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REVIEW

Pharmaceutical Purchasing: a Review of the Landscape and Implications for Antidotal Therapies

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Abstract

The management of the poisoned patient often requires the utilization of uncommonly used pharmaceutical interventions. These interventions can be associated with significant costs to both the patient and treating institution. Pharmaceutical supply shortages and issues with accessibility of antidotal therapies complicate the management of many toxic exposures. These challenges are an inherent property of the pharmaceutical purchasing infrastructure in the United States, which is a complicated network of public and private intra-institutional agreements. The cost and availability of any given therapy is dependent on the individual contracting agreements between the treating institution, payer, pharmacy benefit manager, manufacturer or wholesaler, and in some cases a specialty pharmacy. Small or remote hospitals may experience greater challenges related to insufficient patient volume to achieve predicable prescribing patterns of rare and expensive medications, necessitating consignment purchasing arrangements. Although pharmaceutical costs are the focus of recent legislative attention, these reforms are not expected to significantly alter the cost or availability of antidotal therapies.

Keywords Antidotes · Drug prices · Drug purchasing · Pharmaceuticals · Drug shortages

Introduction

Pharmaceutical costs and drug shortages are a reality of medical practice today. Despite attempts to separate these concerns from the clinical decision-making process, increasing costs, shortages in the supply of drugs, and the downstream effects thereof can affect clinical care. Challenges in the delivery and reimbursement of antidotal therapies are ubiquitous features of the practice of medical toxicology. Although multidisciplinary recommendations regarding antidote stocking in the Emergency Department are available, financial and logistical concerns can prevent these guidelines from being realized in practice [1]. Recent shortages of physostigmine, as well as ongoing difficulties obtaining consistent and timely supplies of chelating agents, have complicated the management of antimuscarinic delirium and metal-related toxicities (note that reversal of anticholinergic symptoms with physostigmine is not an FDA-approved use). Over the 10-year period from 2012 to 2021, 230 individual drug shortages of agents used in the treatment of poisoned patients occurred [2, 3]. In addition to supply issues, cost-related concerns often complicate the decision to administer expensive antidotal therapies, which have become increasingly costly over time [4, 5].

The cost of pharmaceuticals is often discussed as a policy or public health issue ancillary to direct patient care. There is, however, ample evidence that these costs have significant impacts on both short- and long-term patient outcomes. Financial well-being is correlated with longevity [6, 7], and prohibitive cost to the patient is a common barrier to medication adherence [8]. Indeed, a negative wealth shock, defined as a loss of 75% or more in household net worth, holds an adjusted hazard ratio for 20-year all-cause mortality of 1.50 [9]. Healthcare-related expenditure remains an incredibly common cause of household bankruptcy and is at least partially implicated in over 60% of cases [10]. Despite the prevalence and prominence of these issues, the process by which pharmaceuticals are purchased, priced, and

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delivered remains opaque and poorly understood by many clinicians.

Methods

This article is a qualitative, narrative review of the general pharmaceutical purchasing and pricing infrastructure in the United States. A background literature search was conducted in PubMed, HOLLIS, and Google Scholar which included research regarding the effects of healthcare costs on patient outcomes. Search terms included any permutation of "mortality," "longevity," or "adherence" and "drug costs," "pharmaceutical costs," "net worth," "income," or "bankruptcy." The search was limited to results from the past 20 years, 2003–2023. No systematic evaluation of methodology was performed. Very little peer-reviewed research exists regarding the relative commonality and specific structure of hospital drug purchasing agreements, and the remainder of the review is qualitative in nature based on trade literature, health policy literature, and the professional experience of the authors.

Average wholesale price data was obtained from the Micromedex® RED BOOK® database. Search terms included the generic names of all included medications. Exclusions from the calculation of average per-unit pricing included off-market preparations, preparations for alternate routes of administration where specified, and preparations such as pre-mixed or multi-agent dose packs which would not be expected to be utilized in the acute management of a poisoned patient. Included agents were selected to demonstrate a wide range of common and rare antidotal therapies, as well as both high- and low-cost products. Standard dosages were calculated for a 70-kg adult from recommendations provided in "Poisoning & Drug Overdose, 8th Edition" by Olson et al. Aggregate Medicare spending data was obtained from publically available Program Use & Payments data from the Centers for Medicare & Medicaid Services [11, 12].

Discussion of Pharmaceutical Purchasing in the United States

Pharmaceutical purchasing is an increasingly complex enterprise, largely governed by an intricate network of individually negotiated private agreements (Fig. 1). These contracts are, by nature, both unique and inaccessible to the public. However, there are a number of conventions and trends that have emerged which can inform a more general understanding of how drugs are purchased and distributed in the United States.

Foundational to the understanding of pharmaceutical purchasing practices is a general familiarity with the healthcare reimbursement and risk-pooling structure in the United States. Most patients—92% of the population in early 2022 [13]—are covered by a health insurance product. Patients pay in to a plan at a set monthly rate and are subsequently entitled to benefits when they utilize healthcare services. Americans can obtain insurance privately through a government-sponsored marketplace, through their employer, or directly from the government through Medicare for those aged 65 or older, or Medicaid for those who fall below the

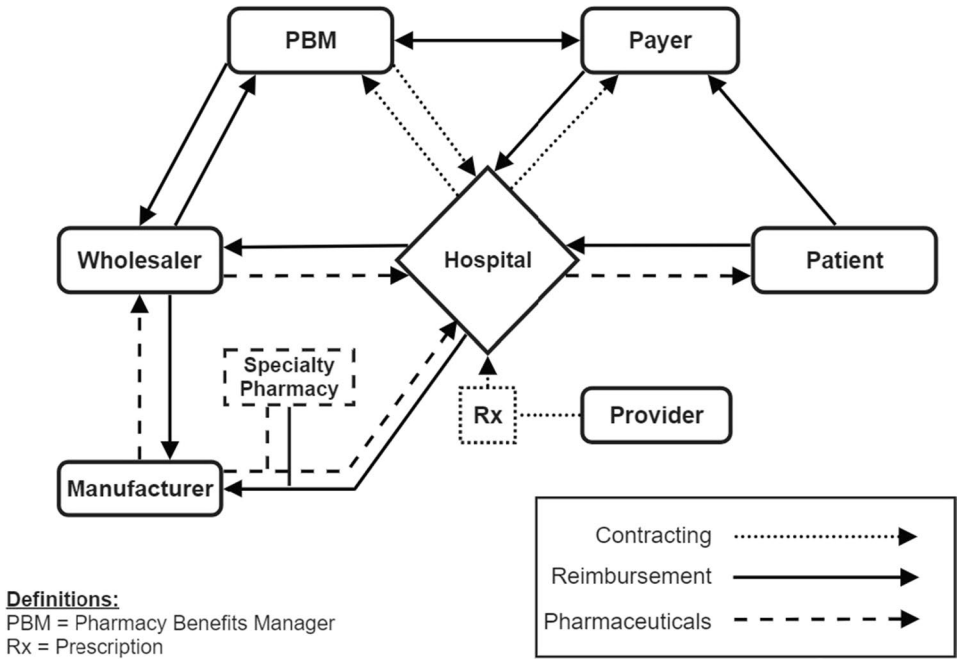

Fig. 1 Simplified schematic view of the pharmaceutical reimbursement ecosystem.

associated income threshold. The Centers for Medicare & Medicaid Services (CMS) is the largest payer in the United States, and its constituent programs accounted for 36% of total national health expenditure in 2020 [14].

When a healthcare provider prescribes a medication in the acute care or inpatient setting, the hospital generates a charge. The exact nature of this charge—how much it is, and who is responsible for paying it—depends on the series of individual arrangements that the patient and provider organization have entered into. While hospitals generally maintain a list price for individual services provided, commonly referred to as a "chargemaster," the final paid rate is negotiated between the provider and insurance organization, with some measure of cost-sharing passed along to the patient in the form of a co-pay or co-insurance. While hospital list prices are highly variable and generally intended as a starting point for these negotiations, patients who are uninsured or forced to seek out-of-network care can be exposed to them directly and incur significant unexpected costs [15, 16].

Within this system, each stakeholder has a number of strategies they employ to reduce costs and protect against financial risk. For example, provider organizations can negotiate bulk purchases of common medications from wholesalers. They can also negotiate preferential reimbursement arrangements with payer organizations (often referred to as being "in-network") wherein enrollees in a plan are incentivized to receive care from a particular hospital or health system in exchange for more favorable rates. Many payer organizations have outsourced management of their prescription drug benefits to third-party organizations called pharmacy benefit managers (PBMs). PBMs develop and maintain formularies on behalf of insurers and negotiate rebates from manufacturers in exchange for guaranteed purchasing volume. The role of PBMs is controversial, and efforts to determine their effect on total costs within the system are significantly hampered by a lack of transparency regarding monetary flow through this system of intermediaries [17].

Cost-saving strategies that insurers use to control pharmaceutical expenditure are more familiar to many clinicians. Payers can require clinicians to provide rationale for prescribing and obtain permission to prescribe as a prerequisite for reimbursement (colloquially known as a "prior authorization"). They can establish guidelines within internal formularies for designated first-line therapies and require a trial of cheaper medications prior to approving payment for a more expensive option (a "step edit"). They can also assign a medication to a lower formulary tier and offer reduced reimbursement as an incentive to prescribe less expensive alternatives. Finally, they can remove items from formulary, excluding them from reimbursement entirely.

Before a medication can be prescribed or dispensed for inpatient use, it must first be acquired by the hospital. The pharmacy can structure these purchases in a number of ways. The most common arrangement is that the hospital will purchase a drug and take primary responsibility for the storage and maintenance of that drug's supply. After the drug is prescribed and administered, the hospital bills the patient who often has some cost-sharing responsibility with the remainder reimbursed by the covering payer. This arrangement, referred to as "buy-and-bill," is the most traditional mode of drug purchasing.

Traditional "buy-and-bill" purchasing, however, has limitations with regard to rarely used but expensive or difficult to store medications. Hospitals that purchase these medications risk expiration prior to use, at which point the hospital will lose the opportunity to bill for the medication and therefore the chance to defray its acquisition cost. While large health systems and tertiary care hospitals may have the requisite patient volume and complexity to utilize these medications with regularity and therefore mitigate the financial risk, this is often not the case for smaller community-based hospitals. Because maintaining a standing stock of these medications is unlikely to be feasible for a hospital which would not anticipate reliably utilizing them within their expiration timeline, many hospitals opt to purchase these items on consignment.

Consignment purchasing involves an arrangement between the hospital and drug manufacturer wherein the manufacturer provides a rotating stock of medication for which the hospital is billed only when the medication is dispensed. This removes the financial risk of underutilizing expiring medications. However, the major downside of this arrangement is that the costs themselves are unpredictable—utilizing a medication purchased on consignment can be a large and unexpected expense. These high-cost, low-utilization medications are often supplied through specialty pharmacies who develop specific expertise in the distribution, storage, and reimbursement of the pharmaceuticals which they manage. Observational data suggests that payer restrictions and distribution challenges substantially alter practice patterns with regard to these medications; one survey suggests that approximately two-thirds of specialty pharmacies ultimately dispense half or fewer of the prescriptions that they receive [18].

Regardless of the structure of the purchasing agreement, hospitals may incur a varying degree of financial risk based on the geography and population characteristics of their catchment area. For example, the magnitude of charitable care—for which there is no element of patient cost-sharing—appears to vary state to state based on the status of Medicaid expansion [19]. This may be offset by increases in unreimbursed Medicaid expenditure, or the gap in Medicaid reimbursements and hospital costs, in these states [20]. Although system or population-level data regarding the payer mix of poisoned patients is limited, reported data from one toxicology consult service was largely consistent with the proportions seen in the overall population [21].

These dynamics pose several challenges for medical toxicologists. Many of the pharmaceutical interventions utilized in the management of acutely poisoned patients are of this exact type: expensive, rarely used, and useful only in specific, acute clinical scenarios. As a result, hospitals—particularly smaller, rural, or community-based institutions—may more often experience significant budgetary impacts from their use. This has practical implications, as it can lead to a lack of availability of expensive antidotal therapies outside of the tertiary care setting. It can also lead to reticence to utilize what resources are available, or to acquire uncommonly used medications via emergent order or from non-preferred distributors which can incur significant additional costs [22]. Finally, antidotal therapies prescribed in the outpatient setting often require patients to fulfill their cost-sharing obligations at the point of sale. As increases in cost-sharing are associated with a negative impact on medication adherence, this may materially impact the utility of these outpatient regimens (Table 1) [23].

The Inflation Reduction Act, passed in August 2022, contains measures intended to curb the large and expanding costs of pharmaceuticals in the United States. The law empowers CMS to directly negotiate drug prices with manufacturers. However, significant caveats to the scope of this new authority will likely limit its effect on the price and supply of antidotal therapies. Initial negotiation will only be permitted for 10 Medicare Part D drugs in 2026 with incremental increases thereafter. Drugs covered by Medicare Part B, including many hospital-administered medications, will not be eligible until 2028. Drugs with generics or biosimilars available are excluded from negotiation, as are drugs approved for market fewer than 9 years ago for small molecules or 13 years ago for biologics. Critically, the drugs to be negotiated will be selected from the 50 drugs with the highest Medicare Part B spend and the 50 drugs with the highest Medicare Part D spend; all drugs with Medicare spending of less than $200 million in 2021 are excluded [24, 25]. These criteria generally exclude antidotal therapies which, while expensive, are utilized in comparatively small volumes and consequently represent a low overall total expenditure [12]. While separate rules which require manufacturers to pay rebates on price increases over inflation for single-source pharmaceuticals may limit upward pricing pressure, there are no included provisions expected to address ongoing supply challenges.

Historically, other strategies to limit the excessive growth of pharmaceutical costs have been proposed. The majority of these strategies involve empowering the government to negotiate or regulate prices, or limiting the scope of the enforced-monopoly system which grants manufacturers upwards of a decade of market exclusivity for new drugs [26]. Similar strategies have been successful in other developed countries, where equivalent pharmaceuticals typically cost much less [27]. However, efforts to introduce such changes in the United States have been unsuccessful. Efforts to stabilize supply of medications have been similarly limited, and with some exceptions in the case of medications for investigative or compassionate use, antivenom, or therapies with certain public health or military applications, the logistics of medication supply are left entirely to private market forces.

Anecdotally, locating and delivering uncommon antidotal therapies remains difficult, and toxicologists rely primarily on ad hoc networks and experiential knowledge of regional supply centers to coordinate resource-sharing when necessary. Larger, multihospital systems have reported systematic optimization of antidote stocking [28]. Such networks are not without their own challenges, however. Transfers of

Table 1 Average wholesale prices of selected antidotal therapies.

Medication	Average Wholesale Price per Unit	Standard Dose	Cost per Use
N-Acetylcysteine (IV)	$0.04 / mg	300 mg/kg per 21-h protocol	$840.00 per 21-h protocol
Hydroxocobalamin	$837.10 / g	5 g	$4185.50
Glucagon	$204.60 / mg	5–10 mg	$1023.00 – $2046.00
Glucarpidase	$43.98 / unit	50 u/kg	$153,930.00
Fomepizole	$1.05 / mg	15 mg/kg followed by 10 mg/kg q12h	$1102.50 loading dose $735.00 subsequent doses
Prothrombin complex concentrate	$3.26 / unit	50 U/kg, max 5000 U	$11,410.00
Digoxin antibody	$5306.40 / vial	1–10 vials	$5306.40 – $53,064.00
Centruroides antivenom	$5995.55 / vial	3 vials	$17,986.65
Crotalid antivenom	$3,837.60 / vial	4–6 vials	$15,350.40 – $23,025.60
Lipid emulsion 20%	$0.19 / mL	100 mL bolus + 0.25–0.5 mL/kg over 30–60 min	$22.33 – $25.65

Standard dosing calculated based on a 70 kg adult patient

Average wholesale price data obtained from Micromedex® RED BOOK®

pharmaceutical products carry robust tracing requirements under the Drug Supply Chain Security Act (DSCSA), which was initially passed in 2013 and contains requirements which phase in through 2023. This act requires manufacturers, distributors, and dispensers, including hospital pharmacies, to provide electronic transaction documentation which follows the product and allows it to be traced throughout the supply chain [29]. Thus, inter-hospital 'borrowing' of uncommon medications may trigger significant documentation requirements, complicating the time-sensitive delivery of antidotal therapies in this manner. However, with no clear systemic intervention on the horizon, the expansion and formalization of these networks may be the only actionable path towards improving the availability of these necessary medications.

Limitations

This article is a narrative review based on the views and experience of the authors. The literature review performed was qualitative and not systematic, without the use of a research librarian. Neither author has direct professional experience in pharmaceutical purchasing, wholesaling, contracting, or billing.

Conclusions

Pharmaceutical purchasing represents a significant portion of overall healthcare costs. It can be a source of sustained financial difficulty for hospitals and healthcare systems and can incur considerable risks for patients up to and including effects on long-term mortality. The specifics of pharmaceutical purchasing, including price, delivery, and availability, are determined by a complicated network of individually negotiated private contracts which are opaque to clinicians. This limits the ability of clinicians to understand in detail the financial and logistical challenges related to medications they prescribe. The institutional effects of high-priced, rarely utilized medications which include several antidotal therapies are likely more challenging to address for smaller or more remote health systems who often purchase these products on consignment. Although new policies intended to address high drug costs as a whole are forthcoming, the specifics of these laws make them unlikely to impact the cost or availability of antidotal therapies.

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Declarations

Conflict of Interest None.

References

1. Dart RC, Goldfrank LR, Erstad BL, Huang DT, Todd KH, Weitz J, et al. Expert consensus guidelines for stocking of antidotes in hospitals that provide emergency care. Ann Emerg Med. 2018;71:314–325.
2. Whitledge J, Fox ER, Amirshahi M. US Shortages of Agents Used to Treat Poisonings Over the Last 10 Years (2012-2021). Clin Toxicol. 2022;60:2 [Abstract].
3. Mazer-Amirshahi M, Fox ER, Routsolias JC, Johnson-Arbor K, Mycyk MB. How can we "get the lead out" without chelators? J Med Toxicol. 2021;17:330–2.
4. Heindel GA, Trella JD, Osterhoudt KC. Rising cost of antidotes in the U.S.: cost comparison from 2010 to 2015. Clin Toxicol (Phila). 2017;55:360–3.
5. Mazer-Amirshahi M, Stolbach A, Nelson LS. ACMT Position statement: addressing the rising cost of prescription antidotes. J Med Toxicol. 2018;14:168–71.
6. Chetty R, Stepner M, Abraham S, Lin S, Scuderi B, Turner N, et al. The association between income and life expectancy in the United States, 2001–2014. JAMA. 2016;315:1750–66.
7. Finegood ED, Briley DA, Turiano NA, Freedman A, South SC, Krueger RF, et al. Association of wealth with longevity in US adults at midlife. JAMA Health Forum. 2021;2:e211652.
8. Khera R, Valero-Elizondo J, Das SR, Virani SS, Kash BA, de Lemos JA, et al. Cost-related medication nonadherence in adults with atherosclerotic cardiovascular disease in the United States, 2013 to 2017. Circulation. 2019;140:2067–75.
9. Pool LR, Burgard SA, Needham BL, Elliott MR, Langa KM, de Mendes Leon CF. Association of a negative wealth shock with all-cause mortality in middle-aged and older adults in the United States. JAMA. 2018;319:1341–50.
10 Himmelstein DU, Lawless RM, Thorne D, Foohey P, Woolhandler S. Medical bankruptcy: still common despite the affordable care act. Am J Public Health. 2019;109:431–3.
11. Olson K, Smollin C, Anderson I, Benowitz N, Blanc P, Kim-Katz SY, Lewis J, and Wu AH, editors. Poisoning & Drug Overdose. 8th ed. New York, NY: McGraw Hill Medical; 2022. pp 480–550.
12. Summary statistics on use and payments - Centers for Medicare & Medicaid Services Data. Available from: https://data.cms.gov/summary-statistics-on-use-and-payments. Accessed 3 Jan 2023.
13. Lee A, Ruhter J, Peters C, Lew ND, Sommers BD. National uninsured rate reaches all-time low in early 2022. ASPE Office of Health Policy Data Point. August 2022. https://aspe.hhs.gov/reports/2022-uninsurance-at-all-time-low. Accessed 3 Jan 2023.
14 Hartman M, Martin AB, Washington B, Catlin A, The NHEAT. growth driven by federal spending in response to the COVID-19 pandemic. Health Affairs. 2020;2022(41):13–25.
15. Batty M, Ippolito B. Mystery of the chargemaster: examining the role of hospital list prices in what patients actually pay. Health Affairs Health Affairs. 2017;36:689–96.
16. Arvisais-Anhalt S, McDonald S, Park JY, Kapinos K, Lehmann CU, Basit M. Survey of hospital chargemaster transparency. Appl Clin Inform. 2021;12:391–8.
17. Schulman KA, Dabora M. The relationship between pharmacy benefit managers (PBMs) and the cost of therapies in the US pharmaceutical market: a policy primer for clinicians. Am Heart J. 2018;206:113–22.
18. Stubbings J, Pedersen CA, Low K, Chen D. ASHP National Survey of Health-System specialty pharmacy practice-2020. Am J Health Syst Pharm. 2021;78:1765–91.

19. Alberti PM, Sutton KM, Baker M. Changes in teaching hospitals' community benefit spending after implementation of the affordable care act. Acad Med. 2018;93:1524–30.
20. Stoecker C, Demosthenidy M, Shao Y, Long H. Association of nonprofit hospitals' charitable activities with unreimbursed Medicaid care after Medicaid expansion. JAMA Netw Open. 2020;3:e200012.
21. Wiegand TJ, Crane PW, Kamali M, Reif M, Wratni R, Montante R, et al. Billing and reimbursement for a bedside toxicology service at a tertiary care academic center during its first fiscal year. J Med Toxicol. 2015;11:48–58.
22. Mazer-Amirshahi M, Fox ER, Farmer BM, Stolbach AI. ACMT position statement: medication shortages during coronavirus disease pandemic. J Med Toxicol. 2020;16:346–8.
23. Fusco N, Sils B, Graff JS, Kistler K, Ruiz K. Cost-sharing and adherence, clinical outcomes, health care utilization, and costs: a systematic literature review. J Manag Care Spec Pharm. 2023;29:4–16.
24. Text - H.R.5376 - 117th Congress (2021–2022): Inflation Reduction Act of 2022 | Congress.gov | Library of Congress. Available from: https://www.congress.gov/bill/117th-congress/house-bill/5376/text. Accessed 3 Jan 2023
25. Hwang TJ, Kesselheim AS, Rome BN. New reforms to prescription drug pricing in the US: opportunities and challenges. JAMA. 2022;328:1041–2.
26. Kesselheim AS, Avorn J, Sarpatwari A. The high cost of prescription drugs in the United States: origins and prospects for reform. JAMA. 2016;316:858–71.
27. Langreth R, Migliozzi B, Gohkale K. The U.S. pays a lot more for top drugs than other countries. Bloomberg.com. Available from: http://www.bloomberg.com/graphics/2015-drug-prices/. Accessed 3 Jan 2023.
28. Antoniello AA, Pauls P, Awad NI, Sobolewski K, Fernández D, Bridgeman P. Optimization of antidote stocking, availability, and administration practices for a large multihospital organization. Am J Health Syst Pharm. 2023;80:S1-10.
29. Le P, Grund L, Marwa J, Ojo W, Otts J, Arab F. Combating substandard and counterfeit medicines by securing the pharmaceutical supply chain: the Drug Supply Chain Security Act (DSCSA) of 2013. Innov Pharm. 2018;9:1–11.