ACMT Position Statement:
Addressing the Rising Cost of Prescription Antidotes

Disclaimer: While individual practitioners may differ, these are the positions of the American College of Medical Toxicology (ACMT) at the time written, after a review of the issue and pertinent literature.

Antidotal therapy is an essential component of poisoning management. In recent years, there have been unprecedented increases in the costs of antidotes. The American College of Medical Toxicology calls upon providers, hospitals, formularies, pharmaceutical industry, government, insurance companies and pharmacy benefit managers to adopt practices to ensure that antidotes are available to our patients, and priced based on value and cost.

Background

Antidotal therapy is an essential component of management of suspected or actual poisoning. Hospitals must also stock antidotes to meet emergency preparedness obligations.[1] Per capita prescription drug spending accounts for 17% of healthcare costs, an amount greater than for any other nation.[2] In recent years, there have been unprecedented and profound increases in the costs of antidotes and other prescription drugs in the U.S. The causes of the high costs of pharmaceutical products are multifactorial and closely tied to market and regulatory factors.

Market Exclusivity

The largest driver of high drug costs in the U.S. is market exclusivity, which is granted to branded medications.[2] Exclusivity refers to restrictive marketing rights granted by the U.S. Food and Drug Administration (FDA), independent of a drug's patent, upon approval of a pharmaceutical. Exclusivity was designed as an incentive to promote pharmaceutical innovation. The right to market exclusivity can be extended for various reasons, such as performance of pediatric studies by the sponsor or the development of orphan indications.[3-5] This, in concept, allows pharmaceutical companies to recover the costs of drug research and development, which was estimated to be $2.6 billion in 2014.[6] In the U.S., brand name drugs comprise approximately 10% of approved pharmaceutical products, however they account for 72% of pharmaceutical spending. In addition, brand name drug prices increased 164% overall from 2008 to 2015, whereas wages increased approximately 8%.[2,7]

Features of the drug approval process and regulation in the U.S. contributes to excessive spending on pharmaceuticals in this country. The more rapid acceptance of new products in the U.S. compared to some other countries results in higher prices, especially in small market share medications.[2,8,9] In some other countries there are generally more restrictions on which products are covered by payers and some countries utilize more rigorous cost-benefit analyses, such as those by the National Institute for Health Care and Excellence (NICE) in the United Kingdom.[2,9,10] In addition, it is more difficult in the U.S. market for payers to negotiate price and there are more stringent requirements for payers to cover a broader spectrum of medications.[2,9]

Because of the financial benefit of limited competition, many pharmaceutical companies aggressively attempt to extend their market exclusivity. This can include litigation against generic companies, reformulation of current products, paying generic drug companies to delay marketing ("pay-to-delay"), self marketing generic versions, seeking additional orphan indications, or performing pediatric trials to gain an exclusivity extension.[4,11] When new competing drugs become available, litigation may be pursued to delay market entry -- e.g., as in the case of Crotalidae (pit viper) equine immune F(ab')2 antivenom.[12]

Generic Medications

Once market exclusivity has expired, new companies can produce the drug in generic form.[3] When there are two generics available, drug prices decline to an average of 55% of the brand name drug price.[2] As additional generic competitors bring their products to market, prices typically drop even further. Unfortunately, drug prices may rise even after market exclusivity expires. In many cases, cost increases of generic antidotes are a result of practice described as "predatory pricing."[13,14] This term refers to the practice of intentionally raising prices of generic medications that do not have competitors in the marketplace. In such cases price increases are not related to the cost of production or development of the drug. In contrast to FDA-granted market exclusivity, increases in the price of generics in this setting does not reward innovation. For example, the sole U.S. supplier of calcium disodium EDTA ($CaNa_2EDTA$) was purchased by Valeant Pharmaceuticals in 2012, at which point the average wholesale price of $CaNa_2EDTA$ was increased 7150% from 2008 to the end of 2014.[15]

Increase in Antidote Prices

Between 2010 and 2015, 15 of 33 key antidotes had increases in average wholesale price of 50% or more. [16] Several clinically important and life saving antidotes, such as naloxone and $CaNa_2EDTA$, have undergone large wholesale price increases over the past several years (See Table). The price of naloxone, even though generic, has more than doubled recently, in part due to the increased demand imparted by the opioid epidemic.[17] The price of $CaNa_2EDTA$, as mentioned earlier, was recently increased from $464 in 2008 to over $26,000 for the standard initial dose to treat lead poisoning (5 vials). This same product can be purchased in France for $75.[18] Crotalidae polyvalent immune Fab (Ovine) has been priced at approximately $6632.40 per vial. Although insurance companies ultimately negotiate a lower final price, such charges may leave many uninsured or underinsured Americans unable to pay their hospital charges.[19] The high cost of medical care and pharmaceuticals inevitably disproportionately harms impoverished patients. In addition to broad healthcare impact, high drug pricing adversely impacts formulary decision-making and may diminish access to life-saving antidotes. Alternatively, cost barriers (e.g., to fomepizole) causes formularies to regress to less safe alternatives (e.g., ethanol).

Medical toxicologists assist in the management of critically ill poisoned patients, and our practice includes the use of antidotal therapy. In this role, medical toxicologists should serve as stewards of healthcare excellence and make recommendations based on available cost- and risk-effectiveness data.

It is the opinion of ACMT that lack of access to affordable antidotes represents an urgent and unacceptable threat to public health in the US and across the globe. We call on stakeholders to take steps to ensure that antidotal medications are priced fairly. In the long term, we should consider

restructuring our regulatory approach so that drugs, including antidotes, are evaluated for clinical value, including assessments of safety, efficacy, and cost.

Recommendations:

Providers

Choose antidotes based on best practices and evidence-based recommendations.

Hospitals and Formularies

Choose medications based on value and cost from a patient-centered perspective.

Employ regional antidote supply and cost sharing agreements especially if scarce or expensive.

Pharmaceutical Industry

Price medications rationally and in a transparent fashion, based on costs of development, production, and distribution.

Eschew reverse settlement payments ("pay-to-delay") practices.

Comply with the spirit and intent of regulations designed to mitigate unnecessary litigation aimed to preclude or delay introduction of generic drugs

Provide reimbursement or new drug to pharmacies and hospitals following expiration of antidotes.

Government

Develop alternative pricing policies for antidotes considered essential.

Employ a broad range of experts to apply evidence to approve medications based on overall value, in consideration of cost and benefit of antidotal drugs to patients. (Analogous to the British NICE.)

Streamline the approval process for generic antidotes.

Develop the authority to negotiate the price of medications paid for by governmental programs.

Insurance Companies and Pharmacy Benefit Managers

Engage patients, providers, and pharmaceutical companies to maintain price of medications in proportion to value provided to patients.

Table [20,21,22]

Average Wholesale Price of Selected Antidotes 2012, 2016, 2017

Antidote	Formulation	Quantity	AWP 2012[1]	AWP 2016[2]	AWP 2017[3]
Acetylcysteine injection (Acetadote®)	200 mg/mL 30 mL	4	$994.38	$994.38	$1034.94 (2016) Per unit: $258.74
scorpion (centruroides) immune $F(ab')_2$ injection (Anascorp®)	1 vial	1	$4,375.00	$4,905.68	$5150.96
antivenin (crotalidae polyvalent immune Fab (Crofab®)	1 gram vial	2	$5121.60	$6169.20	$6632.40 (2016) Per unit: $3316.20
Deferoxamine (Fresenius)	2 gram vial	1	$49.44	$49.44	$49.44 (2009)
Deferoxamine (Hospira)	2 gram vial	4	$176.40	$151.58	$151.58 (2016) Per unit: $37.90
Fomepizole (Bioniche - now part of Mylan)	1 g/mL 1.5 mL	1	$870.00	$1132.50	$1132.50 (2015)
Fomepizole (Sandoz)	1 g/mL 1.5 mL	1	$1,364.85	$1,364.85	$1,364.85

Fomepizole (X-gen Pharmaceuticals)	1 g/mL 1.5 mL	1	$1290.00	$1290.00	$1290.00
Glucarpidase (Voraxaze®)	1000 Units/vial	1	$27,000.00	$31,254.00	$34,456.80
Hydroxocobalamin (Cyanokit)	5 gram	1	$750.75	$750.75	$821.32
Leucovorin (Blue Point Laboratories and Sagent)	200 mg vial powder	1	$48.00	$48.00	$48.00 (2016)
Levoleucovorin (Fusilev®)	50 mg vial powder	1	$240.00	$273.60	$246.00
Naloxone (Hospira)	0.4 mg/mL	10	$45.00	$185.28	185.28 (2014) Per unit: $18.53
Phytonadione (Hospira)	10 mg/mL	25	$404.60	$1,133.10	$1322.40 Per unit: $52.90
Phytonadione (Hospira)	1 mg/0.5mL	25	$172.20	$127.50	$127.50 Per unit: $10.20

Phytonadione (International Medication System)	1 mg/0.5 mL	10	$51.00 in 2013	$216.00	$216.00 (2015) Per unit: $43.20
Succimer (Chemet®)	100 mg capsules	100 caps	$860.10	$1,700.04	$1785.05 Per unit: $17.85
Uridine Triacetate (Vistogard®)	10 g/packet	20	N/A	$90,000.00	$96312.00 Per unit: $4,815.60
Vitamin K (Mephyton®)	5 mg oral tab	100	$1283.00 in 2013	$7,051.21	$7.051.21 (2015) Per unit: $70.51

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