

Review

## An Update and Review of Unconventional Metals Testing and Treatment

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**Abstract:** Most patients who receive unconventional testing for metals do not have any remarkable exposure history and typically lack symptoms or objective findings compatible with classic heavy metal intoxication. Unconventional tests results are usually promoted by alternative practitioners as the basis for recommending, promoting, and selling to the patient questionable and often inappropriate therapies/interventions supposedly aimed at “detoxification”. Most of these patients will have no evidence of overexposure to metals on the basis of a thorough history and will have levels of metals on conventional tests performed at reliable laboratories that are undetectable, within population background ranges or above population background, but well below levels associated with toxicity.

**Keywords:** heavy metals; chelation; provoked urine testing; unconventional; alternative medicine

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## 1. Introduction

Throughout human history, attempts have been made to explain the unexplainable. This is particularly true for human illness. Dating back hundreds of years, illnesses have been blamed on curses, witches, foods, and even the weather. Currently, heavy metal toxicity or “increased body burden of metals” has become a target to help explain the unfortunate presence of some unexplained medical complaints, as well as debilitating illnesses. Some metals such as zinc, iron, and cobalt are present naturally in humans and have important physiologic functions. Other metals like lead, mercury, and arsenic have no known biological function and their presence in tissues is never normal. Yet, because these elements are naturally in the environment, most people will have some present in their bodies. In excessive concentrations, any metal can cause toxicity, and the signs, symptoms, diagnosis, and treatment of these toxicities has been studied and evaluated.

Some practitioners ascribe various illnesses to the effects of heavy metals, sometimes without adequate scientific evidence. Such debilitating conditions as autism spectrum disorder, multiple sclerosis, heart disease, macular degeneration, and various types of cancer, as well as medically unexplained problems (e.g., chronic fatigue, fibromyalgia, “chemical sensitivities” or environmental intolerances) have been attributed to different types of heavy metal toxicity. Because many of these conditions are severe, devastating, and some without a clear etiology, they are targets for alternative explanations. Many people who suffer from these and other conditions are seeking explanations and are looking for additional options to treat their symptoms and decrease their suffering. In these circumstances, many patients turn to alternative testing and treatments. Worldwide, there are other approaches to treating health problems in addition to conventional, allopathic medicine. Healing practices such as Ayurveda, homeopathy, and traditional Chinese medicine have been used to treat illness for thousands of years [1–3]. Some of these practices have migrated, and their use is growing in many countries, including the United States and Europe.

## 2. Epidemiology

Complementary and alternative medicine use has been increasing in the United States and Europe for decades [4], although accurate assessment of the prevalence of usage is challenging. In one 2002 study, as many as one in every three US adults reported using some type of complementary or alternative medical modality [5]. In addition, a 2013 study of twenty European countries found 56% of the general population, including 52% of children under 18, had used some type of complementary or alternative medicine in the prior year [6]. Because a majority of alternative metals testing and treatment is done in nonconventional medical settings, assessing the numbers of people affected by these processes can be challenging. According to the 2007 National Health Statistics Report on complementary and alternative medicine use in the US, 111,000 adults and 72,000 children reported receiving some type of chelation in 2006 [7].

One of the most common conditions in which unconventional metals testing and treatment is used is for autism spectrum disorders (ASD). When vaccines were (mistakenly) associated with ASD, the finger was pointed at the ethyl mercury that was in the vaccine as a component of the preservative, thimerosal [8]. Despite robust scientific and epidemiologic data rejecting mercury as a cause of

ASD [9–12], and that mercury has been removed from most childhood vaccines, many practitioners continue to advocate for testing and chelation for patients with ASD. It has been estimated that about 7%–8% of children with ASD have received chelation [13]. With the prevalence of ASD estimated at 1%, that adds up to almost half a million children who have been chelated for this condition alone [14].

### 3. Unconventional Metal Testing

Standard laboratory practices are diagnostic methods approved by the US Food and Drug Administration and other governmental regulatory agencies after demonstration of reliability, efficacy and safety. According to the American Association of Clinical Chemistry (AACC), “Four indicators are most commonly used to determine the reliability of a clinical laboratory test. Two of these, accuracy and precision, reflect how well the test method performs day to day in a laboratory. The other two, sensitivity and specificity, deal with how well the test is able to distinguish disease from absence of disease” [15]. Unconventional methods are “non-standard” and based on tests that are either (a) ineffective, (b) effective but misinterpreted, (c) effective but misused [16], or (d) developed in a research context and then applied to clinical assessment and decision making. Unfortunately, unconventional testing for heavy metals and other minerals abounds and is utilized by certain physicians, chiropractors, naturopaths, and other types of practitioners usually associated with alternative or unconventional health practices. Results of such testing can generate unnecessary and unproven treatments, delay accurate medical diagnosis, and result in subsequent consultations with alternative as well as conventional physicians. Common methodologies including provoked urine testing, scalp hair analysis, “intraerythrocyte” or red blood cell metal testing, and fecal metals testing. This testing is frequently offered to address a variety of symptoms which are being attributed to metals, and usually in the absence of any clear exposure history. The common feature of these tests is that commercial laboratories make simultaneous determinations of multiple metals and minerals (usually in the range of 15 to 40 elements tested), and the results are then often promoted as characterizing a patient’s general health and nutritional status, as well as exposure to toxic heavy metals [17].

#### 3.1. Provoked Urine Testing

Provoked urine heavy metals testing is done by giving subjects a chelating agent and then testing their urine for the presence of one or multiple metals. This testing is often performed in individuals who have no history of exposure to a particular metal, and usually with little or no specific symptoms characteristic of the toxicity to a particular metal. Patients are given their results showing graphs of their post-chelation urinary metals levels in the low, medium, or high range, which is in comparison to a “healthy population under non-provoked conditions.” Patients and other providers often miss the fine print at the end of the report indicating the definition of the reference population who have not received chelators [18]. Advocates of provoked urine metals testing argue that exposure history is not always adequate for predicting who has excessive heavy metal burden and toxicity. In addition, it has been claimed that pre and post chelation testing can identify which chelator is most effective in increasing urinary elimination in that patient [19]. In other cases, providers will check pre and post-chelation tests, inferring that a difference indicates a “hidden” body burden of a toxic metal that

just needed to be mobilized. However, multiple studies have shown that virtually everyone has a rise in the urinary excretion of metals after a dose of chelation, regardless of exposure or baseline level of the metal [17,20–22], indicating that the technique does not actually predict body burden in a scientific manner. Evidence based scientific studies at this time do not provide evidence to support the value and continued use of provoked urine testing. Concerns for misdiagnosis and the dangers of unnecessary treatments are prevalent. The Pediatric Environmental Health Specialty Units (PEHSU) and the American Academy of Clinical Toxicology do not recommend its use [23]. In addition, the American College of Medical Toxicology has published a position statement advocating against the use of post chelator challenge urinary metal testing based on a lack of scientific validation and a lack of demonstrated benefits to the patients [24].

### 3.2. Scalp Hair Testing

Although hair metals are widely used in epidemiology for specific metals, scalp hair testing with broad metals panels is another controversial method used clinically by alternative providers to evaluate individual patients for heavy metal exposure and toxicity. Office-based hair collection methods are not standardized. Strands are usually obtained from the scalp-neck junction. In the laboratory, it is washed to decrease confounding from external contamination and then dissolved in a solvent to facilitate measurement [25]. At first glance, hair sampling seems like a great option for metal testing: metals stay in hair for a long period of time, and long hair may give a historical record of exposure. In addition, collecting it is not invasive and causes minimal discomfort to the patient. While many experts believe hair analysis can indicate an exposure to a particular metal, particularly methyl mercury [17], it cannot determine dosage. Also, scalp hair is readily contaminated by deposits from external environmental exposures. Positive tests can be the result of external contamination like dust, smoke, or hair care products, since metals can bind to the hair follicle both from external and internal exposures. In addition, there is little consensus on the possibility of contamination during the collection procedure (from metal tools) and the washing and processing during analysis in the laboratory [26]. Further complicating the interpretation of hair analysis, is the fact that background contamination levels have not been established for most metals [27] and results across different commercial laboratories have been found to be very inconsistent [26]. Attempts have been made to establish hair reference limits for some metals, including mercury and arsenic, however, the accuracy of these reference limits is controversial [28]. An exception to this is maternal hair methyl mercury levels and risk for adverse fetal outcomes, which have been shown to correlate in research studies [29] and for which there are also better correlations with hair and blood [30]. Hair analysis has been useful in research situations in which there is a careful standardized collection, and group analysis [30]. Hair analysis can be useful in selected clinical and forensic circumstances, to determine if there has been a past exposure to a metal that is quickly excreted such as arsenic. However, analyzing hair, particularly for multiple elements, has been proven to be highly inaccurate, in which duplicate samples have been sent to the same laboratory and to multiple other laboratories with markedly different results [26].

### 3.3. Red Blood Cell Metal Testing

Red Blood Cell or intra-erythrocyte metal testing is offered by certain commercial laboratories (usually not mainstream clinical laboratories affiliated with hospitals), and is claimed to be useful for determining need for mineral and vitamin supplementation. According to one of these testing laboratories, “RBC element levels are very useful for assessing: cardiotoxic influences (magnesium, potassium); anti-inflammatory processes (selenium, copper, zinc); anemia (copper, iron); immunological function (zinc, copper, magnesium), and glucose tolerance (chromium, manganese, and possibly vanadium)” [31]. In addition, it is claimed that RBC elements testing can be used to assess particular toxic elements that accumulate in erythrocytes, including arsenic, cadmium, lead, methyl mercury, and thallium. One study looked at inorganic and organic mercury levels in whole blood, RBCs, hair, and urine, and found RBC mercury levels to be a reasonable proxy for methylmercury exposure, however, there was large inter-individual variation [32]. Multiple searches of online medical databases were unable to uncover peer-reviewed scientific literature regarding the accuracy, methods, or usefulness of red blood cell testing of other metals.

### 3.4. Fecal Metals Testing

Fecal testing for multiple metals is offered by specialized commercial laboratories as an assessment of environmental exposure to many metals including mercury, cadmium, lead, antimony, and uranium. The rationale for this type of testing is that these metals are excreted via the biliary system after metabolism in the liver and can therefore be measured in the feces. It has also been purported that fecal metals testing can assess the efficacy of “natural” detoxification remedies and the degree that they are enhancing fecal elimination of toxic heavy metals [33]. In addition, fecal metal’s testing is described as an indicator of dietary metal exposure. As advertised from one testing laboratory, it is described as “not developed to replace the pre and post urinary toxic metals provocation test” but is recommended for people in whom a urine collection is challenging, or people wanting to monitor the “efficacy” of their “non-pharmaceutical” detoxification methods [33]. Multiple searches of online medical databases were unable to uncover peer-reviewed scientific literature regarding the accuracy, methods, or usefulness of fecal metals testing.

## 4. Unconventional Treatments

Reported positive results from these different unsubstantiated tests often lead consumers to seek out treatments for their alleged heavy metal toxicity. Many of the purported treatments, such as vitamin supplementation and chelators, can be purchased from the same practitioners and companies that advocated for the testing, creating an inherent conflict of interest. These treatments come with varying consequences. Direct health effects from adverse reactions and side effects of the treatments occur. In addition, many patients elect to take these unproven treatments in place of more conventional treatments, leaving them without access to potentially helpful traditional therapies. The cost of these unconventional treatments is often quite large, ranging from a few dollars for vitamin and herbal supplements, to hundreds of dollars for a course of chelation [18] to thousands of dollars for multiple

modality treatments [34,35]. Because these treatments are unconventional, they are rarely covered by health insurance.

#### 4.1. Chelation

Chelation therapy is the process of giving a medication (chelator) that will bind to a metal atom, creating a complex that is eliminated from the body in a rate or quantity increased from natural physiologic processes. Chelation has been used in standard medical settings to increase the elimination of excess lead, arsenic, mercury, iron and other heavy metals under circumstances of clinically recognized poisoning and/or very large exposures (Table 1). Depending on the chelator, these agents can be administered orally, intravenously, or intramuscularly.

**Table 1.** Common chelation agents.

Chelator	Used for	Known adverse effects
Dimercaptosuccinic Acid (DMSA, Succimer, Chemet, Captomer)	Arsenic, Mercury, Lead, Cadmium, Silver, Tin, Copper	Transaminitis, allergic reactions
Dimercaptopropanesulfonic Acid (DMPS)	Arsenic, Mercury, Lead, Cadmium, Tin, Silver, Copper, Selenium, Zinc, Magnesium	Stevens Johnson Syndrome
Edetate Calcium Disodium (EDTA)	Lead, Cadmium, Zinc Ischemic Heart Disease	Renal Failure, hypotension, cardiac arrhythmias, hypocalcemia (if di-sodium version without calcium used)
D-penicillamine	Copper, Arsenic, Zinc, Mercury, Lead	Allergic reactions, copper deficiency
Dimercaprol (BAL, British Anti-Lewisite)	Arsenic, Gold, Mercury, Lead	Painful injection, peanut oil base

Some practitioners have advocated for unconventional methods for administering chelating agents, such as through topical (dermatological) and/or rectal administration. These are not FDA approved methods for delivery, and since they are still under the category of “supplement” they have not been studied with the same rigor as a medication [36]. In particular, EDTA suppositories are commonly found and promoted on internet sites. Removal of heavy metals by EDTA rectal suppositories is claimed to be non-invasive, quick, ready-to-use, and medically equal to IV chelation [37,38]. The proposed mechanism [39] is that EDTA is absorbed into systemic circulation via the bowel wall, chelates toxic metals in the circulation and from deposits in tissue storage sites and then excretes them. The two most common formulas of EDTA rectal suppositories on the current U.S. market are calcium di-sodium EDTA and magnesium di-potassium EDTA. Although Ellithorpe, R. *et al.* claims that Detoxamin™ (Calcium di-sodium EDTA suppository) has been proven clinically effective to decrease levels of lead, arsenic, cadmium, uric acid, and blood cholesterol in clinical studies [37,38], the amount of systemic absorption of the EDTA suppositories is debated [38].

The manufacturer of one EDTA suppository called Medicardium® claimed that this product could reduce the symptoms of diabetes type 1 [40]. However, the result of the study has been called into question because it was conducted in only 29 subjects and data on the placebo-only subjects is not given, as the majority of them did not complete the study. In addition, the follow up period of blood

glucose level was only 2 months and the study was not designed to control for other confounding factors. In October 2010, concern about the efficacy and safety of these agents prompted the US Food and Drug Administration (FDA) to publish a warning to marketers of some of these suppositories, claiming that they were violating federal law by making fraudulent health claims [23,41]. Even though adequate scientific evidence for these claims is lacking, EDTA suppositories are still being used by practitioners, and sold to consumers without adequate understanding of confirmed benefits or full understanding of potential risks.

While some chelators can be obtained from traditional pharmacies via prescription from a licensed medical practitioner, others are available from alternate sources such as compounding pharmacies and via multiple internet sites. Many of these internet available agents come in atypical formulations and concentrations potentially leading to dosage errors and toxicity from the chelating agents [42]. Toxicity from chelation agents ranges from allergic reactions to alteration of liver and kidney function.

A 2006 MMWR report from the Center for Disease Control describes the deaths of 3 patients who received disodium EDTA, as opposed to the calcium di-sodium EDTA that is used in cases of severe lead toxicity. These deaths were attributed to cardiac arrhythmias from hypocalcemia, since the di-sodium EDTA will bind calcium that is in the blood. In one case, a 53-year-old woman received 700 mg IV di-sodium EDTA in a naturopath's office in an effort to remove toxic heavy metals from her body. Fifteen minutes after the infusion, she experienced a cardiac arrest. Despite extensive calcium repletion during the resuscitation, her calcium level remained extremely low and she was unable to be resuscitated [43,44]. Another concern from chelation includes the depletion of essential metals such as copper, zinc, selenium, cobalt, and iron. Because most chelators are not specific to one type of metal, the enhanced elimination can extend to these other metals that are needed for physiologic functioning [42].

The cost of chelation varies widely depending on the agent, the route of administration, and the length of time it is used. Because the testing leading to a need for chelation is often unconventional, and indications for chelation are not evidence based, most chelation for these purposes is not covered by insurance, potentially incurring large expense upon the patient. One author reports buying a transdermal formulation of DMPS for a study, and paying 420 dollars [36].

It has been proposed that chelation with EDTA has a beneficial effect on ischemic heart disease due to removal of excess calcium and iron thought to contribute to coronary artery vascular plaques, as well as decreased inflammation from heavy metal induced oxidative stress [45–47]. A 2001 study to determine the efficacy of EDTA in patients with stable ischemic heart disease did not find a beneficial effect on any of their end points (exercise time to ischemia, functional reserve for exercise, and quality of life) [48]. In 2013, a large, federally funded trial of di-sodium EDTA in heart disease found modest reductions of risk of adverse cardiac outcomes including need for revascularization compared to placebo [49]. However, the reliability of the findings of this study have been called into question based on concerns of subject retention, unblinding of the sponsors, and use of subjective end points [50,51]. The lack of scientific evidence of benefit from EDTA in ischemic heart disease has not dissuaded thousands of patients who continue to seek out these treatments in hope of improving their health.

#### 4.2. Vitamin and Herbal Supplementation

Supplementation with various vitamins and minerals has been suggested as a method to help increase the elimination of toxic metals, either by chelation or the effects of antioxidants [19,52]. Some agents, such as algal polysaccharides and chlorella are thought to bind certain metals in the gut, preventing enterohepatic recirculation and enhancing elimination. Cilantro has been reported to enhance mercury elimination via unknown mechanisms, although evidence remains limited [53].

Glutathione is frequently recommended as a physiologic chelator and antioxidant. It does not have oral bioavailability due to rapid deactivation in the GI system; however, IV, transdermal, and inhaled preparations have been advertised and used [19]. *N*-acetylcysteine (NAC), a sulfhydryl group donor, acts as a precursor for glutathione in the liver, and also has anti-oxidant and free radical scavenging properties. It is commonly recommended as an oral bioavailable version of glutathione. While it has been scientifically proven as an effective antidote for acetaminophen toxicity [54], its role in chelation or treatment of heavy metal toxicity is unclear [55].

Other proposed supplements for metal toxicity include taurine, methionine, alpha lipoic acid, ascorbic acid, and selenium among others [19]. Adverse effects of these agents, when taken in moderate doses are generally low; however, their efficacy in treating heavy metal toxicity has not been scientifically proven. Improving general nutritional status of patient's with inadequate intake or chronic disease may be of additional benefit. However, ingestion of excessive amounts can be dangerous. For example, excessive selenium intake results in alopecia, nail dystrophy, gastrointestinal upset, and problems with memory and concentration [56].

Bentonite clay has been suggested as an additional agent to chelate multiple metals. The theory is that this particular type of clay creates a large negative charge when applied topically to the skin. Because the metals of interest are positively charged metal ions, it is purported that they will be drawn out through the skin by the large negative charge from the clay. In addition, some people advocate for oral ingestion of this clay to bind metals in the gastrointestinal system. Topical application of the clay is unlikely to have adverse or beneficial effects (except cost); however, oral ingestion raises concerns for intestinal obstruction and electrolyte abnormalities. One case reported in 2006, described a 3-year-old child who had been given bentonite clay orally and rectally, and presented to a hospital with profound hypokalemia (serum potassium 0.9 mmol/L) [57].

In addition, whenever vitamin and mineral supplementation is discussed, it is important to acknowledge that vitamins and minerals are not subject to the same governmental oversight as pharmaceutical medications. Because of this, the actual agent and concentration in vitamin and mineral preparations is not always consistent or accurate with the labeling, and unwanted contaminants or ingredients may be present.

#### 4.3. Amalgam Filling Removal

Dental amalgams have been the object of study and conjecture related to mercury exposure, toxicity, and general health complaints. When swallowed, elemental mercury is not absorbed, making dental amalgams unlikely to be a source of any mercury toxicity. However, when vaporized and inhaled, mercury can be absorbed, and in large enough doses, cause toxicity. Because of this, some

concern persists for patients with significant mercury amalgam fillings that have severe bruxism. In non-bruxism patients, the risk from amalgam removal may exceed the risk from keeping the amalgams. Studies have not shown differences in mercury levels (as measured in blood, urine, or hair), between patients with mercury dental amalgams and matched controls [58]. Although there may be measurable differences in brain and kidney mercury levels in those with amalgam fillings compared to those without [59], there is no evidence this results in any measurable adverse health effects. The New England Children's Amalgam Trial (NECAT), a five-year randomized trial of 534, six- to ten-year-old children that compared the neuropsychological outcomes of those whose caries were restored using dental amalgam with the outcomes of those whose caries were restored using mercury-free resin-based composite, found no evidence that mercury exposure was significantly associated with an increased in neuropsychological dysfunction [60,61]. In addition, studies looking at improvement of amalgam-associated complaints after chelation found no significant differences in patients that received DMSA and those that had a placebo [17,62,63].

## 5. Mitigation of Risk

With the plethora of information available to patients via the internet, providers in all areas of health care are likely to have patients who have undergone unconventional metal testing or treatment, or who have questions about it. Helping patients make informed decisions about the risks and benefits of these tests and treatments is an essential part of modern health care. Keeping abreast of recent developments, fads, and methods is important for providers to help their patients. To assist providers and patients in this education, toxicologists and occupational and environmental medicine physicians are essential. Professional societies from these groups can also be useful sources of information [23,24]. In addition the United States Food and Drug Administration (FDA) Health Fraud and Consumer Outreach Branch has taken an active role in trying to help regulate some of these chelation products. For example, in October 2010, The FDA issued warning letters to eight companies who were marketing their agents as dietary supplements but fraudulently claiming to treat and prevent disease, which is a violation of the Federal Food, Drug, and Cosmetic Act [64]. While these actions can help (two of the companies voluntarily took their product off the market), the FDA is limited by lack of enforcement power and lack of funding to effectively regulate all of the available over-the-counter products.

## 6. Approach to the Patient

A thorough history regarding potential dietary, environmental and occupational sources of metals exposure should be conducted along with a physical examination directed at the patient's complaints. The direction and priorities of the history, physical and further testing should be based on the following considerations: what are the patient's actual complaints; what objective findings and evidence-based diagnoses have been made in the past by reliable physicians; what metals were allegedly found to be elevated by previous unconventional tests; and any treatments such as chelation, amalgam removal, *etc.* that have already been administered.

## 7. Conclusions

The current body of scientific knowledge does not support these non-standard unconventional testing or treatments for heavy metal toxicity. Because the benefits to the patient are not clear, and these tests and treatments pose significant potential risks, their use is not recommended and is strongly discouraged.

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## Author Contributions

Stefanos N. Kales and Rose H. Goldman conceptualized and designed the review. Diana J. Felton drafted the initial manuscript. Stefanos N. Kales and Rose H. Goldman critically reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

## Conflicts of Interest

The authors declare no conflict of interest.

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