



## How Can We “Get the Lead Out” Without Chelators?

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Received: 10 May 2021 / Revised: 10 May 2021 / Accepted: 17 May 2021 / Published online: 24 May 2021  
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**Keywords** Succimer · Chelators · Lead poisoning · Drug shortages

In January 2021, Recordati Rare Diseases announced a disruption in the production of succimer [1]. Succimer is not the only chelator impacted by drug shortages, leaving patients with limited treatment options [2].

Lead toxicity disproportionately impacts vulnerable populations, including children of low socioeconomic status, those living in urban areas and developing nations, refugees, and immigrants [3]. In 2017, over 1 million deaths and 24.4 million years of healthy life years lost were attributed to lead exposure globally. The same study attributed 63% of idiopathic developmental disability to lead exposure [3]. Numerous public health organizations have focused on decreasing environmental exposure, improving screening, and establishing treatment guidelines for lead poisoning [4, 5].

The cornerstone of management of lead poisoning is removal from the exposure, decontamination, and optimizing nutritional status. When blood lead levels are significantly elevated, chelation is indicated [6]. The most commonly used chelators for severe lead toxicity are dimercaprol (British Anti-Lewisite, BAL) and calcium disodium EDTA. For less severe cases and those transitioned to oral therapy, succimer is used. Unithiol (DMPS) and penicillamine are second-line chelators [6]. Timely administration of chelators is essential as

lead encephalopathy is potentially fatal. The World Health Organization (WHO) has listed several chelators on the Model List of Essential Medications for adults and children. [7].

Despite their need, many chelators have been impacted by drug shortages. According to the University of Utah Drug Information Services, there have been 10 different chelator shortages since 2006. BAL has been implicated in the greatest number of shortages (4), with the most recent extending into 2021. The longest shortage was for penicillamine (22 months). Currently, BAL and succimer are on shortage.

Chelator shortages put clinicians in a difficult position. Unlike other shortages where some product may still be available in a different strength or formulation, often no product is available during chelator shortages. Chelators do not have a large market share, commonly manufactured by a single company in one formulation. As such, there is often not an alternative strength, concentration, or formulation that can be used as a substitute [1].

Alternative chelators will be used out of necessity, but outcomes data are limited. Succimer has been used successfully when BAL and calcium disodium EDTA were unavailable [8]. DMPS is efficacious for the treatment of lead poisoning, but it is not approved by the U.S. Food and Drug Administration (FDA). DMPS is not commercially available and must be obtained from a compounding pharmacy [9]. Penicillamine is an effective chelator; however, its use has fallen out of favor because of adverse effects. Penicillamine may still have a role in limited resource settings or large outbreaks [10].

In addition to limited supplies, there are other barriers to chelator access. Chelators are not routinely stocked by local pharmacies. They are more often carried by specialty pharmacies and have to be shipped to patients or healthcare facilities. Insurance authorization may be required, which can further delay treatment. Rising drug costs may limit access to those who are uninsured or underinsured. Hospitals may choose not to stock expensive therapies that may rarely be used and

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Supervising Editor: Michael Hodgman, MD

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purchase on demand. For example, the wholesale acquisition cost for a bottle containing 100 penicillamine 250 mg capsules is nearly \$20,000 [11].

The burden of lead poisoning is greatest on vulnerable populations, often with overlapping socioeconomic problems, creating further disparity. A recent investigation identified nearly 2000 water systems in the USA with elevated lead levels [12]. Schools may have limited testing or no testing of their water supplies due to budgetary constraints, placing children at risk [12]. Communities and families often cannot afford lead mitigation, such as replacing lead pipes, installing new filter systems, or relocating. Patients may be unable to obtain chelators due to aforementioned cost constraints. These problems are magnified in other parts of the world where resources are even scarcer [13].

Chelator shortages have implications for patient care. When there is a shortage of first line-agents, patients receive less effective or more toxic alternatives [1, 14]. Lead poisoning primarily impacts children, and there are limited data for therapeutic alternatives in pediatric patients. Some drugs may not be available in pediatric dosages or palatable formulations [6]. Treatment delays can occur when providers must obtain alternative stock or used compounded product. It can take over 24 hours to obtain DMPS from a compounding pharmacy. Medication errors occur when providers use agents they are less familiar with or when drugs are extemporaneously compounded.

Shortages increase healthcare costs. Patients who have treatment delays or adverse effects stay in the hospital longer [14]. When chelators cannot be obtained for outpatient use, patients will also stay in the hospital longer. Compounded medications are more costly, as specialty pharmacies are used and the product is drop shipped. The wholesale acquisition cost for 10 g of DMPS powder is \$3565 [11].

There have been many proposed mitigation strategies, but there is no simple solution to the shortage problem. Chelator shortages have been largely attributed to a lack of redundancy and resiliency in the supply chain [15]. Chelators are usually produced by a single manufacturer in a single facility. When a problem occurs at a facility, there is no alternative manufacturer to “pick up the slack.” In 2012, progress was made with the passage of the Food and Drug Administration Safety and Innovation Act (FDASIA). FDASIA requires manufacturers to notify FDA of anticipated shortages and expanded FDA authority in managing shortages, but fell short of allowing for penalties for noncompliant manufacturers [16]. FDAISA also called for the establishment of a Drug Shortage Task Force, which recommended developing a quality rating system to incentivize manufacturers to invest in facilities that promote a sustainable supply. More recently, the Coronavirus Aid, Relief, and Economic Security Act required drug manufacturers develop risk management and redundancy plans for their supply chain [17]. Unfortunately, little progress has been

made and mechanisms for implementation and accountability are poorly defined.

FDA cannot force a manufacturer to produce a medication, no matter how great the need. There may be a role for incentives to encourage the production of chelators, which have low profit margins. Incentives could include tax credits or rebates for keeping manufacturing facilities in good repair, temporary market exclusivity, or accelerated approval for another product. Another possibility would be to remove price limitations imposed by Medicare on generic injectable drugs, increasing profit margins; however, this would not have a significant impact on chelators. Incentives have unintended consequences if not appropriately balanced. Shifting production to products on shortage to gain incentives may precipitate shortages of other drug. Allowing for longer market exclusivity and removing reimbursement limits can increase costs [14, 18].

FDA allows for extension of expiration dates if the manufacturer can provide stability data, but this only works to mitigate shortages when manufacturers have the data [19]. In the case of BAL, the manufacturer was not able to provide data beyond November 2020. Manufacturers should be required to collect and disclose stability data in case of shortage, so existing product can be used safely.

FDA has permitted temporary importation of drugs to ensure adequate supply. Importation is a limited mitigation strategy because it is difficult to find a foreign source that can provide drug to the U.S. market that without precipitating a shortage in the exporting nation. This is of ethical importance with chelators because the largest burden of lead toxicity is outside of the USA [4].

Another mitigation strategy is the use of compounded drugs; however, there are limitations to this approach. Treatment of lead toxicity is time critical and the turn around time to obtain a compounded drug is 24 hours in the best circumstances. Because of cost and stability concerns, compounded drugs are rarely kept on hand and are made on demand. Additionally, raw materials may not be available for compounding, as was the case for BAL. Compounded drugs have not undergone the same review process that FDA approved drugs do, and safety and efficacy data may be lacking [20]. Compounding errors and microbial contamination can occur when good manufacturing practices are not followed [21]. Despite these concerns, compounded drugs can serve an important medical need in times of shortage. When parenteral compounded chelators are used, drug should be obtained from compounders that are registered with FDA [20].

In seeking sustainable solutions to chelator shortages, we must consider the immediate need to care for patients. Healthcare systems and poison centers should develop proactive shortage protocols, with careful monitoring of stock. Poison centers and medical toxicologists can serve as resources regarding the use of less familiar chelators and assist in managing patients. Regional poison centers can coordinate

with hospitals they manage to help locate chelators. Toxicologists can assist in ethical allocation of limited chelator supply. Children who are more susceptible to the adverse effects of lead and those with higher levels should receive priority when there is not enough product to meet demand [14].

Medical toxicologists can serve an important role by furthering research regarding the use of alternative chelators. When a different regimen is used because of a shortage, they can collect and publish outcomes data to inform future use. Adverse drug events or inability to administer chelator due to a shortage should be reported to MedWatch and the FDA's drug shortage site. Medical toxicologists and poison centers can collaborate with policymakers, industry, larger healthcare organizations, and other stakeholders.

## Conclusion

Shortages of chelators and barriers to access impact the most vulnerable populations in the USA and globally. Sustainable solutions, with engagement of stakeholders, are critical to address this public health problem and to correct long-standing healthcare and social disparities.

**Sources of Funding** No funding was provided for this study.

## Declarations

**Conflict of Interest** Maryann Mazer-Amirshahi and Mark B. Mycyk are members of the editorial board of *Journal of Medical Toxicology* (JMT).

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