MEDICAL POLICY	Chelation Therapy for Non-Overload Conditions (All Lines of Business Except Medicare)
Effective Date: 4/1/2022  4/1/2022 Medical Officer Date	Medical Policy Number: 102 Medical Policy Committee Approved Date: 9/14; 9/15: 5/16; 7/17; 9/17; 1/19; 2/2020; 2/2021; 2/2022

See Policy HCPCS CODE section below for any prior authorization requirements

SCOPE:

Providence Health Plan, Providence Health Assurance, Providence Plan Partners, and Ayin Health Solutions as applicable (referred to individually as "Company" and collectively as "Companies").

APPLIES TO:

All lines of business except Medicare

BENEFIT APPLICATION

Medicaid Members

Oregon: Services requested for Oregon Health Plan (OHP) members follow the OHP Prioritized List and Oregon Administrative Rules (OARs) as the primary resource for coverage determinations. Medical policy criteria below may be applied when there are no criteria available in the OARs and the OHP Prioritized List.

POLICY CRITERIA

Note: This policy does not address chelation therapy for overload conditions, which may be considered medically necessary and standard of care. Please see the policy description section for more information regarding these conditions.

I. Chelation therapy is considered **not medically necessary and not covered** for the treatment of non-overload conditions, including, but not limited to, the following (A.-J.):

   A. Alzheimer's disease
   B. Autism spectrum disorder
   C. Cancer
   D. Cardiovascular disease
   E. Chronic fatigue syndrome

F. Diabetes
G. Lyme Disease
H. Multiple sclerosis
I. Parkinson's disease
J. Rheumatoid arthritis

BILLING GUIDELINES

The following codes are not specific to chelation therapy, but may be billed in conjunction with M0300 or S9355.

- 96365-96368
- J0470
- J0600
- J0895
- J3520

M0300 and S9355 will be covered if billed with one of the following diagnosis codes:

- D56.1
- D57.00–D57.819
- D61.01
- E72.01
- E83.01
- E83.111
- E83.52
- K74.3
- K74.4
- K74.5
- T36-T65 with fifth or sixth character 1-4 or 6
- T45.4x1A - T45.4x5S
- T46.0x1A – T46.0x4S
- T47.1X5A –T47.1x5S
- T56.0x1A - T56.0x4S
- T56.1x1A - T56.1x4S
- T56.3x1A - T56.3x4S
- T56.4x1A - T56.4x4S
- T56.5x1A - T56.5x4S
- T56.811A - T56.814S
- T56.891A - T56.894.S
- T56.91xA - T56.94xS
- T57.0x1A - T57.0X4S
- T80.92xA - T80.92xS
- K71.XXX
- N14.3
- T57.2XX

HCPCS CODES

All Lines of Business Except Medicare	
No Prior Authorization Required	
G0068	Professional services for the administration of anti-infective, pain management, chelation, pulmonary hypertension, and/or inotropic infusion drug(s) for each infusion drug administration calendar day in the individual's home, each 15 minutes
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

Overload Conditions

The presence of certain heavy metals (e.g., iron) within the body is essential for bodily functions.[1] However, the build-up of heavy metals or metals that do not naturally occur within the body is toxic. The most common heavy metals to cause overload toxicity are iron, lead, copper, and aluminum.

Iron overload is primarily due to hereditary hemochromatosis, a genetic disease that causes excess absorption of iron from the diet. This iron accumulates in body organs, which can eventually cause inflammation and organ damage. Serious health effects of hemochromatosis include liver cirrhosis, liver cancer, heart abnormalities, and diabetes. Iron overload can also occur in patients with genetic hemoglobin disorders (e.g., sickle cell anemia and thalassemia major) who require frequent blood cell transfusions. The frequent blood transfusions can cause excess iron build-up and eventual toxicity.

Although decreasing, "lead poisoning continues to be the leading environmental threat to children in the United States."[1] Lead poisoning can cause severe symptoms and neurological deficits, including seizures, coma, and permanent neurologic loss or death over an extended period of time.

Copper overload is commonly due to Wilson's disease, a genetic disease that causes an abnormal amount of copper to accumulate in the body. Wilson's disease can cause liver disease and neurological or psychiatric abnormalities. If untreated, Wilson's disease is fatal.

Aluminum overload is frequently present in patients with renal failure who are undergoing dialysis. "Aluminum can be present in the water used to prepare dialysate and in aluminium-containing phosphate binders, and can cause adverse effects on bone, the haematopoietic system, and the brain."[1]

Non-Overload Conditions

Non-overload conditions are those not related to heavy metal overload toxicity. Chelation therapy is purported to treat other conditions, including, but not limited to the following:

- Alzheimer's disease- a chronic neurodegenerative disease that destroys memory and other neurologic functions
- Autism spectrum disorder- a developmental disorder that affects "a spectrum" of social and behavioral skills
- Cardiovascular disease- a heart and blood vessel disease that includes numerous problems (e.g, heart attack, stroke) primarily due to atherosclerosis (the build-up of plaque on artery walls)[2]
- Rheumatoid arthritis- an autoimmune disease that causes chronic inflammation of the joints.[3]

Chelation Therapy

"To reduce heavy metal build-up, patients who have heavy metal overload undergo chelation therapy. During chelation therapy, heavy metals bind to a molecule called a chelator, natural or synthetic compounds that have a high affinity and specificity for heavy metal ions. When the chelator and heavy metal ion bind together, they form a water-soluble complex that can then be excreted in the urine or feces."[1]

REVIEW OF EVIDENCE

A review of the ECRI, Hayes, Cochrane, and PubMed databases was conducted regarding the use of chelation therapy as a treatment for non-overload conditions. Below is a summary of the available evidence identified through December 2021.

Alzheimer's Disease

In 2008, Sampson et al. conducted a Cochrane systematic review to evaluate metal protein attenuating compounds for the treatment of Alzheimer's dementia.[4] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcome of interest was cognitive function (as measured by psychometric tests). Secondary outcomes included clinical global impression, quality of life, functional performance, safety, and death.

After systematic review, the authors identified two randomized double-blind, placebo-controlled trials (RCTs) as eligible for inclusion (n=114). The first RCT found no statistically significant difference in cognition (measured using the Alzheimer's Disease Assessment Scale-Cognition [ADAS-Cog]) between the treatment and control groups at 36 weeks follow-up. "The difference in mean change from baseline ADAS-Cog score in the treatment arm compared with the placebo arm at weeks 24 and 36 was a difference of 7.37 (95% confidence interval (CI) 1.51 to 13.24) and 6.36 (95% CI -0.50 to 13.23), respectively."[4] The second RCT found no significant difference in the Neuropsychological Test Battery (NTB) composite, memory, or executive scores between the treatment and placebo groups at 12 weeks follow-up.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers, contacting study authors for additional information, assessment of heterogeneity, and sensitivity analyses. Limitations were present in the small number of included studies (possible publication bias) and the inability to conduct a meta-analysis due to significant heterogeneity between studies. Ultimately, the authors concluded "there is an absence of evidence as to whether metal protein attenuating compounds has any positive clinical benefit for patients with AD, or whether the drug is safe."[4]

Autism Spectrum Disorder

In 2015, James et al. conducted a Cochrane systematic review to evaluate chelation for autism spectrum disorder (ASD).[5] Independent reviewers systematically identified eligible studies, assessed quality, and extracted data. Study authors were also contacted, if necessary, for additional information or data. The primary outcomes of interest were core symptoms of ASD (social interaction, communication, and stereotypy) and adverse events. Secondary outcomes included non-core behaviors of ASD (irritability, aggression, hyperactivity, insomnia, and self-injury), quality of life, and heavy metal levels.

After systematic review, the authors only identified one study as eligible for inclusion (n=77). The study included 2 phases. During phase 1, all children were randomized to the treatment or placebo groups for 7 days. The children who were found to be high excreters of heavy metals during phase 1 (n=49) continued to phase 2. During phase 2 they received 3 more days of treatment or placebo, followed by 11 days off. The cycle of 3 days on and 11 days off was repeated up to 6 times. Overall, there was no evidence to suggest that multiple rounds of chelation therapy had an effect on ASD symptoms.

Strengths of this systematic review include the gathering of evidence, assessment of quality, and extraction of data by several independent reviewers. However, significant methodological limitations are present due to the small number of included studies and the small sample size. The authors concluded "no clinical trial evidence was found to suggest that pharmaceutical chelation is an effective intervention for ASD. 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."[5]

Cardiovascular Disease

- In 2020, Cochrane published a systematic review evaluating the safety and efficacy of chelation therapy for the treatment of atherosclerotic cardiovascular disease.[6] In total, 5 studies assessing 1,993 randomized participants were included for review. Follow-up varied from 1 year to 5 years. Sample sizes in individual studies ranged from 10 to 1,708 participants, with all studies comparing chelation to a placebo. Two studies with coronary artery disease participants reported no evidence of a difference in all-cause mortality between chelation therapy and placebo. One study with coronary artery disease participants reported no evidence of a difference in coronary heart disease deaths between chelation therapy and placebo. Two studies with coronary artery disease participants reported no evidence of a difference in myocardial infarction, angina, and coronary revascularization. Two studies (one with coronary artery disease participants and one with peripheral vascular disease participants) reported no evidence of a difference in stroke. Meta-analysis of maximum and pain-free walking distances three months after treatment included participants with peripheral vascular disease and showed no evidence of a difference between the treatment groups. Quality of life outcomes were reported by two studies that included participants with coronary artery disease, but authors were unable to pool the data due to different methods of reporting and varied criteria. The quality of evidence was determined to range from "very low" to "low." Investigators concluded that evidence was insufficient to determine the effectiveness or

ineffectiveness of chelation therapy in improving clinical outcomes of people with atherosclerotic cardiovascular disease.

- In 2017, Sultan and colleagues conducted a narrative review of evidence published through February 2017, evaluating the use of chelation therapy in the treatment of cardiovascular disease.[7] Among recent studies, only the results from the largest RCT to date – the 2013 TACT study (n = 1,708; mean follow-up time= 4.6 years) – were analyzed in detail.
  The TACT study's primary outcome was the assessment of a composite endpoint comprising total mortality, recurrent myocardial infarction (MI), stroke, coronary revascularization, or hospitalization for angina. Investigators found that patients treated with chelation experienced fewer events than patients treated with placebo (26% versus 30%; HR, 0.82, 95% CI 0.69–0.99; *p* = 0.035.) However, there was no significant difference among patient groups in either total mortality (10% vs. 11% in placebo group; HR, 0.93[95% CI, 0.70–1.25]; *p* = 0.64) or any other individual components of the primary endpoint. Subgroup analysis showed significant reductions among chelation group patients with anterior MI (37% HR, 0.63, 95% CI 0.47–0.86; *p* = 0.03) and diabetes (39% reduction, HR: 0.61; 95% CI: 0.45–0.83; *p* = 0.02). Limitations of the TACT study included inadequate blinding among both patients and investigators, and a substantial loss to follow-up (18%), nearly all due to withdrawal of consent following discovery that the therapy was not FDA-approved. The trial's investigators concluded that these results were not sufficient to support the routine use of chelation therapy in the treatment of cardiovascular disease.

  Given the paucity of evidence to date, review authors concluded that chelation therapy remains unproven for treatment of atherosclerosis. Reviewers noted that an ongoing clinical trial (i.e. TACT2) trial may clarify chelation therapy's use in post-MI diabetic patients.

- In 2016, Ibad and colleagues conducted a non-systematic review, evaluating the general effects of chelation therapy on cardiovascular disease.[8] Investigators searched PubMed for eligible studies, assessed quality, and extracted data. Sample sizes ranged from 10 to 1708; follow-up times were unreported in the review. In total, investigators reviewed 38 studies, including 20 case series, and 7 RCTs, including the TACT study referenced above. Reviewers determined the overall quality of evidence to be low: each of the reviewed case series was uncontrolled, observational or retrospective with a small sample size, and most available RCT's suffered from small sample sizes, incomplete randomization and inadequate blinding. Review authors concluded that chelation therapy's safety and efficacy for the treatment of cardiovascular disease remains unclear and that additional, rigorous trials are needed.

- In 2013, Lamas and colleagues conducted a double-blind, placebo-controlled, randomized trial (RCT) to assess the effect of disodium EDTA chelation regimen on cardiovascular events in patients with previous myocardial infarction (the TACT RCT).[9] A total of 1,708 patients were enrolled and randomized to receive either 40 infusions of chelation solution (n=839) or a placebo (n=869). The infusions were administered for weekly for 30 weeks, followed by 10 infusions 2 to 8 weeks apart. The primary outcome of interest was a composite endpoint of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The secondary outcome of interest was the rate of cardiovascular death, reinfarction, or stroke.

A total of 38 patients (16%) in the chelation group and 41 patients (15%) in the placebo group discontinued infusions due to adverse events. The results indicated no statistically significant difference between groups on total mortality (chelation: 87 deaths [10%]; placebo: 93 death [11%]). "The effect of EDTA chelation on the components of the primary end point other than death was of similar magnitude as its overall effect (MI: chelation, 6%; placebo, 8%; HR, 0.77 [95% CI, 0.54-1.11]; stroke: chelation, 1.2%; placebo, 1.5%; HR, 0.77 [95% CI, 0.34-1.76]; coronary revascularization: chelation, 15%; placebo, 18%; HR, 0.81 [95% CI, 0.64-1.02]; hospitalization for angina: chelation, 1.6%; placebo, 2.1%; HR, 0.72 [95% CI, 0.35-1.47])."[9]
Methodological strengths of this RCT included the prospective, randomized, controlled design, use of a placebo group, large sample size, double blinding, and conducting intention-to-treat analysis. Limitations of this study include the losses to follow-up (n=79) and the use of a composite, invalidated primary endpoint. Ultimately, the authors concluded "among stable patients with a history of MI, use of an intravenous chelation regimen with disodium EDTA, compared with placebo, modestly reduced the risk of adverse cardiovascular outcomes, many of which were revascularization procedures. These results provide evidence to guide further research but are not sufficient to support the routine use of chelation therapy for treatment of patients who have had an MI."[9]

- In 2014, Escolar et al. conducted a subgroup analysis of the TACT RCT to evaluate the effect of EDTA-chelation regimen on patients with diabetes mellitus and prior myocardial infarction.[10] Of the 1,708 patients enrolled into the TACT RCT, 633 patients had diabetes mellitus (n=322 EDTA; n=311 placebo). A statistically significant difference was observed between the treatment and placebo group for the primary composite endpoint (total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina). A statistically significant reduction was also seen between groups for all-cause mortality and the secondary endpoint (cardiovascular death, reinfarction, or stroke); however, after adjustment for multiple subgroups, the results were no longer statistically significant.

  Methodological strengths of this RCT included the prospective, randomized, controlled design, use of a placebo group, large sample size, double blinding, and conducting intention-to-treat analysis. Limitations are present due to the post hoc subgroup analysis and use of a composite, invalidated, primary endpoint. The authors concluded "Post-myocardial infarction patients with diabetes mellitus aged ≥50 demonstrated a marked reduction in cardiovascular events with EDTA chelation. These findings support efforts to replicate these findings and define the mechanisms of benefit. However, they do not constitute sufficient evidence to indicate the routine use of chelation therapy for all post-myocardial infarction patients with diabetes mellitus."[10]

Rheumatoid Arthritis

No systematic reviews or randomized controlled trials evaluating chelation therapy for rheumatoid arthritis were identified. Two nonrandomized studies were identified[11,12]; however, the significant methodological limitations and the historical nature of these studies does not permit meaningful conclusions.

Other Non-Overload Conditions

Due to insufficient evidence, no conclusions were possible regarding chelation therapy for autism spectrum disorder, cancer, chronic fatigue syndrome, diabetes, multiple sclerosis, Parkinson's disease, or rheumatoid arthritis.

CLINICAL PRACTICE GUIDELINES

No clinical practice guidelines were identified that specifically addressed chelation therapy for the treatment of Alzheimer's disease or rheumatoid arthritis.

Autism Spectrum Disorder

National Institute for Health and Care Excellence (NICE)

In 2021, NICE recommended against the use of chelation in managing autism symptoms in adults.[13] In 2021, NICE recommended against the use of chelation in any context to manage autism symptoms in children and young people.[14]

Cardiovascular Disease

Canadian Cardiovascular Society (2014)

In 2014, the Canadian Cardiovascular Society reviewed published evidence and recommended against the use of chelation therapy in improving angina or exercise tolerance in patients with stable ischemic heart disease (conditional recommendation, moderate-quality evidence).[15]

American College of Cardiology

The 2014 evidence-based clinical practice guideline for the diagnosis and management of patients with stable ischemic heart disease stated, "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 writing group finds that the usefulness of chelation therapy in cardiac disease is highly questionable."[16]

American Academy of Family Physicians (AAFP)

The 2013 evidence-based AAFP policy states the following:

> "The AAFP endorses the 1983 AMA Diagnostic and Therapeutic Assessment of Chelation Therapy which reads as follows: chelation therapy with ethylenediaminetetraacetic acid or its sodium salt is not an established treatment for atherosclerotic vascular disease."[17]

INSTRUCTIONS FOR USE

Company Medical Policies serve as guidance for the administration of plan benefits. Medical policies do not constitute medical advice nor a guarantee of coverage. Company Medical Policies are reviewed annually and are based upon published, peer-reviewed scientific evidence and evidence-based clinical practice guidelines that are available as of the last policy update. The Companies reserve the right to determine the application of Medical Policies and make revisions to Medical Policies at any time. Providers will be given at least 60-days notice of policy changes that are restrictive in nature.

The scope and availability of all plan benefits are determined in accordance with the applicable coverage agreement. Any conflict or variance between the terms of the coverage agreement and Company Medical Policy will be resolved in favor of the coverage agreement.

REGULATORY STATUS

Mental Health Parity Statement

Coverage decisions are made on the basis of individualized determinations of medical necessity and the experimental or investigational character of the treatment in the individual case. In cases where medical necessity is not established by policy for specific treatment modalities, evidence not previously considered regarding the efficacy of the modality that is presented shall be given consideration to determine if the policy represents current standards of care.

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