

CHELATION THERAPY FOR NON-OVERLOAD CONDITIONS

Policy Number: REHABILITATION 015.26 T1

Effective Date: November 1, 2018

[Instructions for Use](#) ⓘ

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Related Policy

- [Omnibus Codes](#)

CONDITIONS OF COVERAGE

Applicable Lines of Business/Products	This policy applies to Oxford Commercial plan membership.
Benefit Type	General benefits package
Referral Required (Does not apply to non-gatekeeper products)	No
Authorization Required (Precertification always required for inpatient admission)	Yes
Precertification with Medical Director Review Required	No
Applicable Site(s) of Service (If site of service is not listed, Medical Director review is required)	Outpatient, Inpatient, Skilled Nursing Facilities, Home

COVERAGE RATIONALE

Chelation for heavy metal toxicity and overload conditions (e.g., iron, copper, lead, aluminum) is proven and medically necessary and not addressed in this policy.

Chelation therapy is unproven and not medically necessary for treating "mercury toxicity" from dental amalgam fillings.

Randomized controlled trials do not identify a causal association between amalgam fillings and various systemic symptoms and disorders attributed to mercury.

Chelation therapy is unproven and not medically necessary for treating chronic, progressive diseases (not involving heavy metal toxicity or overload conditions) and other disorders including but not limited to:

- Alzheimer's disease
- Apoplectic coma
- Autism spectrum disorder
- Cancer
- Cardiovascular disease
- Cholelithiasis
- Chronic fatigue syndrome
- Chronic renal insufficiency
- Defective hearing
- Diabetes
- Diabetic ulcer
- Gout

- Erectile dysfunction
- Multiple sclerosis
- Osteoarthritis
- Osteoporosis
- Parkinson's disease
- Raynaud's disease
- Renal calculus
- Rheumatoid arthritis
- Schizophrenia
- Scleroderma
- Snake venom poisoning
- Varicose veins
- Vision disorders (glaucoma, cataracts, etc.)

Much of the evidence supporting chelation treatment for other chronic progressive disease is based on testimonials and single-case studies. Thus, there still is no scientific evidence that demonstrates any benefit from this form of therapy.

APPLICABLE CODES

The following list(s) of procedure and/or diagnosis codes is provided for reference purposes only and may not be all inclusive. Listing of a code in this policy does not imply that the service described by the code is a covered or non-covered health service. Benefit coverage for health services is determined by the member specific benefit plan document and applicable laws that may require coverage for a specific service. The inclusion of a code does not imply any right to reimbursement or guarantee claim payment. Other Policies may apply.

HCPCS Code	Description
J3490	Unclassified drugs
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

DESCRIPTION OF SERVICES

Chelation therapy involves the administration of naturally occurring or chemically designed molecules to bind and excrete a specific toxin in the body. The specific medication, route, method and site of administration of the chelating agent vary depending on the specific agent used, the level of toxicity, and other clinical indications. Heavy metal toxicity most often treated with chelation therapy includes that caused by iron, copper, lead, aluminum, and mercury.

Mercury Poisoning: Chelation therapy has been proposed to treat metal toxicity from dental amalgam fillings, but it has not been shown that mercury amalgams cause harm to individuals with dental fillings, except in rare cases of allergy.

Non-Overload Conditions: Chelation therapy has been proposed as a treatment for a variety of Non-Overload Conditions in which the removal of heavy metal ions is hypothesized to reduce oxidative damage caused by the production of hydroxyl radicals. However, the possible mechanism of chelators as therapeutic agents for Non-Overload Conditions is not fully understood. Chelation has been investigated as a treatment of numerous Non-Overload Conditions including, but not limited to, cardiovascular disease, rheumatoid arthritis (RA), cancer, and diabetes.

CLINICAL EVIDENCE

Non-Overload Conditions

Well-designed, published and peer-reviewed studies do not support chelation treatment for chronic, progressive diseases such as cardiovascular disease, atherosclerosis, diabetes, cancer, Alzheimer's disease, autism spectrum disorder, or RA. There are no studies available regarding chelation therapy for the treatment of apoplectic coma, chronic fatigue syndrome, chronic renal insufficiency, defective hearing, diabetic ulcer, cholelithiasis, gout, erectile dysfunction, multiple sclerosis, osteoarthritis, osteoporosis, Parkinson's disease, Raynaud's disease, renal calculus, schizophrenia, scleroderma, snake venom poisoning, varicose veins, or vision disorders. There is insufficient evidence that chelation therapy is safe and effective to remove other undesirable metabolites or toxins, or have a positive impact on clinical outcomes for other disease states.

Alzheimer's Disease (AD)

Increased levels of aluminum have been discovered in several brain regions of individuals with AD. Epidemiological studies have linked the concentration of aluminum in drinking water and the increased occurrence of the disease. Scientists have postulated that chelation therapy might promote beneficial results in AD patients by inhibiting the deposition of aluminum in the brain or by preventing iron from catalyzing the formation of toxic hydroxyl radicals. Aluminum chelators may also reactivate aluminum metalloenzyme complexes in AD patients and permit redistribution of aluminum in the brain.

A Cochrane systematic review was conducted by Sampson et al. to evaluate the efficacy of metal protein attenuating compounds (MPACs) for the treatment of cognitive impairment due to AD. The primary outcome measure was cognitive function (measured by psychometric tests). Two MPAC trials were identified. One trial compared clioquinol (PBT1) with placebo in 36 patients and 32 had sufficient data for per protocol analysis. There was no statistically significant difference in cognition (as measured on the Alzheimer's Disease Assessment Scale - Cognition (ADAS-Cog)) between the active treatment and placebo groups at 36 weeks, and there was no significant impact on non-cognitive symptoms or clinical global impression. In the second trial a successor compound, PBT2, was compared with placebo in 78 participants with mild AD. There was no significant difference in the Neuropsychological Test Battery (NTB) composite or memory between placebo and PBT2 at week 12. However, 2 executive function component tests of the NTB showed significant improvement over placebo in the PBT2 250 mg group from baseline to week 12. There was no significant effect on cognition on Mini-Mental State Examination (MMSE) or ADAS-Cog scales. PBT2 did have a favorable safety profile. The authors concluded that there is an absence of evidence as to whether clioquinol (PBT1) is safe or has any positive clinical benefit for patients with AD, and cited that further development of PBT1 has been abandoned. The second trial of PBT2 was more rigorously conducted and appeared to be safe and well tolerated in individuals with mild AD after 12 weeks. Larger trials are now required to demonstrate cognitive efficacy (2014).

Several studies have reported some improvement in cognitive function or slowing of the rate of decline in patients treated with clioquinol or deferoxamine (Crapper Mclachlan, 1991; Regland, 2001; Ritchie, 2003). However, these studies were small, only two were placebo-controlled, and none were double-blind, and therefore no conclusions regarding efficacy of chelation therapy for AD can be made on the basis of these studies.

Autism Spectrum Disorder (ASD)

A Cochrane systematic evidence review found no clinical trial evidence to suggest that pharmaceutical chelation is an effective intervention for ASD. One study was found, which was conducted in 2 phases. During Phase 1, 77 children with ASD were randomly assigned to receive 7 days of glutathione lotion or placebo lotion, followed by 3 days of oral dimercaptosuccinic acid (DMSA). A total of 49 children who were found to be high excretors of heavy metals during Phase 1 continued on to Phase 2 and received 3 days of oral DMSA or placebo followed by 11 days off, with the cycle repeated up to 6 times. The second phase assessed the effectiveness of multiple doses of oral DMSA compared with placebo in children who were high excretors of heavy metals and who received a 3 day course of oral DMSA. Overall, no evidence suggests that multiple rounds of oral DMSA had an effect on ASD symptoms. The authors concluded that given prior reports of serious adverse events, such as hypocalcaemia, renal impairment and reported death, the risks of using chelation for ASD currently outweigh proven benefits. In their opinion, evidence that supports a causal link between heavy metals and autism must be identified and methods that ensure the safety of participants are imperative before further trials are conducted (James, et al. 2015).

A National Institute for Health and Care Excellence (NICE) guideline on autism does not recommend the use of chelation for the management of core symptoms of autism in adults. (2016)

Cardiovascular Disease

Chelation therapy has been proposed as a treatment of coronary artery disease, based in part on the hypothesis that chelation could remove atherosclerotic calcium deposits or provide an antioxidant benefit.

In November 2012, the American Heart Association (AHA) announced preliminary results of the Trial to Assess Chelation Therapy (TACT). TACT was a multicenter, double-blind, randomized efficacy trial that took place from 2002 to 2011. Patients (n=1700) were randomized to receive 40 infusions of a 500-mL chelation solution or a placebo infusion, with a second randomization to an oral vitamin and mineral regimen or an oral placebo. Each patient received 40 infusions, each lasting at least 3 hours. Researchers found that patients receiving the chelation solution had fewer serious cardiovascular events than the control group: 26% versus 30%. Cardiovascular events were defined as death, heart attack, stroke, coronary revascularization, and hospitalization for angina. Because the level of statistical difference between the groups was small, it is not known whether the effect will be reproducible in a real-world scenario. Investigators cautioned that the results need to be reproduced and understood before consideration of clinical application.

Further analysis of the TACT data by Lamas et al. (2013) reported that in stable patients with a history of myocardial infarction (MI), the use of an intravenous chelation regimen with Edetate calcium disodium (EDTA) modestly reduced

the risk of a variety of adverse cardiovascular outcomes compared to placebo. The authors stated that while these results should guide further research, there still is not sufficient evidence to support routine use of chelation therapy in post-MI patients.

Using the TACT data, an initial subgroup analysis showed a greater effect of EDTA treatment among participants with a self-reported history of diabetes. Further examination of the data in patients with diabetes demonstrated a 41% overall reduction in the risk of any cardiovascular event; a 40% reduction in risk of cardiovascular mortality, non-fatal stroke, or non-fatal MI; a 52% reduction in recurrent heart attacks; and a 43% reduction in death from any cause. In contrast, there was no significant benefit of EDTA treatment in the subgroup of 1,045 participants who did not have diabetes. The authors note that results of this analysis support the initiation of clinical trials in patients with diabetes and vascular disease to replicate these findings, and to define the mechanisms of benefit. However, it was also concluded that there is not enough evidence to support the routine use of chelation therapy for this population (Escolar et al. 2013).

Trial to Assess Chelation Therapy 2 (TACT2) is a randomized, double blind controlled factorial clinical trial of edetate disodium-based chelation and high-dose oral vitamins and minerals to prevent recurrent cardiac events in diabetic patients with a prior MI. This study is currently recruiting participants. Additional information is available at www.clinicaltrials.gov.

Rheumatoid Arthritis

In a review of chelation for non-overload conditions, Voest et al. (1994) summarized the available literature regarding RA. In 6 small studies with patient populations ranging from 6 to 18 patients, deferoxamine improved the clinical symptoms and reduced anemia in the majority of patients. However, the authors concede that the preponderance of evidence regarding chelation for RA is derived from small numbers of patients treated for a short amount of time. The authors assert that larger studies are needed to determine the role of iron chelators in the treatment of RA.

In a second review, Ghio et al. (1997) hypothesized that iron chelation may play a vital role in reducing neutrophilic inflammation. Thus, these investigators also contend that additional trials of iron chelation for RA are warranted.

Professional Societies

American Academy of Family Physicians (AAFP)

The AAFP endorses the 1983 American Medical Association (AMA) Diagnostic and Therapeutic Assessment of Chelation Therapy which states, "Chelation therapy with ethylene diamine tetraacetic acid or its sodium salt is not an established treatment for atherosclerotic vascular disease" (2013).

American College of Cardiology (ACC)

The ACC concluded that although disodium EDTA is approved by the U.S. Food and Drug Administration for specific indications, such as iron overload and lead poisoning, it is not approved for use in preventing or treating cardiovascular disease. Accordingly, the group finds that the usefulness of chelation therapy in cardiac disease is highly questionable (Fihn et al. 2014).

American College of Physicians (ACP)

A clinical practice guideline published by the ACP recommended against the use of chelation therapy to prevent MI or to reduce symptomatic angina (Snow et al. 2004).

Mercury Poisoning

Randomized controlled trials have concluded that mercury amalgams used in dental restorations cause no harm to patients. (Shenker et al., 2008; Bellinger, 2006; DeRouen, 2006)

Langworth et al (2002) conducted a study evaluating residents in the Stockholm County area with morbidities attributed to dental fillings ('amalgam disease'). Participants were referred to a special Amalgam Clinic and received examination by a dentist (n=428), a physician (n=379), and a psychologist (n=360). Gender ratio was 69% women and 31% men and the mean patient age was 46 years. No positive correlation was found between the amount of amalgam and somatic symptoms or psychological effect parameters. The authors concluded that the data gathered did not support the hypothesis that release of mercury from amalgam fillings is the cause of 'amalgam disease', but suggest that there may be various explanations for the patients' complaints.

Professional Societies

American Cancer Society (ACS)

The ACS stated that chelation therapy is a proven treatment for lead poisoning and poisoning from other heavy metals. However, available scientific evidence does not support claims that the treatment benefits patients with cancer, heart disease, or any medical problems other than heavy-metal poisoning. (2014)

American Dental Association (ADA)

The ADA website contains statements from a number of organizations that there is no known association between dental amalgam and a specific disease. Examples of these organizations include but are not limited to:

- Alzheimer's Association
- Lupus Foundation of America
- Mayo Clinic
- National Multiple Sclerosis Society

U.S. FOOD AND DRUG ADMINISTRATION (FDA)

Edetate calcium disodium, also called EDTA is approved for the treatment of lead poisoning in adults and children.

Desferal which is the trade name for DFO (deferoxamine mesylate, deferoxamine B mesylate, deferoxamine, desferrioxamine, desferrioxamine) and Jadenu (deferasirox) are FDA-approved chelators for iron overload.

Dimercaprol (BAL oil) is also approved for the heavy metal chelation of iron.

Deferiprone (Ferriprox) is FDA approved for the treatment of iron overload in patients with hematologic disorders requiring chronic transfusion therapy.

Additional information is available at: <http://www.accessdata.fda.gov/scripts/Cder/ob/default.cfm>. (Accessed January 19, 2018)

The FDA reaffirmed its position that amalgam is a safe and effective dental material after thoroughly reviewing the current science and updating its consumer advisory on dental amalgam fillings. Additional information is available at: <http://www.ada.org/en/press-room/news-releases/2015-archive/january/fda-updates-consumer-advisory>. (Accessed January 19, 2018)

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The foregoing Oxford policy has been adapted from an existing UnitedHealthcare national policy that was researched, developed and approved by UnitedHealthcare Medical Technology Assessment Committee. [2018T0051Q]

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POLICY HISTORY/REVISION INFORMATION

Date	Action/Description
11/01/2018	<ul style="list-style-type: none"> • Reorganized policy template: <ul style="list-style-type: none"> ○ Simplified and relocated <i>Instructions for Use</i> ○ Removed <i>Benefit Considerations</i> section • Updated coverage rationale; modified language to clarify the listed services are: <ul style="list-style-type: none"> ○ Proven and medically necessary (as described) ○ Unproven and not medically necessary (as described) • Archived previous policy version REHABILITATION 015.25 T1

INSTRUCTIONS FOR USE

This Clinical Policy provides assistance in interpreting UnitedHealthcare Oxford standard benefit plans. When deciding coverage, the member specific benefit plan document must be referenced as the terms of the member specific benefit plan may differ from the standard plan. In the event of a conflict, the member specific benefit plan document governs. Before using this policy, please check the member specific benefit plan document and any applicable federal or state mandates. UnitedHealthcare Oxford reserves the right to modify its Policies as necessary. This Clinical Policy is provided for informational purposes. It does not constitute medical advice.

The term Oxford includes Oxford Health Plans, LLC and all of its subsidiaries as appropriate for these policies. Unless otherwise stated, Oxford policies do not apply to Medicare Advantage members.

UnitedHealthcare may also use tools developed by third parties, such as the MCG™ Care Guidelines, to assist us in administering health benefits. UnitedHealthcare Oxford Clinical Policies are intended to be used in connection with the independent professional medical judgment of a qualified health care provider and do not constitute the practice of medicine or medical advice.