Medical Policy

BlueCross BlueShield Kansas
An Independent licensee of the Blue Cross Blue Shield Association

Title: Chelation Therapy for Off-Label Uses

Professional
Original Effective Date: October 29, 2009
Revision Date(s): November 19, 2012; March 31, 2014, August 19, 2016; April 11, 2018; May 21, 2019; April 16, 2021
Current Effective Date: August 19, 2016

Institutional
Original Effective Date: October 29, 2009
Revision Date(s): December 19, 2012; March 31, 2014; August 19, 2016; April 11, 2018; May 21, 2019; April 16, 2021
Current Effective Date: August 19, 2016

Populations	Interventions	Comparators	Outcomes
Individuals: • With Alzheimer disease,	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With cardiovascular disease	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

Populations	Interventions	Comparators	Outcomes
Individuals: • With autism spectrum disorder	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With diabetes	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With multiple sclerosis	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity
Individuals: • With arthritis	Interventions of interest are: • Chelation therapy	Comparators of interest are: • Standard medical care	Relevant outcomes include: • Symptoms • Change in disease status • Morbid events • Functional outcomes • Health status measures • Quality of life • Treatment-related morbidity

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

Objective
The objective of this evidence review is to determine whether chelation therapy, when used as a treatment for various off-label applications such as Alzheimer disease, cardiovascular disease, autism spectrum disorder, diabetes, multiple sclerosis, and arthritis, improves the net health outcome.

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

aluminum, mercury, arsenic, zinc, iron, copper, and calcium from the body (see Appendix Table 1). Specific chelating agents are used for particular heavy metal toxicities. For example, desferrioxamine (not approved by the U.S. Food and Drug Administration (FDA)] is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (EDTA) is used for patients with lead poisoning. Disodium-EDTA is not recommended for acute lead poisoning due to the increased risk of death from hypocalcemia.[1,]

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

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

REGULATORY STATUS

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

Several iron-chelating agents are FDA approved:

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

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

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

POLICY

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

1. Alzheimer's disease
2. atherosclerosis (e.g., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)
3. autism
4. diabetes
5. multiple sclerosis
6. arthritis (includes rheumatoid arthritis)

Policy Guidelines

1. A number of indications for chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:
   a. extreme conditions of metal toxicity
   b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia (NTDT)
   c. Wilson disease (hepatolenticular degeneration)
   d. lead poisoning
   e. control of ventricular arrhythmias or heart block associated with digitalis toxicity
   f. emergency treatment of hypercalcemia

2. For items 1 e and 1 f, 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. NaEDTA was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

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

RATIONALE

This evidence review has been updated regularly with searches of the PubMed database. The most recent literature update was performed through December 8, 2020.

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

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

Alzheimer Disease

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of chelation therapy improve the net health outcome in patients with Alzheimer disease?

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

Populations

The population of interest is patients with Alzheimer disease.

Interventions

The intervention of interest is chelation therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Review
A Cochrane review (2008) evaluated metal protein attenuating compounds for treating Alzheimer disease.[3] Reviewers identified a placebo-controlled randomized trial. This study by Ritchie et al. (2003) assessed patients treated with PBT1, a metal protein attenuating compound also known as clioquinol, which is an antifungal medication that crosses the blood-brain barrier.[4] The U.S. Food and Drug Administration (FDA) withdrew clioquinol for oral use from the market in 1970 because of its association with subacute myelo-optic neuropathy. Ritchie et al (2013) administered oral clioquinol to 16 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 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. The update of this Cochrane review (2012) included trials through December 2011.[5] Only the Lannfelt et al. (2008) trial (discussed next) was identified.

Further study of PBT1 was abandoned in favor of a successor compound, PBT2. Lannfelt et al (2008) completed a double-blind, placebo-controlled randomized trial of 78 Alzheimer disease patients who were treated for 12 weeks with PBT2 50 mg (n=20), PBT2 250 mg (n=29), or placebo (n=29).[6] There was no statistically significant difference in Alzheimer Disease Assessment Scale–Cognitive or Mini-Mental Status Examination scores among groups in this short-term study. The most common adverse event was headache. Two serious adverse events (urosepsis, transient ischemic event) were reported in the placebo arm.

Section Summary: Alzheimer Disease
There is insufficient evidence on the safety and efficacy of chelation therapy for treating patients with Alzheimer disease. The few published RCTs did not find that chelation was superior to placebo for improving health outcomes.

Cardiovascular Disease

Clinical Context and Therapy Purpose
The purpose of chelation therapy is to provide a treatment option that is an alternative to or an improvement on existing therapies for patients with cardiovascular disease.

The question addressed in this evidence review is: Does the use of chelation therapy improve the net health outcome in patients with cardiovascular disease?

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

Populations
The population of interest is patients with cardiovascular disease.

Interventions
The intervention of interest is chelation therapy.

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

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Systematic Review

Villarruz-Sulit et al (2020) published a Cochrane review that evaluated ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease.[7,] 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.

The largest trial included in this Cochrane review is the multicenter, 2$\times$2 factorial, double-blind, randomized Trial to Assess Chelation Therapy (TACT), which was published by Lamas et al. in 2013.[8,] TACT included 1708 patients, ages 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 0.036. 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% 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 (p=0.035). 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=0.08). 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=0.64). 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.[9]

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], double placebo [n=437 patients]).[10] The proportions of patients who discontinued treatment withdrew consent, or were lost to follow-up per treatment group were not reported. Five-year Kaplan-Meier estimates for the primary composite endpoint were 32%, 34%, 37%, and 40%, respectively. The reduction in primary endpoint by double-active treatment compared with double placebo was statistically significant (hazard ratio [HR], 0.74; 95% CI, 0.57 to 0.95). In 633 patients with diabetes (≈36% of each treatment group), the primary endpoint reduction in the double-active group compared with the double placebo group was more pronounced (HR=0.49; 95% CI, 0.33 to 0.75). A post-hoc analysis showed that chelation was associated with a lower risk of the primary endpoint compared with placebo in patients with post anterior myocardial infarction (n=674; hazard ratio [HR], 0.63, 95% CI, 0.47 to 0.86; p=0.003); however, this effect was not seen in post non-anterior myocardial infarction.[11]

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.[12] Editorialists commenting on the subsequent (2014) publication suggested that further research would be warranted to replicate the findings.[13] 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.

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. Additional RCTs reporting health outcomes would be needed to establish treatment efficacy. The largest of these RCTs 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.[14,] 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.[15,] A meta-analysis by Ng et al. (2007) concluded that there was no association between mercury poisoning and autism.[16,]

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 autism spectrum disorder.

The question addressed in this evidence review is: Does the use of chelation therapy improve the net health outcome in patients with autism spectrum disorder?

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

Populations

The population of interest is patients with autism spectrum disorder.

Interventions

The intervention of interest is chelation therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

Review of Evidence

Observational Studies

Rossignol (2009) published a systematic review of novel and emerging treatments for autism and identified no controlled studies.[17,] Rossignol (2009) stated that case series had suggested a potential role for chelation in treating some autistic people with known elevated heavy metal levels, but this possibility needed further investigation in controlled studies.

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

Diabetes

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

The question addressed in this evidence review is: Does the use of chelation therapy improve the net health outcome in patients with diabetes?

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

Populations
The population of interest is patients with diabetes.

Interventions
The intervention of interest is chelation therapy.

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

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

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

Review of Evidence

Randomized Controlled Trials

Cardiovascular Disease in Patients With Diabetes
A trial by Cooper et al. (2009) in New Zealand evaluated the effect of copper chelation using oral trientine on left ventricular hypertrophy in 30 patients with type 2 diabetes.[18,] Twenty-one (70%) of 30 participants completed 12 months of follow-up. At 12 months, there was a significantly greater reduction in left ventricular mass indexed to body surface area in the active treatment

group (-10.6 g/m^2) than in the placebo group (-0.1 g/m^2; p=0.01). 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.[19,] 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=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; p=0.73).[8,] 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=0.002). 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.[20,] 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=0.0069). 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.[21,] Chelation therapy was associated with a lower frequency of the primary outcome compared with placebo in patients on insulin (n=162; 26% versus 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.

Diabetic Nephropathy

Chen et al (2012) conducted a single-blind RCT assessing the effects of chelation therapy on the progression of diabetic nephropathy in Chinese patients with high-normal lead levels.[22,] Fifty patients with diabetes, high-normal body lead burden (80 to 6000 µg), and serum creatinine of 3.8 mg/dL or lower were included. Baseline mean blood lead levels were 6.3 µg/dL in the treatment group and 7.1 µg/dL in the control group; baseline mean body lead burden was 151 µg in the treatment group and 142 µg in the control group. According to the U.S. Occupational and Health Safety Administration, the maximum acceptable blood lead level in adults is 40 µg/dL.[23,] Patients were randomized to 3 months of calcium disodium EDTA or to placebo. During 24 months of treatment follow-up, patients in the chelation group received additional chelation treatments as needed (i.e., for serum creatinine level above pretreatment levels or body lead burden >60 µg), and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month trial. The primary outcome was change in estimated glomerular filtration rate. Mean yearly rate of decrease in estimated glomerular filtration rate was 5.6 mL/min/173 m^2 in the chelation group and 9.2 mL/min/173 m^2 in the control group, a statistically significant difference (p=0.04). The secondary endpoint was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. Nine (36%) patients in the treatment group and 17 (68%) in the control group attained the secondary endpoint, a statistically significant difference (p=0.02). There were no reported adverse events of chelation therapy during the trial.

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 (e.g., cardiovascular events, end-stage renal disease, mortality) are needed.

Other Potential Indications: Multiple Sclerosis and Arthritis

Clinical Context and Therapy Purpose

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

The question addressed in this evidence review is: Does the use of chelation therapy improve the net health outcome in patients with MS or arthritis?

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

Populations

The population of interest is patients with MS or arthritis.

Interventions

The intervention of interest is chelation therapy.

Comparators

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

Outcomes

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

Study Selection Criteria

Methodologically credible studies were selected using the following principles:

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

- Studies with duplicative or overlapping populations were excluded.

Review of Evidence

No RCTs or other controlled trials evaluating the safety and efficacy of chelation therapy for other conditions (e.g., MS, arthritis) were identified. Iron chelation therapy is being investigated for Parkinson disease[24,25,] and endotoxemia.[26,]

Summary of Evidence

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

SUPPLEMENTAL INFORMATION

Practice Guidelines and Position Statements

The purpose of the remaining sections in Supplemental Information is to provide reference material regarding existing practice guidelines and position statements, U.S. Preventive Services Task Force Recommendations and Medicare National Coverage Decisions and registered, ongoing clinical trials. Inclusion in the Supplemental Information does not imply endorsement and information may not necessarily be used in formulating the evidence review conclusions.

Guidelines or position statements will be considered for inclusion in 'Supplemental Information if they were issued by, or jointly by, 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.[27,]

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."[28,] 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).[29,]

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.[30,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Ongoing and Unpublished Clinical Trials

Some currently unpublished trials that might influence this review are listed in Table 1.

CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); each additional hour (List separately in addition to code for primary procedure)
96374	Therapeutic, prophylactic, or diagnostic injection (specify substance or drug); intravenous push, single or initial substance/drug
J0470	Injection, dimercaprol, per 100 mg
J0600	Injection, edetate calcium disodium, up to 1,000 mg
J0895	Injection, deferoxamine mesylate, 500 mg
J3520	Edetate disodium, per 150 mg
M0300	IV chelation therapy (chemical endarterectomy)
S9355	Home infusion therapy, chelation therapy; administrative services, professional pharmacy services, care coordination, and all necessary supplies and equipment (drugs and nursing visits coded separately), per diem

Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS	
11-19-2012	Policy added to the bcbsks.com web site.
	Effective for Institutional providers 12-19-2012.

<table>
<tr><td colspan="2"><u>REVISIONS</u></td></tr>
<tr><td rowspan="5">03-31-2014</td><td>Description section updated</td></tr>
<tr><td>In Policy section:
▪ Added to A 4 "and due to nontransfusion-dependent thalassemia (NDTD)" to read, "4. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to nontransfusion-dependent thalassemia (NDTD)"
▪ Added to B 1 "secondary prevention in patients with myocardial infarction" to read, "1. atherosclerosis (i.e., coronary artery disease, secondary prevention in patients with myocardial infarction, or peripheral vascular disease)"</td></tr>
<tr><td>Rationale section updated</td></tr>
<tr><td>In Coding section:
▪ Removed ICD-9 Diagnoses Codes: 427.9, 440.0-440.9
▪ Added ICD-10 Diagnoses Codes</td></tr>
<tr><td>References updated</td></tr>
<tr><td rowspan="4">08-19-2016</td><td>Published 07-20-2016. Effective 08-19-2016</td></tr>
<tr><td>Policy title changed to "Chelation Therapy for Off-Label Uses" from "Chelation Therapy"</td></tr>
<tr><td>Description section updated</td></tr>
<tr><td>In Policy section:
▪ Removed the following from the Policy language and restated the FDA approved indications in Policy Guidelines:
"Chelation therapy may be considered medically necessary in the treatment of each of the following conditions:
1. extreme conditions of metal toxicity
2. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT) (NDTD)
3. Wilson's disease (hepatolenticular degeneration)
4. lead poisoning
5. control of ventricular arrhythmias or heart block associated with digitalis toxicity
6. emergency treatment of hypercalcemia"
▪ In policy statement removed "Other" and added "Off-label" and "(see Policy Guidelines section for uses approved by the Food and Drug Administration)" to read "Off-label applications of chelation therapy (see Policy Guidelines section for uses approved by the Food and Drug Administration) are considered experimental / investigational, including, but not limited to:"
▪ Removed Off-label indication "hypoglycemia"
▪ Added Policy Guidelines to read:
" 1. A number of indications for chelation therapy have received Food and Drug Administration (FDA) approval and for which chelation therapy is considered standard of care treatment. They include:
a. extreme conditions of metal toxicity
b. treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) and due to non-transfusion-dependent thalassemia (NTDT)
c. Wilson disease (hepatolenticular degeneration)
d. lead poisoning
e. control of ventricular arrhythmias or heart block associated with digitalis toxicity
f. emergency treatment of hypercalcemia
2. For items 1 e and 1 f, 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.
3. Suggested toxic or normal levels of select heavy metals are listed in Appendix Table 1."</td></tr>
</table>

REVISIONS	
	Rationale section updated
	In Coding section: ▪ CPT Code Correction: Replaced 96375 with 96374 ▪ Removed ICD codes and replaced with the phrase "Experimental / Investigational for all diagnoses related to this medical policy."
	References updated
	Added "Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals"
04-11-2018	Description section updated
	Revision section updated
	References updated
	Appendix updated
05-21-2019	Description section updated
	In Policy section: ▪ Updated Policy Guideline 1 b changing "and" to "or" to read "treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia (NTDT)"
	Revision section updated
	References updated
04-16-21	Description section updated
	Revision section updated
	References updated

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. 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

8. 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
9. 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
10. 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
11. 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
12. Nissen SE. Concerns about reliability in the Trial to Assess Chelation Therapy (TACT). JAMA. Mar 27 2013; 309(12): 1293-4. PMID 23532246
13. 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
14. 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
15. Nelson KB, Bauman ML. Thimerosal and autism?. Pediatrics. Mar 2003; 111(3): 674-9. PMID 12612255
16. 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
17. 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
18. 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
19. 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
20. 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
21. 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
22. 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
23. 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.

24. 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
25. 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
26. 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
27. 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
28. 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
29. 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
30. 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
31. 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 December 8, 2020.
32. 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 December 8, 2020.
33. 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 26, 2021.
34. 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
35. Agency for Toxic Substances and Disease Registry. Toxicological profile for mercury. 1999 March; https://www.atsdr.cdc.gov/ToxProfiles/tp46.pdf. Accessed January 23, 2020.

36. 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 25, 2021.
37. Adal A. Medscape. Heavy metal toxicity. 2018; http://emedicine.medscape.com/article/814960-overview. Accessed January 24, 2021.
38. 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

APPENDIX

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

Appendix Table 1. Toxic or Normal Concentrations of Heavy Metals

Metal	Toxic Levels (Normal Levels Where Indicated)
Arsenic	24-h urine: ≥50 µg/L urine or 100 µg/g creatinine
Bismuth	No clear reference standard
Cadmium	Proteinuria and/or ≥15 µg/g creatinine
Chromium	No clear reference standard
Cobalt	Normative excretion: 0.1-1.2 µg/L (serum), 0.1-2.2 µg/L (urine)
Copper	Normative excretion: 25 µg/24 h (urine)
Iron	• Nontoxic: <300 µg/dL • Severe: >500 µg/dL
Lead	**Pediatric** • Symptoms or blood lead level ≥45 µg/dL (blood) • CDC level of concern: 5 µg/dL[40] **Adult** • Symptoms or blood lead level ≥70 µg/dL • CDC level of concern: 10 µg/dL[41]
Manganese	No clear reference standard
Mercury	Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[42,a]
Nickel	• Excessive exposure: ≥8 µg/L (blood) • Severe poisoning: ≥500 µg/L (8-h urine)
Selenium	• Mild toxicity: >1 mg/L (serum) • Serious toxicity: >2 mg/L
Silver	Asymptomatic workers have mean levels of 11 µg/L (serum) and 2.6 µg/L (spot urine)
Thallium	24-hour urine thallium >5 µg/L[43]
Zinc	Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

Adapted from Adal (2018).[44]
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]