BlueCross
BlueShield
Federal Employee Program.

Federal Employee Program®
1310 G Street, N.W.
Washington, D.C. 20005
202.942.1000
Fax 202.942.1125

8.01.02

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Last Review Status/Date: September 2014

Chelation Therapy for Off–Label Uses

Description

Chelation therapy, an established treatment for treating heavy metal toxicities, has been investigated for a variety of off label applications including treatment of atherosclerosis, Alzheimer's disease, and autism.

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 consists of the 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, desferoxamine is used for patients with iron toxicity, and calcium-ethylenediaminetetraacetic acid (-EDTA)) is used for patients with lead poisoning. Note that 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's 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's disease, they promote the solubilization and clearance of Aβ-amyloid protein by binding its metal-ion complex and also inhibit redox reactions that generate neurotoxic free radicals. MPACs therefore interrupt two putative pathogenic processes of Alzheimer's disease. However, no MPACs have received U.S. Food and Drug Administration (FDA) approval for the treatment of Alzheimer's 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

Calcium-EDTA was approved by the FDA for lowering blood lead levels among patients with lead poisoning. Disodium-EDTA was approved by the FDA 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,

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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 have received FDA approval. 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 age 2 years and older. Under the accelerated approval program, the FDA expanded approval of deferasirox in 2013 to include the treatment of patients age 10 and older with chronic iron overload due to nontransfusion-dependent thalassemia (NTDT). In 2011, the FDA approved the iron chelator deferiprone 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.

Policy

This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Off-label applications of chelation therapy (see Policy Guidelines for FDA-approved uses) are considered **investigational**, including, but not limited to:

- atherosclerosis (e.g.., coronary artery disease, secondary prevention in patients with myocardial infarction or peripheral vascular disease);
- multiple sclerosis;
- arthritis (includes rheumatoid arthritis);
- hypoglycemia;
- autism;
- Alzheimer's disease; and
- diabetes

Policy Guidelines

There are a number of indications for chelation therapy that have received FDA approval and for which chelation therapy is considered standard of care treatment. These include:

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

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For the last two bullet points, most patients should be treated with other modalities. Digitalis toxicity is currently treated in most patients 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. This was the most common chelation agent used to treat digitalis toxicity and hypercalcemia.

Rationale

Chelation therapy is an established treatment for the treatment of metal toxicity and transfusional hemosiderosis. These uses are not covered in this policy. Literature searches have focused on the use of chelation therapy for off-label conditions including, but not limited to atherosclerosis, autism, Alzheimer's disease, multiple sclerosis and diabetes.

Atherosclerosis

In 2002, a Cochrane review was published evaluating studies on ethylenediaminetetraacetic acid (EDTA) chelation therapy for treating patients with atherosclerotic cardiovascular disease. (3) Five placebo-controlled randomized-controlled trials (RCTs) were identified, none of which reported mortality, non-fatal events, and cerebrovascular vascular events. Four of the 5 studies (total n=250) found no significant benefits 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 not available. 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 needed.

Among the published randomized controlled trials (RCTs), Knudtson and colleagues randomized 84 patients with coronary artery disease and a positive treadmill test to receive EDTA chelation therapy or placebo, 3 hours per treatment twice weekly for 15 weeks, and once per month for an additional 3 months. (4) The main 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, randomized controlled study of EDTA chelation or placebo showed no change in short- or long-term improvement in vasomotor response to EDTA when compared to placebo. (5) Two small randomized trials have also reported no benefit of chelation therapy as a treatment of peripheral arterial disease. (6, 7)

Section summary: Several RCTs have been published on chelation therapy for treating atherosclerosis; these have generally 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.

Autism

Based on similarities between mercury poisoning and autism spectrum disorder symptoms, Bernard and colleagues hypothesized a link between environmental mercury and autism. (8) This theory was rejected by Nelson and Bauman, who found that many of the characteristics of mercury poisoning such as ataxia, constricted visual fields, peripheral neuropathy, hypertension, skin eruption, and

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thrombocytopenia, are never seen in autistic children. (9) In 2007, a systematic review by Ng and colleagues demonstrated no association between mercury poisoning and autism. (10)

In 2009, Rossignol published a systematic review of novel and emerging treatments for autism and did not identify any studies that included a control group. (11) The author stated the case series suggests that chelation might be a viable form of treatment in some autistic individuals with known elevated heavy metal levels and that this possibility needs to be further investigated in controlled studies.

Section summary: There is a lack of controlled studies on the effect of chelation therapy on health outcomes in patients with autism.

Alzheimer's Disease

A 2008 Cochrane Review evaluated metal protein attenuating compounds (MPAC) for treating Alzheimer's disease.(12) The review identified one placebo-controlled RCT. This study, by Ritchie and colleagues, was published in 2003. Patients were treated with PBT1, an MPAC also known as clioquinol, an anti-fungal medication that crosses the blood-brain barrier. (13) Clioquinol was withdrawn for oral use in 1970 because of its association with subacute myelo-optic neuropathy. In the study, oral clioquinol was administered in doses increasing to 375 mg twice daily to 16 Alzheimer's disease patients, and the effects were compared to 16 matched controls who received placebo.(14) 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 while she was receiving 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 below was identified. (14)

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2. Lannfelt and colleagues (2008) 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). (15)There was no statistically significant difference in ADAS-Cog scale or Mini-Mental Status Exam 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.

Ongoing investigations in chelation therapy for the treatment of Alzheimer's disease and other neurodegenerative diseases include linking a carbohydrate moiety to drug molecules to enhance drug delivery across the blood-brain barrier; this strategy may solve the potential problem of premature and indiscriminate metal binding. In addition, multi-function drugs that not only bind metal but also have significant antioxidant capacity are in development. (16)

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

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Diabetes

Cardiovascular disease in patients with diabetes

A 2009 trial by Cooper and colleagues in New Zealand evaluated the effect of copper chelation using oral trientine on left-ventricular hypertrophy in 30 patients with type 2 diabetes. (17) A total of 21/30 (70%) of the participants completed the 12-month follow-up. At 12 months, there was a significantly greater change in left ventricular mass indexed to body surface area (LVM) in the group receiving active treatment compared to placebo (-10.6 g/m2 vs. -0.1 g/m2, p=0.01). The study was limited by the small sample size and high drop-out rate.

Diabetic nephropathy

Chen and colleagues in China investigated the effect of chelation therapy on the progression of diabetic nephropathy in patients with high-normal lead levels. Their 2012 single-blind study included 50 patients with diabetes, high-normal body lead burden (80-6,000 ug) and serum creatinine 3.8 mg/dL or lower. (18) At baseline, the mean blood lead level was 6.3 ug/dL in the treatment group and 7.1 ug/dL in the control group and the mean body lead burden was 151 ug for patients in the treatment group and 142 ug for patients in the control group. According to the U.S. Occupational and Health Safety Administration (OSHA), the maximum acceptable blood lead level in adults is 40 ug/dL. (19) Patients were randomized to 3 months of calcium disodium EDTA or placebo. During the following 24 months, patients in the chelation group received additional chelation treatments as needed (i.e., if serum creatinine level exceeded pre-treatment levels or body lead burden was >60 ug) and patients in the placebo group continued to receive placebo medication. All patients completed the 27-month study. The primary outcome was change in estimated glomerular filtration rate (eGFR). The yearly rate of decrease in eGFR was 5.6 mL/min/173 m^2 (standard deviation [SD]: 5.0) in the chelation group and 9.2 mL/min/173 m^2 (SD: 3.6) in the control group. The difference between groups was statistically significant, p=0.04. The secondary endpoint was the number of patients in whom the baseline serum creatinine doubled or who required renal replacement therapy. A total of 9 patients (36%) in the treatment group and 17 (68%) in the control group attainted the secondary endpoint; the difference between groups was statistically significant (p=0.02). There were no reported side effects of chelation therapy during the 27-month study period.

Section summary: 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 and that report health outcomes such as cardiovascular events, end-stage renal disease and mortality are needed.

Myocardial infarction (MI)

In 2013, findings of the randomized double-blind multicenter Trial to Assess Chelation Therapy (TACT) study were published. (20) The study included 1,708 individuals, age 50 or older, who had a history of a myocardial infarction at least 6 weeks previous 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). The first 30 infusions were given weekly, and the remaining 10 infusions were given 2 to 8 weeks apart. The

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primary endpoint was a composite outcome that included death from any cause, reinfarction, stroke, coronary revascularization or hospitalization for angina at 5 years. A total of 361 patients in the chelation group (43%) and 464 patients in the placebo group (57%) discontinued treatment after starting it, withdrew consent during follow-up or were lost to follow-up. The Kaplan-Meier 5-year estimates for the primary endpoint were 32.8% (95% confidence interval [CI]: 29.1% to 36.5%) in the chelation group and 38.5% (95% CI: 34.6% to 42.3%) in the control group. The difference between groups was statistically significant; the p value was 0.035, which was below the significance threshold required due to multiple (11) interim analyses, 0.036. The most common individual clinical endpoint was coronary revascularization, which occurred in 130 of 839 patients (15%) in the chelation group and 157 of 869 patients (18%) in the control group, p value=0.08. The next most frequent endpoint was death. This occurred in 87 of 839 (10%) of patients in the chelation group and 93 of 869 (11%) of patients in the placebo group, p value=0.64. None of the individual components of the primary outcome differed significantly between groups; however, the study was not powered to detect difference in individual components. Four severe adverse events occurred that were definitely or possibly related to study therapy. There were 2 events each in the treatment and control group, including 1 death in each group.

The study is limited by the low follow-up rate, including a greater number of patients who withdrew consent in the placebo group compared to the treatment group. The primary endpoint included components of varying clinical significance, with most of the difference between groups occurring for revascularization events. The primary endpoint barely met the significance threshold and if more patients had been retained in the study and experienced events, results could have differed. Moreover, as noted in an editorial accompanying the 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 clinical care. (21)

Escolar et al (2014) published results of a prespecified subgroup analysis of diabetic patients in TACT. (22) In TACT, there was a statistically significant interaction between treatment (EDTA or placebo) and presence of diabetes: Among 538 self-reported diabetics (31% of the trial sample), those randomized to EDTA had a 39% reduced risk of the primary composite outcome compared with placebo (hazard ratio [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). (20) 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 ≥126 mg/dL 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 congestive 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 adjusted for multiple subgroups, 0.39 to 0.88]; 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. There were 36 adverse events attributable to study drug that led to trial withdrawal, 16 in the EDTA group and 20 in the placebo group.

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This substudy has the same limitations as the parent study described above, namely, high and differential withdrawal and heterogeneous composite end point. Additionally, because diabetes was not a stratification factor in TACT, results of this subgroup analysis are preliminary and require replication.

Section summary: One RCT with limitations, including high dropout with differential drop-out 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.

Other potential indications

No RCTs or other controlled studies were identified that evaluated the safety and efficacy of chelation therapy for other conditions such as multiple sclerosis or arthritis. Iron chelation therapy is being investigated for Parkinson disease (23) and endotoxemia. (24)

Ongoing Clinical Trials

A search of online site, ClinicalTrials.gov, for randomized trials of chelation therapy in heavy metal intoxication returned 14 actively-recruiting trials. All identified trials examined iron toxicity. Investigational indications are listed in Table 1 and include pantothenate kinase-associated neurodegeneration (PKAN) (NCT01741532), Parkinson disease (NCT01539837), hypotension (NCT00870883), and multiple sclerosis (NCT01627938).

Table 1. Ongoing Randomized Trials of Chelation Therapy for Investigational Uses (Current May 2014)

Title	Ages	Enrollment[a]	Completion[a]
Phase 4 Trial			
A Two-arm Efficacy and Safety Study of Deferiprone in Patients With Pantothenate Kinase-associated Neurodegeneration (PKAN) (NCT01741532)	Child Adult	90	Aug 2015
Phase 2 Trials			
A Pilot Clinical Trial With the Iron Chelator Deferiprone in Parkinson's Disease (DeferipronPD) (NCT01539837)	Adult	36	Dec 2013
N-acetylcysteine Plus Deferoxamine for Patients With Hypotension (NCT00870883)	Adult	140	Mar 2014
Study to Evaluate the Reduction of Cardiac Problems in Multiple Sclerosis Patients With Mitoxantrone and Dexrazoxane in Combination (MSCardioPro) (NCT01627938)	Adult	50	Mar 2015

NR, not reported.

[a] Estimated.

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Practice Guidelines and Position Statements

In 2012, the American College of Physicians, American College of Cardiology Foundation, American Heart Association, 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). (25) The organizations 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)"

In 2005, the American College of Cardiology (26) 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.)"

A 2004 clinical practice guideline from the American College of Physicians (27) states that chelation "should *not* be used to prevent myocardial infarction or death or to reduce symptoms in patients with symptomatic chronic stable angina. (Level of evidence B: Based on evidence from a limited number of randomized trials with small numbers of patients, careful analyses of nonrandomized studies, or observational registries.)"

The National Institute for Health and Care Excellence (NICE) issued clinical guidance on autism in children and young people in 2013 (28) and autism in adults in 2012. (29) Both documents specifically recommend against the use of chelation therapy for the management of autism.

Summary

Chelation therapy is an established treatment for metal toxicities and transfusional hemosiderosis. There is insufficient evidence that chelation therapy improves health outcomes for patients with conditions that are off-label for FDA-approved chelating agents, including, but not limited to, atherosclerosis, autism, Alzheimer disease, and diabetes. One RCT, the TACT study, reported that chelation therapy reduced cardiovascular events in patients with a previous MI, and that the benefit was greater in diabetic patients compared to non-diabetic patients. However, this study had significant limitations, including high dropout rates, and therefore the conclusions are not definitive. Thus, chelation therapy for these off-label applications is considered investigational.

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Policy History

Date	Action	Reason
December 2011	New Policy	
September 2013	Update 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." changed to "e.g."

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September 2014 Update 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." Medically necessary policy statement for on-label uses deleted from policy statement and moved to policy guidelines. Investigational policy statement unchanged.

Keywords

Chelation Therapy
Chemical Endarterectomy

This policy was approved by the FEP® Pharmacy and Medical Policy Committee on September 12, 2014 and is effective October 15, 2014.

Signature on File
Deborah M. Smith, MD, MPH