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Trends in Shortages of Lead Chelators From 2001 to 2022

James D. Whitledge, MD; Pelayia Soto, PharmD; Kieran M. Glowacki, BA; Diane P. Calello, MD; Erin R. Fox, PharmD; and Maryann Mazer-Amirshahi PharmD, MD, MPH, PhD

OBJECTIVE The study aims to describe drug shortages affecting lead chelators in the United States from 2001 through 2022.

METHODS Drug shortage data were retrieved from the University of Utah Drug Information Service from January 1, 2001, through December 31, 2022. Shortages of first- and second-line lead chelators were analyzed. Drug class, formulation, administration route, shortage reason, shortage duration, generic status, single-source status, and presence of temporally overlapping shortages were examined. Total shortage months, percentages of study period on shortage, and median shortage durations were calculated.

RESULTS Thirteen lead chelator shortages were reported during the study period. Median duration was 7.4 months and the longest shortage (24.8 months) involved calcium disodium edetate. Calcium disodium edetate and dimercaprol had the greatest number of shortages, 4 each, and 61.5% of shortages involved parenteral medications. Median shortage duration was 14.2 months for parenteral agents and 2.2 months for non-parenteral agents. All shortages involved generic, single-source products. Supply/demand and manufacturing problems were the most common shortage reasons provided. Overlapping shortages occurred for 3.7% of the study period. Median shortage duration increased from 3 to 11 months in the second half of the study period, and 61.5% of shortages occurred in the second half of the study period.

CONCLUSIONS All chelators experienced multiple shortages, which became increasingly frequent and prolonged over time. Concurrent shortages occurred, potentially hampering substitution between different agents. Health care stakeholders must build supply chain resilience and develop guidelines regarding how to modify chelation therapy based on shortage conditions.

ABBREVIATIONS ASHP, American Society of Health-System Pharmacists; AWP, average wholesale price; BAL, British Anti-Lewisite or dimercaprol; BLL, blood lead level; $CaNa_2EDTA$, calcium disodium edetate; DMPS, 2,3-dimercaptopropanol-sulfonic acid or unithiol; DMSA, dimercaptosuccinic acid or succimer; FDA, US Food and Drug Administration; UUDIS, University of Utah Drug Information Service

KEYWORDS calcium disodium edetate; dimercaprol; drug shortage; lead poisoning; penicillamine; succimer

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Introduction

Lead is a posttransition metal that is toxic to humans. It is commonly encountered in man-made products, including paint, pipes, and ammunition, and in the natural world through activities such as artisanal mining.[1–3] Average US population blood lead concentrations (blood lead levels [BLLs]) have declined over time because of successful public health interventions. This is reflected in the Centers for Disease Control and Prevention's blood lead reference value, representing the 97.5th percentile of US children ages 1 to 5 years, decreasing from 60 mcg/dL in 1960 to 3.5 mcg/dL in 2021.[4,5] There is, however, no accepted safe BLL.[5] Neurocognitive development may be adversely affected by values below 10 mcg/dL.[6] As BLL increases, behavior, coordination, and nerve conduction are also affected, and BLLs greater than 70 mcg/dL may cause encephalopathy, cerebral edema, and seizures.[2,7] Lead poisoning can also have non-neurologic effects, including decreased growth, delayed puberty, anemia, abdominal pain and constipation, impaired renal function, and hypertension.[2,8] These effects occur via multiple mechanisms, including interference with reactions mediated by thiol group–containing enzymes; chemical mimicry of other divalent cations essential to cellular processes, such as calcium, magnesium, and zinc; and disruption of synaptic pruning necessary for normal neurologic development in young children.[4]

Pediatric patients are at high risk for lead toxicity for multiple reasons. Infants and toddlers may place lead-containing objects in their mouths during environmental exploration, and ingest or inhale lead dust due to proximity to floors and windowsills. Children also have increased gastrointestinal tract lead uptake compared

Table 1. Chelation Therapy in Children

BLL	Chelator
<45 mcg/dL	Chelation not routinely indicated
45–69 mcg/dL without encephalopathy	Outpatient: oral DMSA (consider oral penicillamine as second-line if DMSA unavailable) Inpatient: intravenous $CaNa_2EDTA$
≥70 mcg/dL or encephalopathic	Intramuscular BAL + intravenous $CaNa_2EDTA$*

BAL, British Anti-Lewisite or dimercaprol; BLL, blood lead level; $CaNa_2EDTA$, calcium disodium edetate; DMSA, dimercaptosuccinic acid

*Some clinicians may administer $CaNa_2EDTA$ monotherapy if encephalopathy is not present and BLL is <100 mcg/dL, because of BAL's adverse effects. If combination therapy is administered, first dose of BAL is given 4 hours prior to initiation of $CaNa_2EDTA$.

with adults, particularly if iron-deficient. Finally, children possess an immature blood-brain barrier more permeable to lead, especially before 6 years of age, which is compounded by the developing brain's vulnerability to neurotoxic substances.[7]

Treatment of lead toxicity at lower BLLs consists of source removal, optimizing nutrition (including adequate iron and calcium intake), educational enrichment programs, and gastrointestinal decontamination if lead is present in the gastrointestinal tract.[9] In the United States, pharmacotherapy consists of 4 lead chelators. Chelation is indicated at higher BLLs, typically at least 45 mcg/dL, in pediatric patients.[10] Adult patients are less vulnerable to the toxic effects of lead, particularly neurotoxicity, and therefore usually have a higher BLL treatment threshold but may still require timely access to chelator therapy.[11] Oral dimercaptosuccinic acid (DMSA, succimer), intravenous calcium disodium edetate ($CaNa_2EDTA$), and intramuscular British Anti-Lewisite (BAL, dimercaprol) are first-line agents, and oral penicillamine is a second-line agent (Table 1). Parenthetically, 2,3-dimercaptopropanol-sulfonic acid (DMPS, unithiol) is a lead chelator approved for oral and parenteral use in Europe, but it is only available on a limited basis in the United States in compounded form, which is not approved by the US Food and Drug Administration (FDA).[12–14]

The 4 commercially available lead chelators in the United States have a crucial role in treating lead poisoning. Unfortunately, they have been affected by recurrent drug shortages, and no viable therapeutic alternative is currently available.[12,15,16] These shortages, which may be prolonged and affect multiple chelators simultaneously, have negative implications for all patients meeting chelation criteria, and may disproportionately affect vulnerable pediatric populations already at risk for undertreatment because of decreased access and financial means to obtain pharmacotherapy.[12] Although data describing adverse pediatric outcomes in the United States from lead chelator shortage are lacking, the 2010 mass lead poisoning in Zamfara State, Nigeria, exemplifies the danger of insufficient access to chelators. In Zamfara, more than 400 pediatric fatalities attributable to lead toxicity occurred during 3 months prior to chelation therapy becoming available. Following implementation of DMSA monotherapy and environmental remediation by Médecins Sans Frontières, only 6 deaths attributable to lead toxicity occurred during 13 months.[17] Given this need for adequate access to lead chelators and their repeated scarcity within the United States, a better understanding of the shortage landscape is needed. The objective of this investigation is to describe trends in drug shortages affecting lead chelators in the United States from 2001 through 2022.

Materials and Methods

Drug shortage data were retrieved from the University of Utah Drug Information Service (UUDIS) from January 1, 2001 through December 31, 2022.[18] UUDIS began collecting national drug shortage data in January 2001, and they publish drug shortage information on a public Web site (https://www.ashp.org/Drug-Shortages/) hosted by the American Society of Health-System Pharmacists (ASHP). UUDIS and ASHP define a drug shortage as "a supply issue that affects how the pharmacy prepares or dispenses a drug product or influences patient care when prescribers must use an alternative agent." UUDIS receives voluntary reports of shortages via the ASHP Web site, and clinical pharmacists at UUDIS then research and verify each reported shortage. This includes determining all potential manufacturers and drug presentation National Drug Codes for the product in question. Each manufacturer is contacted to determine which National Drug Codes are in shortage (backorder, allocation, etc.) nationally. UUDIS does not track regional shortages and cannot reliably distinguish limited drug availability from complete absence. UUDIS considers a shortage resolved when all suppliers have all presentations available or have discontinued their products. UUDIS also follows the FDA drug shortage Web site and will resolve shortages when the FDA considers the shortage resolved unless clinically relevant presentations remain unavailable.[19]

Using UUDIS, all shortages of first-line chelators for lead poisoning (BAL, $CaNa_2EDTA$, DMSA) reported between January 1, 2001, and December 31, 2022, were examined. Shortages of penicillamine, a second-line lead chelator, occurring during this time period were also examined. Data were analyzed focusing on formulation, administration route, shortage reason, shortage duration, generic status, and whether drugs were single-source (made by only 1 manufacturer). The presence of temporally overlapping shortages was also evaluated. Business decisions resulting in

Table 2. Lead Chelators Affected by Shortage 2001–2022

Medication	Number of Shortages (n = 13)	Total Shortage, mo	Percent of Study Period on Shortage	Median (IQR) Shortage Duration, mo
$CaNa_2EDTA$	4 (1 active)	60.3	22.5	21.2 (5.3)*
BAL	4	29.5	11.0	5.8 (4.5)
DMSA	2	8.3	3.1	4.2 (3.5)
Penicillamine	3	25.2	9.4	2.2 (11)

BAL, British Anti-Lewisite or dimercaprol; $CaNa_2EDTA$, calcium disodium edetate; DMSA, dimercaptosuccinic acid

* Includes 1 ongoing shortage.

Table 3. Reported Reasons for Shortage

Shortage Reason	Number of Shortages (n = 13)	Total Shortage, mo	Percent of Study Period on Shortage	Median (IQR) Shortage Duration, mo
Unknown	7 (1 active)	61.5	33	7.7 (15.4)*
Supply/demand	2	21.3	8	10.7 (3.6)
Manufacturing	2	25.7	9.6	12.9 (8.4)
Business decision	1	0.5	0.2	0.5†
Discontinued	1	n/a	n/a	n/a

n/a, not applicable

* Includes 1 ongoing shortage.
† Only 1 shortage, therefore no IQR calculated.

permanent product discontinuation were included in the counting of overall shortage number but not included in shortage duration calculations. Total shortage months, percent of study period on shortage, median shortage duration, and associated IQR were calculated for all chelators. UUDIS was not evaluated for DMPS shortages because DMPS is not commercially available in the United States.

Results

There were 13 shortages of lead chelators reported to UUDIS during the study period, January 1, 2001, to December 31, 2022, only 1 of which was active at study period end (Table 2). The first shortage, involving BAL, occurred in 2006.

Median shortage duration for all chelators, including 1 ongoing shortage of $CaNa_2EDTA$, was 7.4 months (range, 0.5–24.8; IQR, 12.6). The single longest, and only active, shortage at study period end involved $CaNa_2EDTA$ and was 24.8 months in duration. $CaNa_2EDTA$ and BAL experienced the greatest number of shortages, 4 each. Parenteral medications accounted for 61.5% of shortages. Shortages of parenteral agents lasted for a median duration of 14.2 months (IQR, 12), and non-parenteral agents had a median shortage duration of 2.2 months (IQR, 7.1). All shortages involved generic, single-source products. Suppliers reported multiple reasons for shortage (Table 3).

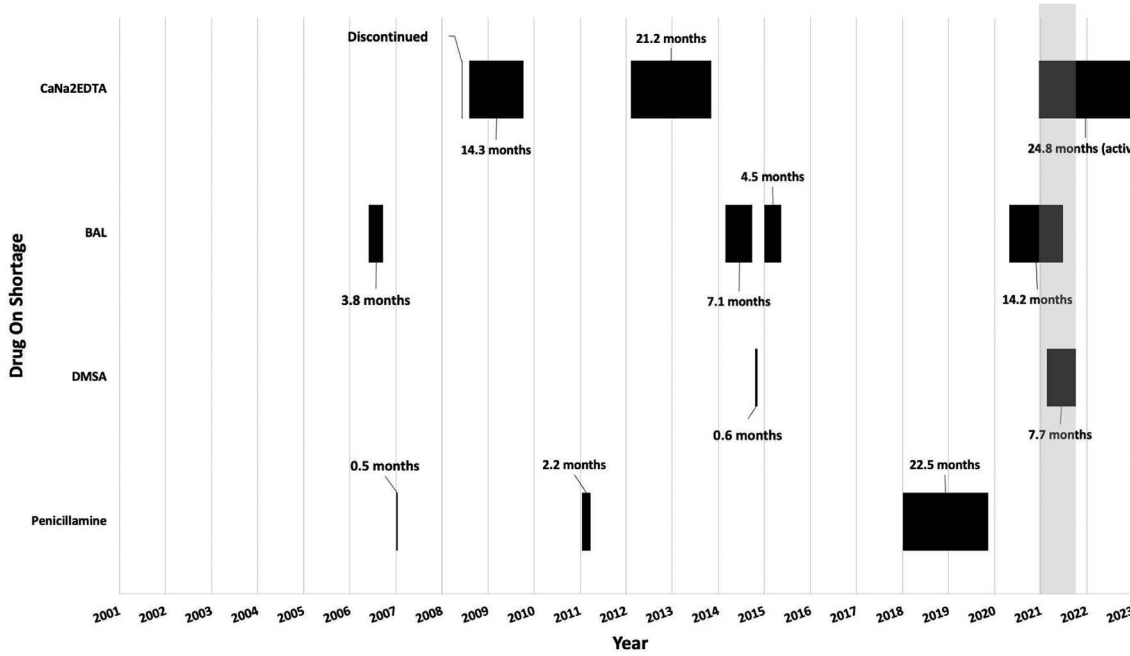
For 53.8% of shortages, the supplier did not provide a reason. When a reason was provided, supply/demand (15.4%) and manufacturing (15.4%) issues were most commonly reported. Shortages often lasted multiple months, and late in the study period concurrent shortages occurred (Figure 1).

Concurrent shortages of different chelators did not occur until 2020, at which point 2 parenteral shortages, 1 involving BAL and 1 involving $CaNa_2EDTA$, were reported. These 2 shortages temporally overlapped for 6.5 months, or 2.4% of the study period. A single non-parenteral DMSA shortage in 2021 also coincided with these shortages. Including all contemporaneous shortages, overlapping shortages occurred for a total of 9.8 months, or 3.7% of the 22-year study period. Most (61.5%) of the shortages occurred after January 1, 2012, during the second half of the study period. Median duration of resolved shortages increased from 3 months (IQR, 4.6) in the first half of the study period to 11 months (IQR, 15.1) in the second half.

Discussion

Treatment of pediatric lead poisoning with chelators is a cornerstone of therapy that rapidly lowers BLL, and

Figure 1. Shortage durations and overlapping Shortages 2001–2022. Individual shortage durations are noted in months, excepting a 2008 calcium disodium edetate ($CaNa_2EDTA$) shortage when the product was permanently discontinued. Grey shading indicates a 9.8-month period of overlapping shortages.



timely administration becomes increasingly important as BLL rises.[10] If clinicians cannot access these pharmacotherapies promptly, medication rationing or a complete lack of therapy may adversely affect patient outcomes.[17,20,21] This study's findings demonstrate numerous and prolonged chelator shortages, which also temporally overlapped late in the study period. All agents were affected by shortage, and the frequency and duration of shortages increased over time.

$CaNa_2EDTA$ and BAL were most frequently on shortage (4 episodes each), and $CaNa_2EDTA$ spent the greatest percentage of the 22-year study period on shortage, 22.5%. Patients with BLLs above 70 mcg/dL or encephalopathy require hospitalization and timely parenteral chelation with BAL and $CaNa_2EDTA$ to rapidly lower lead concentrations, which may be precluded by shortage of either agent. Animal data and human case reports suggest the possibility of $CaNa_2EDTA$-mediated lead redistribution from soft tissues across the blood-brain barrier into the central nervous system, which can either cause or exacerbate encephalopathy in severely lead-poisoned children.[22] Therefore, BAL is concurrently administered (with the first dose given 4 hours prior to $CaNa_2EDTA$ initiation) to prevent redistribution and more rapidly decrease BLL.[23] Some clinicians have suggested BAL initiation in asymptomatic patients at a higher threshold of 100 mcg/dL because of weak evidence supporting improved outcomes and the adverse effects of BAL (e.g., pain at administration site with intramuscular injection every 4 hours, fever, hypertension, and leukopenia).[10,22,24,25] Unfortunately, in 2020 and 2021, both of these agents were simultaneously on shortage, placing lead-poisoned patients with the greatest potential for severe toxicity and mortality at highest risk for undertreatment.[26] Even if dual-agent parenteral therapy is not indicated, when intravenous $CaNa_2EDTA$ is unavailable, patients requiring parenteral treatment may experience the aforementioned adverse effects of BAL, in contrast to nephrotoxicity associated with $CaNa_2EDTA$, which may be mitigated by adequate hydration and monitoring of renal function.[27] Additionally, BAL is dissolved in peanut oil and cannot be given to patients with a peanut allergy.[10] Unfortunately, because of the ongoing $CaNa_2EDTA$ shortage without a projected end date and the permanent shutdown of Akorn Pharmaceuticals, the sole BAL manufacturer, in February 2023 due to Chapter 7 bankruptcy, protracted and severe shortages of parenteral chelators will likely continue for the foreseeable future.[15,16]

DMSA is the preferred non-parenteral chelator for asymptomatic children with BLL less than 70 mcg/dL because of decreased adverse effects (primarily gastrointestinal distress, transaminitis, malaise) compared with penicillamine.[22] DMSA experienced the fewest total shortages (2) and spent the least amount of time (3.1% of study period) on shortage. This relative insulation from scarcity may suggest a therapeutic alternative in the future when parenteral therapy is indicated yet

neither BAL nor $CaNa_2EDTA$ is available, as was the case in Zamfara, Nigeria, in 2010.[28] In this instance 1156 children 5 years or younger, 33% of whom had an initial BLL of at least 80 mcg/dL, were treated with DMSA monotherapy. Prior to the availability of DMSA, approximately 400 deaths occurred in 3 months in Zamfara; however, after initiation of chelation only 6 deaths attributable to lead toxicity were documented during 13 months.[17] In the case of BAL absence alone, DMSA and $CaNa_2EDTA$ combination therapy in asymptomatic children with BLL exceeding 70 mcg/dL has also been suggested.[25,29] When DMSA shortage does occur, however, clinicians wishing to administer oral outpatient therapy may be forced to use penicillamine, which carries risks of gastrointestinal upset, nephrotoxicity, bone marrow suppression, and allergic reactions that may discourage prescribing and result in undertreatment.[30,31] Penicillamine itself experienced 3 shortages, none of which overlapped with DMSA. Should clinicians not wish to administer penicillamine as a DMSA alternative, hospital admission for parenteral $CaNa_2EDTA$ or BAL therapy may not be feasible should these agents also be on shortage, as was the case in 2021 when overlapping DMSA, $CaNa_2EDTA$, and BAL shortages occurred.

Chelator shortages most severely affected generic parenteral agents, similarly to national shortage trends involving other medications.[20,32] Manufacturers do not face financial or non-monetary penalties for failure to report or prevent shortage.[33] Perhaps because of this, 54% of shortages in this study did not have a reported reason; however, 31% of shortages, all involving parenteral agents, were attributable to a supply-and-demand mismatch or manufacturing problem. When quality or manufacturing problems occur in a sterile parenteral drug production facility, remediation may be prolonged. In the case of lead chelators, all of which are single-source agents produced by 1 manufacturer often in a single production facility, there is no alternative supplier to compensate for the resultant supply and demand mismatch by increasing production, which may explain the particularly prolonged nature of parenteral versus non-parenteral shortages (median 14.2 versus 2.2 months, respectively).[34,35] It is difficult to determine why shortage frequency increased in the second half of the study period, largely because of poor manufacturer reporting of shortage reason. Heightened awareness of the shortage problem, leading to increasing voluntary reporting to UUDIS via the ASHP Web site, may have contributed. Compared with many other medications, lead chelators are infrequently used generic agents. Thus, there is little financial incentive for existing manufacturers to produce large batches of drug or for new manufacturers to enter the market, resulting in a lack of surplus medication when manufacturing problems arise with a single-source manufacturer. Generic drugmakers face growing challenges, including: downward pressure on drug prices from consolidating purchasers, such as pharmacy benefit managers and wholesale buying consortia; FDA regulatory oversight requiring costly factory upkeep; increasing competition from overseas generics manufacturers; and difficulty maintaining access to active pharmaceutical ingredients. In the face of these challenges, it can be difficult to maintain adequate quality control and even solvency.[36] Illustrating this point, Akorn Pharmaceuticals, the sole manufacturer of BAL, experienced recurrent quality control issues during the last decade prior to bankruptcy, which may have contributed to the 3 BAL shortages specifically.[37]

A concerning aspect of chelator shortages is their potential for disproportionately affecting socioeconomically disadvantaged, minority, and immigrant populations. These populations may reside in older housing with leaded paint and pipes that can be prohibitively expensive to mitigate; use lead-tainted products, such as imported cookware and spices; and engage in occupations with lead-exposure risk, including painting and demolition.[2] They are also at greater risk for nutritional deficiencies, including iron, which increases enteral lead absorption. These vulnerable groups may also have inadequate healthcare access and insurance, resulting in decreased screening for lead exposure, a trend exacerbated by the COVID-19 pandemic, and limited financial means to procure scarce drugs that may be prohibitively expensive.[2,38]

To this point, average wholesale prices (AWPs) of all 4 commercially available chelators steadily increased during the study period. In 2001, AWPs of $CaNa_2EDTA$, BAL, DMSA, and penicillamine were $42.40 for 5 mL, $74.76 for 3 mL, $469 for 100 capsules, and $115 for 100 capsules, respectively. In 2022, AWPs of $CaNa_2EDTA$, BAL, DMSA, and penicillamine were $6,730 for 5 mL (15,948% increase), $192.53 for 3 mL (258% increase), $2,671 for 100 capsules (570% increase), and $31,426 for 100 capsules (27,327% increase), respectively.[39] Some of these increases may represent "predatory pricing," wherein the price of a generic medication without manufacturing competitors is raised more than can be justified by development and production costs. For example, following Valeant Pharmaceuticals' purchase of the only US supplier of $CaNa_2EDTA$, $CaNa_2EDTA$ AWP increased from $228 in 2013 to $6730 in 2014, whereas in France in 2014 an equivalent quantity of $CaNa_2EDTA$ was approximately $75.[40] When chelators are unavailable, compounding may be considered, but this can further increase cost and necessitate payment in cash.[12,26,41] Although AWP may not represent true drug cost after hospitals and insurance companies negotiate a lower final price, higher AWP may discourage hospitals from stocking expensive drugs that are infrequently used, and underinsured or uninsured patients may be unable to purchase crucial medication because of insufficient financial assets.[40,42,43] Even if patients and their families are able to purchase

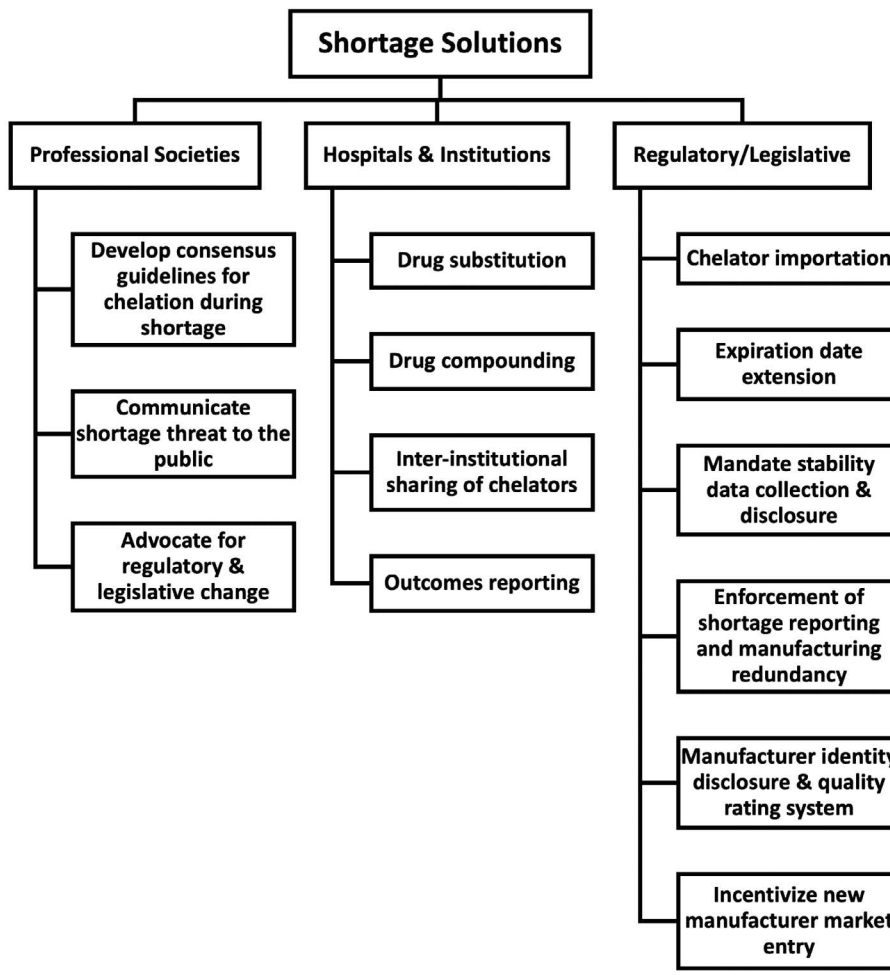
a medically indicated chelator, resultant debt may have negative health ramifications independent of lead toxicity.[43,44] To ensure chelators are priced in a rational and transparent manner that truly reflects production and distribution costs, legislators could consider price caps, negotiated pricing, and indexing price to inflation similar to drugs included in the Inflation Reduction Act of 2022; however, care must be taken to avoid removing manufacturers' financial incentive to produce generic chelators that already may have a lower profit margin than brand-name drugs.[40,43,45]

Numerous solutions to drug shortages, including chelator shortages, have been proposed and employed (Figure 2).

At the hospital level, substitution between agents, for example, BAL for $CaNa_2EDTA$ or penicillamine for DMSA, is a common practice that may cause patient harm from increased adverse effect profiles and prescriber error from lack of familiarity with rarely used medications.[21,46,47] Pharmacy, toxicology, and pediatric environmental health specialist consultation may facilitate safe substitution; however, this may not even be possible when multiple simultaneous shortages occur.[12] Drug compounding may be employed; however, this can delay administration, and carry risks of contamination, suprapotency, and subpotency.[12,19,41,46] Because DMPS is not FDA approved, and it is only rarely available via compounding in the United States, it is not a feasible large-scale solution.[12–14] Interinstitutional coordination with the aid of poison control centers to share chelators may facilitate acute treatment during shortage, but it does not address the underlying scarcity and may necessitate lengthy interhospital medication transport times.[20,26,43]

Because of limits of institutional mitigation, action by regulatory and legislative bodies and the pharmaceutical industry is also required. The FDA may temporarily permit importation of a non–FDA-approved drug as a stopgap, as is the case currently for $CaNa_2EDTA$ imported by BTG International Inc. of France. This example illustrates 2 risks of using non-approved drugs: imported $CaNa_2EDTA$ has a concentration of 50 mg/mL,

Figure 2. Proposed lead chelator shortage solutions.



whereas the US concentration is 200 mg/mL, and the imported product's bar code cannot be scanned, both of which increase medication error risk.[48]

However well-intentioned, chelator importation is also ethically fraught because it may strain international supply, precipitating shortage in other nations.[49] This phenomenon has not been described with lead chelators, and the FDA does take into account the potential for causing shortage abroad during importation deliberations. However, during a time of increasingly fragile international drug supply chains (for example, the Organisation for Economic Co-operation and Development reported a 60% increase in shortages in member nations from 2017 to 2019, with further worsening during the pandemic), "shortage transfer" could have negative implications for patients experiencing lead poisoning abroad.[50] The World Health Organization has noted increased shortages in recent years due in part to shortage transfer between countries.[51] This risk is compounded by already limited access to chelation and an increased burden of lead poisoning internationally compared with the United States.[50,51] In 2020 approximately 33% of children worldwide had a BLL exceeding 5 mcg/dL compared with approximately 2.5% of US children ages 1 to 5 years.[5,52] Despite DMSA, BAL, $CaNa_2EDTA$, and penicillamine being listed on the World Health Organization's Model List of Essential Medicines, the availability of these chelators in low- and middle-income nations is limited compared with high-income nations such as the United States, although a lack of international shortage databases similar to UUDIS prevents quantitative comparison between countries.[25] DMPS is only approved in Europe and is not on the Model List of Essential Medicines; therefore, its role in combating shortage is likely limited to Europe at this time.[53] Frequency of DMPS use relative to other chelators in Europe is not known.

If manufacturers possess stability data, the FDA may extend chelator expiration dates; however, this information is not always available. This could be addressed through regulatory and legislative action requiring uniform stability data collection and disclosure.[54] Continued reporting of illegal chelation therapies for non–FDA-approved indications is essential to discourage diversion of scarce drug and minimize patient harm, although the degree to which these non-approved therapies contribute to shortage is unclear.[55,56]

Because of the single-source nature of US chelators, where a manufacturing problem at a single facility may precipitate prolonged and severe national shortage, legislatively mandated manufacturing redundancy and supplier business continuity plans, as well as prompt shortage reporting to facilitate FDA stopgap interventions, are needed.[12,21,33] Likewise, disclosure of manufacturer identity and location, and creation of a manufacturer quality rating system, would facilitate transparent purchasing by health care systems. New manufacturer entry into a relatively unlucrative generic chelator market could be incentivized by tax credits, factory upkeep rebates, temporary market exclusivity, and expedited approval of novel chelators or other medications being developed by a manufacturer.[12,21,40] Given the shutdown of Akorn Pharmaceuticals, encouraging market entry of new manufacturers is particularly crucial in the case of BAL.[16] Unlike $CaNa_2EDTA$, no active pharmaceutical ingredient is available for compounding of BAL, and no foreign equivalent is available for importation. Unfortunately, except for DMPS, most potential alternative therapies, such as the chelator N,N'bis-(2-mercaptoethyl) isophthalamide and ingestible lead-binding polymers, are in the early stages of development.[57–60] Diethylenetriamine pentaacetic acid, normally administered for plutonium, americium, or curium poisoning, decreases tissue concentrations of lead in animal studies, although there is a lack of human data.[61–63]

Some legislative progress in addressing drug shortages was made with the 2012 passage of the Food and Drug Administration Safety and Innovation Act, which required manufacturer notification to the FDA for expected shortages, including shortage reason.[64] Subsequently the 2020 Coronavirus Aid, Relief, and Economic Security Act required manufacturers to develop supply chain redundancy and risk management plans.[65] Further action is needed, however, including appropriate financial penalties in cases of non-compliance with the Food and Drug Administration Safety and Innovation Act and Coronavirus Aid, Relief, and Economic Security Act (which have not been reported for chelator manufacturers).[33] Documenting patient harm from chelator shortages through databases such as the FDA's MedWatch and the American College of Medical Toxicology's ToxIC Registry for toxicovigilance, and communicating these findings and advocating for change through elected representatives and professional medical organizations is crucial to encouraging necessary regulatory and legislative action.[66]

This multipronged regulatory and legislative strategy to mitigate shortages will likely not be rapidly implemented. More immediately, because current guidelines do not take into account how to modify pharmacotherapy based on shortage conditions, a consensus set of guidelines is needed.[2,9,67] These guidelines should incorporate input from all relevant stakeholders, including pharmacy, pediatric, environmental health, and toxicology experts, and provide guidance to clinicians regarding appropriate lead chelator selection and regimen depending upon which agents are on shortage.

This study has multiple limitations because of characteristics of the UUDIS database. The first is an inability to assess shortage effects on individual patients and institutions, both in terms of patient outcomes and hospital resources expended. Institutional responses to shortages that may be informative, such as substituting DMSA for $CaNa_2EDTA$, and the resultant outcomes,

could not be assessed. Shortage severity, for example, whether a drug's supply was limited or completely depleted, could not be ascertained. Institutional and regional variation in severity is not captured by UUDIS; for example, an academic tertiary care hospital in the midwestern United States may, through supplier purchasing relationships, maintain adequate stockpiles of $CaNa_2EDTA$ and substitute agents and be relatively unaffected by a $CaNa_2EDTA$ shortage, whereas a rural community hospital in the northeastern United States may have no access to $CaNa_2EDTA$ and minimal substitute agents stockpiled during shortage and therefore be adversely affected to a greater extent.[43] Only US chelator shortages could be evaluated using UUDIS, which tracks solely domestic shortages, yet the international supply chain is overall more fragile and the burden of lead toxicity higher abroad.[12,49] Finally, shortage reason was not reported for most shortages, which limits analysis of causes of worsening shortage frequency and duration during the study period.

Conclusion

The US shortages of lead chelating agents have become increasingly frequent and prolonged, and are sometimes overlapping. This may hamper the ability of clinicians to appropriately treat lead-poisoned patients and disproportionately affect vulnerable pediatric populations. The National Academies of Science, Engineering, and Medicine published a report in 2022 detailing how to improve the resilience of the medical product supply chain. Stakeholders, including pharmacists, physicians, health care institutions, drug suppliers, legislators, and regulatory agencies, should work to implement this report's recommendations.[68] In addition, consensus guidelines regarding how to modify lead chelation pharmacotherapy based on shortage conditions are urgently needed.

Article Information

Affiliations. Harvard Medical Toxicology Fellowship (JDW), Boston Children's Hospital, Boston, MA; Department of Emergency Medicine (JDW), Beth Israel Deaconess Medical Center, Boston, MA; National Capital Poison Center (PS, MMA), Washington, DC; Department of Emergency Medicine (PS), The George Washington University School of Medicine, Washington, DC; Georgetown University School of Medicine (KMG), Washington, DC; Rutgers New Jersey Medical School (DPC), Newark, NJ; New Jersey Poison Information and Education System (DPC), Newark, NJ; Department of Pharmacy Services (ERF), University of Utah Health, Salt Lake City, UT; Department of Emergency Medicine (MMA), MedStar Washington Hospital Center, Washington, DC.

Correspondence. James D. Whitledge, MD; james.whitledge@childrens.harvard.edu

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