JPPT | National Database Study

Drug Shortages for Prescription Amphetamine Derivatives

Mana Sheykhsoltan, BS; Joshua Drobina, BSN; Michele M. Burns, MD, MPH; Erin R. Fox, PharmD; and Maryann Mazer-Amirshahi, PharmD, MD, MPH, PhD

OBJECTIVE Amphetamine derivatives are first-line medications for attention-deficit/hyperactivity disorder (ADHD). Recently, there have been increasing reports of drug shortages involving amphetamine derivatives. The objective of this study is to describe trends in drug shortages impacting prescription amphetamine derivatives.

METHODS Drug shortage data were retrieved from the University of Utah Drug Information Service (UUDIS) from January 2001 to December 2023. Using UUDIS data, we analyzed all reported shortages of amphetamine derivatives, including amphetamine salts, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and methylphenidate. Specific dosage forms, including extended-release and immediate-release oral preparations and transdermal patch formulations were examined. Data were analyzed focusing on shortage trends over time, specific amphetamine product involved, product formulation, reason for shortage, shortage duration (for resolved shortages), and single source status (made by 1 manufacturer/facility).

RESULTS There were a total of 26 shortages impacting amphetamine derivatives verified by UUDIS from January 1, 2001 to December 31, 2023. The years with the greatest number of amphetamine shortages were 2012, 2013, 2015, and 2023, each with 7 total shortages. The mean shortage duration for resolved shortages was 20.7 months, with a range of 1.3 months to 61.6 months. The longest shortage (61.6 months) was for methylphenidate extended-release tablets. The majority of manufacturers (58%) did not disclose a reason for shortage.

CONCLUSIONS Shortages for amphetamine derivatives have increased recently, limiting access to first-line therapy for ADHD. Inaccessibility of these agents can have negative implications for the cognitive development and functioning of children and adolescents, leading to comorbid mental health disorders.

ABBREVIATIONS ADHD, attention-deficit/hyperactivity disorder; ASHP, American Society of Health-Systems Pharmacists; DEA, Drug Enforcement Agency; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; ER, extended-release; FDA, US Food and Drug Administration; IR, immediate-release; UUDIS, University of Utah Drug Information Service

KEYWORDS amphetamine; attention-deficit/hyperactivity disorder; drug shortages; shortage trends

J Pediatr Pharmacol Ther 2025;30(2):206–211

DOI: 10.5863/1551-6776-30.2.206

Introduction

Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric condition that is associated with patterns of inattention and/or hyperactivity that interfere with functioning. ADHD globally affects 5% to 7.2% of youth and 2.5% to 6.7% of adults.[1] Diagnosis typically occurs in childhood, with criteria including experiencing challenges in at least 6 of the 9 symptoms of inattention and/or hyperactivity outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).[2] While non-drug therapy is indicated in many cases, particularly in young children, the primary pharmacologic treatment of ADHD is stimulant medications; specifically, amphetamine derivatives.[3] Amphetamines increase norepinephrine and dopamine neurotransmission in the prefrontal cortex through the inhibition of dopamine and norepinephrine transporter, vesicular monoamine transporter 2, and monoamine oxidase activity. The increase in dopamine and norepinephrine allow for enhanced executive and attentional function.[4] There are also non-amphetamine options for the management of ADHD, including antidepressants, atomoxetine, and alpha-2 adrenergic agonists; however, these options have been shown to be less effective for the treatment of ADHD.[3]

There are multiple formulations of different amphetamine derivatives that are currently marketed, including immediate- and extended-release preparations, as well

as transdermal patches, chewable tablets, and liquid formulations. Long-acting formulations have shown to be associated with a lower risk of rebound effects and better adherence, while short-acting formulations allow titrating and changing dosing frequency.[4] An individualized treatment approach is recommended to guide the chosen medication and formulation for children. The most common ADHD medications and combinations used in patients 2 to 24 years old are amphetamine derivatives, particularly amphetamine salts and methylphenidate, with alpha-2 agonists (67.1%).[5] Behavioral therapy, such as cognitive-behavioral training (CBT), is also recommended, especially in children younger than 6 years of age.[6] Receiving effective treatment for ADHD is important not only for the mental health, but overall wellbeing of patients. Undiagnosed or inadequately treated ADHD is associated with a range of negative outcomes in children, adolescents, and adults, including higher rates of depression, lower quality of life ratings, increased suicide attempts, anxiety, substance use disorders, and higher rates of criminality and motor vehicle accidents.[7,8]

Prescription drug shortages are commonplace in the United States and have been an ongoing public health problem for the past 2 decades. The University of Utah Drug Information Service (UUDIS) and the American Society of Health-System Pharmacists (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."[9] The majority of reported drug shortages have involved generic injectable medications.[10] More recently, there have been increasing reports of drug shortages involving amphetamine derivatives. Given the consequences that these drug shortages can have on academic, social, and functional aspects of the lives of children and adolescents, we sought to describe trends in drug shortages impacting prescription amphetamine derivatives.[11,12]

Materials and Methods

Drug shortage data were retrieved from the UUDIS from January 2001 to December 2023. UUDIS began collecting national drug shortage data in January 2001, and they publish drug shortage information on a public website (https://www.ashp.org/Drug-Shortages/) hosted by the ASHP. UUDIS receives voluntary reports of drug shortages via the reporting feature on the ASHP website. Clinical pharmacists at UUDIS conduct research on each reported shortage to verify if it exists and any pertinent details. This research includes determining all potential manufacturers and all drug presentation National Drug Codes for the product in question. Then each manufacturer is contacted to determine which National Drug Codes are in shortage (backorder, allocation, etc.) at the national level. If most suppliers are having a national shortage, then UUDIS will post information at the ASHP drug shortage website noting which products are affected, which products are available, specific methods for accessing the product, reasons for the shortage, estimated resupply dates, and if applicable, implications for patient care, safety concerns, and alternatives and management strategies. UUDIS does not track regional shortage trends and cannot reliably distinguish between limited availability of a drug versus complete absence. Shortages rarely result in the complete absence of a product; however, not all pharmacies stock all products from all manufacturers. Many may not stock brand products when generics are available. Wholesalers many also not stock all marketed products making it difficult for some pharmacies to access a product if their wholesaler does not carry the product, even if technically "available" on a national level. UUDIS considers a shortage to be resolved when all suppliers have all presentations available or have discontinued their products. UUDIS also follows FDA's drug shortage website and will generally resolve shortages when the FDA considers the shortage resolved unless there are specific presentations that are clinically relevant that remain unavailable.[13]

Using UUDIS data, we analyzed all reported shortages of amphetamine derivatives during the study period. Specific dosage forms, including extended-release and immediate-release oral preparations and transdermal patch formulations, were examined. Data were analyzed focusing on shortage trends over time, specific amphetamine product involved, product formulation, reason for shortage, shortage duration (for resolved shortages), and single source status (made by one manufacturer). Overlapping shortages were also examined. This study is not considered human subjects research.

Results

There were a total of 26 shortages impacting amphetamine derivatives verified by UUDIS from January 1, 2001 to December 31, 2023 (Table 1). There were no shortages reported from 2001 to 2008. The first shortages were reported in 2009. The years with the greatest number of amphetamine shortages were 2012, 2013, 2015, and 2023, each with 7 total shortages (combined ongoing and new shortages). The most recent increase in amphetamine shortages was driven largely by new shortages (see Figure). At the end of the study period, 7 active shortages remained.

The individual amphetamine derivatives with shortages reported during the study period were as follows: amphetamine salts, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and methylphenidate. Amphetamine salts was the most common agent (including all dosage forms of the medication) impacted, with a total of 10 shortages reported over the study period, followed by methylphenidate products, with a total of 7 shortages. The mean shortage duration for

Table 1. Amphetamine Derivates Affected by Drug Shortages, 2001–2023

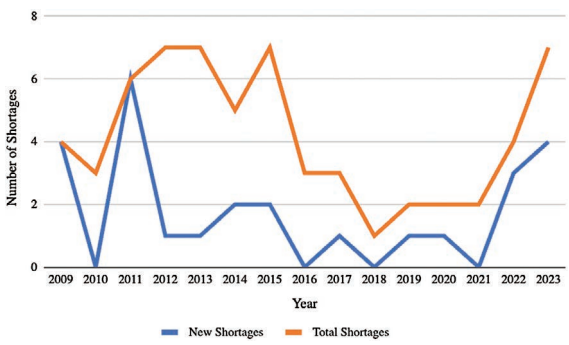
Drug Formulation	Total Number of Shortages*	Resolved Shortages	Ongoing Shortages at Time of Submission	Longest Duration (Resolved, mo)	Average Duration (Resolved, mo)	Duration of Ongoing Shortages (mo)†
Amphetamine Salts – ER	5	4	1	24.7	13.3	21.1
Amphetamine Salts – IR	5	4	1	37.4	16	17.4
Dexmethylphenidate – unspecified	2	2	0	13.2	12	N/A
Dexmethylphenidate – ER	2	1	1	3.9	3.9	11.8
Dexmethylphenidate – IR	1	0	1	N/A	N/A	1
Dextroamphetamine	3	3	0	10.3	5.6	N/A
Lisdexamfetamine	1	0	1	N/A	N/A	6.5
Methylphenidate IR	3	2	1	80.4	66	8
Methylphenidate ER suspension	1	1	0	17.4	17.4	N/A
Methylphenidate ER tabs	2	1	1	61.6	61.6	13.7
Methylphenidate patch	1	1	0	19.9	19.9	N/A
Totals:	26	19	7			

ASHP, American Society of Health-Systems Pharmacists; ER, extended-release; IR, immediate-release; N/A, not applicable

* Total number of shortages defined as number of resolved shortages plus any ongoing shortages across all manufactures who reported shortage information to ASHP during the study period, January 1, 2001–December 31 2023.

† Duration of ongoing shortages across all manufacturers who reported shortage information to ASHP as of the end of the study period, January 1, 2001–December 31 2023.

Figure. ADHD drug shortage trends.



ADHD, attention-deficit/hyperactivity disorder

resolved shortages was 20.7 months, with a range of 1.3 months to 61.6 months. The longest shortage (61.6 months) was for methylphenidate extended-release tablets. All of the products involved in shortage were for oral products, except 1 shortage for methylphenidate transdermal patches. Of the oral products, all were tablets or capsules with the exception of 1 shortage for methylphenidate suspension. Fifteen (58%) of shortages involved immediate-release oral products, and 10 (38%) involved oral extended-release products. The shortages involved both brand and generic products. Of note, dextroamphetamine products were the only product made by a single manufacturer (sole-source).

The majority of manufacturers (58%) did not disclose a reason for shortage (Table 2). When a reason was provided, the most common reported cause was a supply/demand mismatch (15%), followed by manufacturing problems and delays (11.5%).

Discussion

The treatment of ADHD symptoms remains important for children and adolescents in reaching their full potential in academic, social, and family settings. Stimulants, specifically amphetamines, are the first-line pharmacological interventions for ADHD.[3] If patients with a diagnosis of ADHD are unable to receive their prescribed stimulant medication appropriately, there may be long-term impacts, extending beyond academic progress. Studies have supported beneficial outcomes not only in academics, but driving, social function, and self-esteem with adequate ADHD treatment.[14] Limited access to first-line treatment can have long term outcomes for children, adolescents, and adults with ADHD.

The 2 most commonly prescribed agents, amphetamine salts and methylphenidate experienced the

Table 2. Reported Reasons for Shortage

Reasons for Shortage	Count
Unknown	15
Business decision/facility closure	1
Supply/demand	4
Manufacturing delay	3
Discontinued	1
Raw materials/DEA quota	2

DEA, Drug Enforcement Agency

greatest number of shortages. Studies have shown that stimulant medications improve ADHD symptoms similarly and are approximately equivalent in safety and adverse effects; however, specific patients may respond better to one stimulant over another.[15] Shortages may require switching between different medications and formulations due to changes in availability. Even when an alternative product is available, there may be formulary restrictions making the alternative cost-prohibitive, particularly when generic preparations are impacted. There are other considerations in pediatric patients in that there may be less flexibility with available strengths and dosage forms, particularly with younger children. Extended-release products can often not be split to make the appropriate dose, when the desired strength is not available due to a shortage. Shortages of extended-release products may impact adherence with multiple daily doses being required for immediate-release substitutes. In addition, there may be palatability issues in younger children who take liquids or chewable forms. During the study period, there were overlapping shortages, limiting the ability to substitute another agent. Such scenarios can potentially lead to medication errors. In fact, 1 recent study found a 300% increase in errors for ADHD medications reported to poison centers over time. While these errors cannot directly be attributed to shortages, this study demonstrates this class of medications is prone to errors and underscores the importance of medication safety initiatives and the burden of illness associated with medication errors.[16] The direct impact of shortages on medication errors represents an important area of future study.

Shortages of ADHD medications are difficult for patients to navigate. The amphetamine derivatives are all classified as Schedule II controlled substances, Drug Enforcement Agency's (DEA) highest level for prescription drugs which also includes medications such as morphine and oxycodone. This means patients must obtain a new prescription regularly and cannot fill prescriptions early. During a shortage situation, patients may be advised to contact other pharmacies to obtain their needed medications and may have to drive long distances to obtain the medication, particularly in rural or underserved areas. Additionally, they may have to contact insurance companies to obtain coverage for brand products if generics are not available or pay much higher sums out-of-pocket to obtain the medication. These tasks are difficult for patients and caregivers to navigate, particularly in patients/families with limited English proficiency or health care literacy and consume both time and financial resources.[17]

The underlying reasons for shortages of amphetamines are complex and multifactorial. The upward trend in amphetamine shortage since 2021 may, in part, be attributed to the COVID-19 pandemic. The second quarter of 2020, when preventative measures for spreading COVID-19 were taken, aligns with a drop in medication consumption in most countries. This drop during these isolation precautions may be attributed to fewer health care visits and increased school closures. However, in 2021, when COVID-19 restrictions loosened, the consumption of ADHD medications trended upward. This increase may be attributed to worsening ADHD symptoms of individuals who did not receive sufficient treatment in 2020 and worsening mental health disorders during the more stringent precautionary measures of the pandemic.[18] Additionally, there were allowances for electronic prescribing of these agents during the pandemic, which could account for some of the increase. Overall, there was a 14% increase in stimulant prescriptions from 2020–2022.[19]

In addition to increased demand, there are other factors that contribute to drug shortages of amphetamine derivatives.[20] Because they are Schedule II controlled substances, the DEA sets limits or quotas on production for these medications. However, for the most recent shortages, it is important to note that manufacturers of these agents actually manufactured only 70% of the quota in 2022. The FDA and DEA have called upon drug manufacturers to increase production to meet the quotas to help address the shortage. Manufacturers have provided very little information about why they are not manufacturing to capacity and are not required to provide any public information about why they have a manufacturing shortfall. Even with DEA's quota system, no manufacturer is required to make any product, regardless of whether the medication is critically needed. The Government Accountability Office has outlined deficits in the process for DEA to provide quota to manufacturers, particularly during times of shortage. For example, DEA did not respond in a timely manner to quota requests during any year between 2001 to 2014. DEA also lacked performance measures related to setting quotas. It is not clear how DEA decides which manufacturer will receive quota and how much. At the same time, given manufacturing costs and competing priorities, it may be difficult for manufacturers to ramp up production of a product

in a timely manner when the timeframe to receive raw materials (quota) is uncertain. In addition, there is a lack of resilience in the drug supply, with some products being made by a single manufacturer. As such, a quality or manufacturing problem at 1 facility can have a profound effect on the drug supply. Even if a manufacturer is able to increase supply, they may lack the quota from DEA to do so in a timely manner.

Advocacy efforts are needed to improve the drug shortage situation. For amphetamine derivatives in particular, more transparency is needed to understand why sufficient supplies are not being manufactured. Information regarding how much quota DEA provided to a specific manufacturer is not available, nor are the total amounts manufactured. This lack of transparency makes it impossible to understand which manufacturers may not be producing or if some manufacturers may need more quota to make up the difference if another supplier has a manufacturing delay. In November, 2023, DEA announced their intent to provide quota on a quarterly basis rather than on an annual basis.[21,22]

Of note, DEA announced in May of 2024 that they would be moving away from the quarterly quota system due to unintended consequences of a quarterly quota system on injectable controlled substance batch sizes. DEA now plans a semi-annual quota system for non-injectables.[23] Manufacturers didn't receive quotas in 2024 while these changes were being implemented which will likely mean continued shortages throughout 2024 and into the following years. Changes to quota allocations affect manufacturing schedules. It is not yet known if DEA changes will improve or worsen the shortage situation. While the FDA has been actively working to mitigate shortages, amphetamines, because of their controlled substance status, have barriers to some of traditional means of alleviating shortages. At the same time, other strategies, such as requiring notice of an anticipated shortage or development of a risk management plan, are feasible and will continue.[24]

Advocacy efforts may not be possible in navigating some of the unintended consequences as a result of the National Opioid Settlement. This legal settlement requires wholesalers to limit the amount of product that pharmacies can purchase. Pharmacies must provide data to the wholesaler that they are unable to fill all prescriptions and therefore require an increase. This system results in patients not being able to obtain prescriptions. The algorithms the wholesalers use to set purchasing limits are not transparent and pharmacies and hospitals are unable to proactively increase their purchasing limits, even with evidence.[25]

Limitations

This study has some limitations secondary to the data that UUDIS collects. The first is an inability to assess shortage effects in particular regions or on individual patients. Patients in rural areas and those of lower socioeconomic status may be disproportionately impacted by these shortages. The database does not evaluate adverse patient outcomes or costs and health care resources expended mitigating shortages. Furthermore, institutional and regional variation in severity is not captured by UUDIS. There were several active shortages at the end of the study period, which would underestimate the current total shortage burden.

Conclusions

Shortages for amphetamine derivatives have increased, limiting access to first-line drug therapy for ADHD. Inaccessibility of these agents have negative implications for the cognitive development and functioning of children and adolescents, leading to comorbid mental health disorders. It is imperative for physicians, pharmacists, health systems, drug suppliers, lawmakers, and government agencies to work together to address these drug shortages.

Article Information

Affiliations. Georgetown University School of Medicine (MS, MMA), Washington, DC; National Capital Poison Center (JD, MMA), Washington, DC; Harvard Medical Toxicology Program (MB), Division of emergency Medicine, Boston Children's Hospital, Boston, MA; Department of Pharmacy Services (EF), University of Utah Health, Salt Lake City, UT.

Correspondence. Maryann Mazer-Amirshahi, PharmD, MD, MPH, PhD; amirshahi@poison.org

Disclosure. The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors attest to meeting the 4 criteria recommended by the ICMJE for authorship of this manuscript.

Submitted. May 13, 2024

Accepted. June 24, 2024

References

1. Abdelnour E, Jansen MO, Gold JA. ADHD diagnostic trends: increased recognition or overdiagnosis? *Missouri Med*. 2022;119(5):467–473.
2. American Psychiatric Association. Diagnostic and statistical manual of mental disorders (5th ed.). 2013. Accessed June 20, 2024. https://doi.org/10.1176/appi.books.9780890425596
3. Magnus W, Nazir S, Anilkumar AC, Shaban K. Attention deficit hyperactivity disorder. Treasure Island, FL: 2024. Accessed June 20, 2024. https://www.ncbi.nlm.nih.gov/books/NBK441838/

4. Mechler K, Banaschewski T, Hohmann S, et al. Evidence-based pharmacological treatment options for ADHD in children and adolescents. *Pharmacol Ther*. 2022;230(12):e107940.
5. Girand HL, Litkowiec S, Sohn M. Attention-deficit/hyperactivity disorder and psychotropic polypharmacy prescribing trends. *Pediatrics*. 2020;146(1):e20192832.
6. Martin D, Le JK. Amphetamine. Treasure Island, FL: 2024. Accessed June 20, 2024. https://www.ncbi.nlm.nih.gov/books/NBK556103/
7. French B, Daley D, Groom M, et al. Risks associated with undiagnosed ADHD and/or autism: a mixed-method systematic review. *J Atten Disord*. 2023;27(12):1393–1410.
8. Hamed AM, Kauer AJ, Stevens HE. Why the diagnosis of attention deficit hyperactivity disorder matters. *Front Psychiatry*. 2015;6:168.
9. Fox ER, McLaughlin MM. ASHP guidelines on managing drug product shortages. *Am J Health Syst Pharm*. 2018;75(21):1742–1750.
10. Mazer-Amirshahi M, Hawley KL, Zocchi M, et al. Drug shortages: implications for medical toxicology. *Clin Toxicol*. 2015;53(6):519–524.
11. Sibley MH, Ortiz M, Gaias LM, et al. Top problems of adolescents and young adults with ADHD during the COVID-19 pandemic. *J Psychiatr Res*. 2021;136:190–197.
12. Danielson ML, Bohm MK, Newsome K, et al. Trends in stimulant prescription fills among commercially insured children and adults — United States, 2016–2021. *MMWR Morb Mortal Wkly Rep*. 2023;72:327–332.
13. FDA and ASHP Shortage Parameters. Bethesda, Maryland. Accessed June 20, 2024. https://www.ashp.org/drug-shortages/current-shortages/fda-and-ashp-shortage-parameters
14. Arnold LE, Hodgkins P, Caci H, et al. Effect of treatment modality on long-term outcomes in attention-deficit/hyperactivity disorder: a systematic review. *PloS One*. 2015;10(2):e0116407.
15. Brown KA, Samuel S, Patel DR. Pharmacologic management of attention deficit hyperactivity disorder in children and adolescents: a review for practitioners. *Transl Pediatr*; 2018;7(1):36–47.
16. DeCoster MM, Spiller HA, Badeti J, et al. Pediatric ADHD medication errors reported to United States Poison Centers, 2000 to 2021. *Pediatrics*. 2023; 152(4):e2023061942.
17. Arora DS, Mey A, Maganlal S, et al. Provision of pharmaceutical care in patients with limited English proficiency: preliminary findings. *J Res Pharm Pract*. 2015;4(3):123–128.
18. Gimbach S, Vogel D, Fried R, et al. The impact of the COVID-19 pandemic on ADHD medicine consumption in 47 countries and regions. *Eur Neuropsychopharmacol*. 2023;73:24–35.
19. Chai G, Xu J, Goyal S, et al. Trends in incident prescriptions for behavioral health medications in the US, 2018–2022. *JAMA Psychiatry*. 2024;81(4):396–405.
20. US Drug Enforcement Agency. Springfield, VA: 2023. Accessed June 20, 2024. https://www.dea.gov/sites/default/files/2023-11/Quota-Shortages%20Letter.pdf
21. Federal Register. Proposed Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2024. Washington, DC: 2023. Accessed June 20, 2024. https://www.federalregister.gov/documents/2023/11/02/2023-24282/proposed-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment-of
22. Federal Register. Established Aggregate Production Quotas for Schedule I and II Controlled Substances and Assessment of Annual Needs for the List I Chemicals Ephedrine, Pseudoephedrine, and Phenylpropanolamine for 2024. Washington, DC: 2024. Accessed June 20, 2024. https://www.federalregister.gov/documents/2024/01/03/2023-28962/established-aggregate-production-quotas-for-schedule-i-and-ii-controlled-substances-and-assessment
23. US Drug Enforcement Agency. Letter to Manufacturers. Springfield, VA: 2024. Accessed June 20, 2024. https://news.ashp.org/-/media/assets/advocacy-issues/docs/2024/DEA_Letter_to_Manufacturers.pdf
24. US Food and Drug Administration. Coronavirus Aid, Relief, and Economic Security Act (CARES Act) Drug Shortage Mitigation Efforts. Washington, DC: 2024. Accessed June 20, 2024. https://www.fda.gov/drugs/drug-shortages/coronavirus-aid-relief-and-economic-security-act-cares-act-drug-shortage-mitigation-efforts
25. National Opioid Settlements. Executive Summary of National Opioid Settlements. USA: 2024. Accessed June 20, 2024. https://nationalopioidsettlement.com/executive-summary/