia from exclusions as this indication is not reviewed in the policy. Added J0895 to policy. Routine policy maintenance.</td>
</tr>
<tr>
<td>5/1/18</td>
<td>2/20/18</td>
<td>2/20/18</td>
<td>Updated rationale section, removed reference 8, added references 38, 39 and 46.</td>
</tr>
<tr>
<td>5/1/19</td>
<td>2/19/19</td>
<td></td>
<td>Routine policy maintenance. No change in policy status.</td>
</tr>
<tr>
<td>5/1/20</td>
<td>2/18/20</td>
<td></td>
<td>Routine policy maintenance. No change in policy status.</td>
</tr>
<tr>
<td>5/1/21</td>
<td>2/16/21</td>
<td></td>
<td>Routine policy maintenance. No change in policy status.</td>
</tr>
</tbody>
</table>

Next Review Date: 1st Qtr. 2022

### Pre-Consolidation Medical Policy History

<table>
<thead>
<tr>
<th>Original Policy Date</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCN: 4/1/99</td>
<td>Revised: 6/28/01</td>
</tr>
<tr>
<td>BCBSM: N/A</td>
<td>Revised: N/A</td>
</tr>
</tbody>
</table>
### BLUE CARE NETWORK BENEFIT COVERAGE
**POLICY: CHELATION THERAPY, INCLUDING OFF-LABEL USES**

### I. Coverage Determination:

<table>
<thead>
<tr>
<th>Plan Type</th>
<th>Coverage Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial HMO (includes Self-Funded groups unless otherwise specified)</td>
<td>Covered for FDA approved indications; criteria apply. Not covered for off-label uses.</td>
</tr>
<tr>
<td>BCNA (Medicare Advantage)</td>
<td>See government section</td>
</tr>
<tr>
<td>BCN65 (Medicare Complementary)</td>
<td>Coinsurance covered if primary Medicare covers the service.</td>
</tr>
</tbody>
</table>

### 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.