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

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, desferroxamine 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, Alzheimer’s disease, 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, 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. 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.

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**Policy**

Chelation therapy may be considered **medically necessary** in the treatment of each of the following conditions:

- Control of ventricular arrhythmias or heart block associated with digitalis toxicity;
- Emergency treatment of hypercalcemia;
- Extreme conditions of metal toxicity
- treatment of chronic iron overload due to blood transfusions (transfusional hemosiderosis)
- Wilson’s disease (hepatolenticular degeneration); and
- Lead poisoning.

Other applications of chelation therapy are considered **investigational**, including, but not limited to:

- atherosclerosis (i.e., coronary artery disease or peripheral vascular disease)
- multiple sclerosis;
- arthritis;
• hypoglycemia;
• autism
• Alzheimer’s disease; and
• diabetes

Policy Guidelines
None

Rationale
The policy was created in 1995 with a search of the MEDLINE database. The policy was updated regularly with literature searches using MEDLINE, most recently the literature was searched through February 2012.

Chelation therapy is an established treatment for the medically necessary indications listed here, particularly for the treatment of metal toxicity and transfusional hemosiderosis. Thus, literature searches have focused on the use of chelation therapy for other conditions including, but not limited to, atherosclerosis, autism, Alzheimer’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
celation 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)

Conclusions: 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 thrombocytopenia, are never seen in autistic children. (9) In 2007, a
systematic review by Ng and colleagues concluded that there was 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 suggest 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.

Conclusions: 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
Richie and colleagues, was published in 2003. Patients were treated patients with PBT1, a
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. At 36 weeks, there was no statistically significant
between-group difference in cognition measured by the Alzheimer’s Disease Assessment Scale
– Cognitive (ADAS-Cog scale). One patient in the treatment group developed impaired visual
acuity and color vision during weeks 31 to 36 while she was receiving clioquinol, 375 mg twice
daily. Her symptoms resolved on treatment cessation.

Further studies of PBT1 have been abandoned in favor of a successor compound, PBT2.
Lannfelt and colleagues 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). (14) 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. (15)

Conclusions: 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.

Left ventricular hypertrophy in patients with diabetes

One RCT was identified; it was published in 2009 by Cooper and colleagues in New Zealand and evaluated the effect of copper chelation using oral trientine on left-ventricular hypertrophy in 30 patients with type 2 diabetes. (16) 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.

Conclusions: One small RCT with limitations represents insufficient evidence that chelation therapy is effective for treating cardiovascular disease in patients with diabetes. Additional RCTs with larger numbers of patients and that report health outcomes such as cardiovascular events and mortality are needed.

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.

Ongoing clinical trials

Trial to Assess Chelation Therapy (TACT) (NCT00044213) (17): This placebo-controlled RCT is sponsored by the National Heart, Lung, and Blood Institute, in collaboration with the National Center for Complementary and Alternative Medicine. The trial is evaluating the impact of EDTA chelation therapy on mortality in patients with coronary artery disease; estimated enrollment is n=1,700. The estimated study completion date is June 2012.

Summary

Chelation therapy is an established treatment for the medically necessary indications listed in the policy statement, such as treatment of metal toxicity and transfusional hemosiderosis. There is insufficient evidence that chelation therapy improves health outcomes for patients with other conditions including, but not limited to, atherosclerosis, autism, Alzheimer’s disease, diabetes and arthritis. Thus, chelation therapy for these other applications is investigational.

Practice Guidelines and Position Statements
A 2004 clinical practice guideline from the American College of Physicians (18) 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.)"

In 2005, the American College of Cardiology (19) 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.)"

References:


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<tr>
<th>Codes</th>
<th>Number</th>
<th>Description</th>
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<td>Intravenous infusion, for therapy, prophylaxis, or diagnosis (specify substance or drug); initial, up to 1 hour</td>
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<td>96366</td>
<td>each additional hour (list separately in addition to code for primary procedure)</td>
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<td>Injection of antidote (heavy metal antagonist)</td>
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**Type of Service:** Injection
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Chemical endarterectomy