FEP Medical Policy Manual

FEP 8.01.02 Chelation Therapy for Off-Label Uses

Annual Effective Policy Date: July 1, 2024

Original Policy Date: December 2011

Related Policies:

None

Chelation Therapy for Off-Label Uses

Description

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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.

POLICY STATEMENT

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

- Alzheimer disease
- atherosclerosis (eg, coronary artery disease, secondary prevention in individuals with myocardial infarction, or peripheral vascular disease)
- autism
- diabetes
- multiple sclerosis
- arthritis (includes rheumatoid arthritis).

POLICY GUIDELINES

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

- extreme conditions of metal toxicity
- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis) or due to non-transfusion-dependent thalassemia
- Wilson disease (hepatolenticular degeneration)
- lead poisoning
- control of ventricular arrhythmias or heart block associated with digitalis toxicity
- emergency treatment of hypercalcemia.

For the last 2 bullet points, most individuals should be treated with other modalities. Digitalis toxicity is currently treated in most individuals with Fab monoclonal antibodies. The FDA removed the approval for 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.

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: 3.5 µg/dL[39,] **Adult** • Symptoms or blood lead level ≥70 µg/dL • CDC level of concern: 10 µg/dL[40,]
Manganese	No clear reference standard
Mercury	Background exposure normative limits: 1-8 µg/L (whole blood); 4-5 µg/L (urine)[41,,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[42,]
Zinc	Normative range: 0.6-1.1 mg/L (plasma), 10-14 mg/L (red cells)

Adapted from Adal (2018).[43,]
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.[44,]

BENEFIT APPLICATION

Experimental or investigational procedures, treatments, drugs, or devices are not covered (See General Exclusion Section of brochure).

FDA REGULATORY STATUS

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

Several iron-chelating agents are FDA approved:

- In 1968, deferoxamine (Desferal; Novartis) was approved by the FDA for subcutaneous, intramuscular, or intravenous injections to treat acute iron intoxication and chronic iron overload due to transfusion-dependent anemia. Several generic forms of deferoxamine have been approved by the FDA.
- In 2005, deferasirox (Exjade; Novartis) was approved by the FDA, is available as a tablet for oral suspension, and is indicated for the treatment of chronic iron overload due to blood transfusions in patients age 2 years and older. Under the accelerated approval program, the FDA expanded the indications for deferasirox in 2013 to include treatment of patients age 10 years and older with chronic iron overload due to non-transfusion-dependent thalassemia syndromes and specific liver iron concentration and serum ferritin levels. A generic version of deferasirox tablet for oral suspension has also been approved by the FDA. In 2015, an oral tablet formulation for deferasirox (Jadenu) was approved by the FDA. All formulations of deferasirox carry a boxed warning because it may cause serious and fatal renal toxicity and failure, hepatic toxicity and failure, and gastrointestinal hemorrhage. As a result, treatment with deferasirox requires close patient monitoring, including laboratory tests of renal and hepatic function.
- In 2011, the iron chelator deferiprone (Ferriprox) was approved by the FDA for treatment of patients with transfusional overload due to thalassemia syndromes when another chelation therapy is inadequate. Deferiprone is available in tablet and oral solution. Ferriprox carries a boxed warning because it can cause agranulocytosis, which can lead to serious infections and death. As a result, absolute neutrophil count should be monitored before and during treatment.

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

RATIONALE

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 (eg, 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

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 stated that chelation therapy (eg, ethylenediaminetetraacetic acid) is not beneficial for the treatment of claudication.[31,]

In 2014, the ACC and AHA published a focused update of the guideline for the management of stable ischemic heart disease, in conjunction with the American Association for Thoracic Surgery, Preventative Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons. This update included a revised recommendation on chelation therapy stating that the "usefulness of chelation therapy is uncertain for reducing cardiovascular events in patients with stable IHD."[32,] Compared to the original publication of this guideline in 2012, the recommendation was upgraded from a class III (no benefit) to class IIb (benefit ≥ risk), and the level of evidence from C (only consensus expert opinion, case studies, or standard of care) to B (data from a single randomized trial or nonrandomized studies).[33,]A 2023 guideline from these organizations on managing chronic coronary disease provided comments about chelation therapy but no formal recommendations.[34,]

American Heart Association

In 2023, the AHA published a scientific statement about the cardiovascular risk of contaminant metals.[35,] The authors cited the TACT trial findings of a reduced relative risk of cardiovascular events among patients who received chelation therapy, but also noted that TACT did not evaluate metal levels. Results of the TACT2 trial (which finished in 2023), are awaited to provide objective data on the metal level lowering effects of chelation therapy.

American Academy of Pediatrics

In 2019, the American Academy of Pediatrics published guidance for the management of children with autism spectrum disorder. The guidance cautioned against the use of chelation therapy due to safety concerns and lack of supporting efficacy data.[36,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

The Centers for Medicare & Medicare have issued 2 national coverage determinations on chelation therapy relevant to this evidence review. Section 20.21 states[37,]:

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

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

Section 20.22 states[38,]:

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

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

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POLICY HISTORY - THIS POLICY WAS APPROVED BY THE FEP® PHARMACY AND MEDICAL POLICY COMMITTEE ACCORDING TO THE HISTORY BELOW:

Date	Action	Description
December 2011	New policy	
September 2013	Replace policy	Policy updated with literature review. References 16-21 added, others removed or renumbered. Chronic iron overload due to nontransfusion-dependent thalassemia (NDTD) added to medically necessary statement based on new FDA approval. Secondary prevention in patients with myocardial infarction added to bullet point in investigational statement on atherosclerosis; in that bullet point, "i.e.€š changed to "e.g.€š
September 2014	Replace policy	Policy updated with literature review through May 21, 2014; references 14, 22-24, and 28-29 added; references 2, 19, and 25 updated. Title changed to "Chelation Therapy for Off-Label Uses.€š Medically necessary policy statement for on-label uses deleted from policy statement and moved to policy guidelines. Investigational policy statement unchanged.
September 2015	Replace policy	Policy updated with literature review through May 21, 2015; references 3, 4, 23-25, 27, 33, 35, 36, 38 and 41 added. Hypoglycemia deleted from policy statement; this indication is not reviewed in the policy. Policy statements otherwise unchanged.
June 2018	Replace policy	Policy updated with literature review through December 11, 2017; reference 8 removed; reference 38 and 44 updated; reference 39 added. Policy statement unchanged.
June 2019	Replace policy	Policy updated with literature review through January 3, 2019; no reference added. Policy statement unchanged.
June 2020	Replace policy	Policy updated with literature review through December 9, 2019; no references added. Policy statement unchanged.
June 2021	Replace policy	Policy updated with literature review through December 8, 2020; references added. Policy statement unchanged.
June 2022	Replace policy	Policy updated with literature review through November 15, 2021; no references added. Policy statements unchanged.
June 2023	Replace policy	Policy updated with literature review through December 28, 2022; references added. Minor editorial refinements to policy statements; intent unchanged
June 2024	Replace policy	Policy updated with literature review through December 20, 2023; references added. Policy statements unchanged.