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REVIEW

Economic considerations in the treatment of systemic allergic reactions

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Abstract: Epinephrine is a life-saving medication used to treat systemic allergic reactions including anaphylaxis. Epinephrine autoinjectors (EAIs) are expensive and worldwide availability is limited. Epinephrine prefilled syringes and epinephrine kits are potentially lower-cost alternatives to EAIs. Advantages, disadvantages, and costs of available products are discussed. The socioeconomic factors impacting access to EAIs are described.

Keywords: epinephrine, anaphylaxis, cost, price, autoinjector

Introduction

Epinephrine is the first-line treatment for systemic allergic reactions (SARs) to foods, insect stings or bites, medications, and other allergens. The early use of epinephrine in SARs can be life-saving; delayed use has been associated with death.[1–3] Cox et al updated the World Allergy Organization (WAO) grading system for SARs as summarized in Table 1 to clarify the early signs and symptoms of an SAR and to encourage early use of epinephrine.[4] The term "SAR" applies to all grades with the term "anaphylaxis" also appropriate for grade 4 or 5 reactions.

Epinephrine autoinjectors (EAIs) were developed in the 1970s and were first approved by the US Food and Drug Administration (FDA) in the United States in 1987 with the EpiPen® (Mylan, Canonsburg, PA, USA). EAIs available in the USA include: EpiPen; epinephrine injection, United States Pharmacopeia autoinjector, generic (Mylan); epinephrine injection, USP autoinjector (Impax Generics, Hayward, CA, USA); and Auvi-Q® (Kaléo, Richmond, VA, USA).

The annual direct costs in year 2010 in the USA for EAIs are estimated to be $294 million, accounting for about 25% of the $1.2 billion annual cost to treat SARs including anaphylaxis.[5,6] The average wholesale price (AWP) of each EAI is included in Table 2, except for the Auvi-Q. Accurate wholesale pricing for the Auvi-Q is not available as it is distributed through a single specialty pharmacy network. The complexity of drug pricing is beyond the scope of this article. Costs for the EpiPen were relatively stable until Mylan acquired this product from Merck (Kenilworth, NJ, USA) in 2007. The AWP since that time for two EpiPens has increased 545% from $113.27 to $730.33.[4] This price increase persists even after accounting for inflation (Figure 1).[7,8] Although the out-of-pocket expenses for individual subjects may have decreased since the public outcry about EpiPen costs in 2016, the effective date of the most recent AWP available is May 16, 2016 and does not reflect the impact of price cuts or patient assistance programs.[7]

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Table 1 Proposed modification of the 2010 World Allergy Organization grading system

Grading system for SARs				
Grade 1	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**
			Anaphylaxis	
Symptom(s)/sign(s) from 1 organ system present Cutaneous • Urticaria and/or erythema-warmth and/or pruritus, other than localized at the injection site And/or • Tingling, or itching of the lips* or • Angioedema (not laryngeal)* Or Upper respiratory • Nasal symptoms (eg, sneezing, rhinorrhea, nasal pruritus, and/or nasal congestion) And/or • Throat-clearing (itchy throat)* And/or • Cough not related to bronchospasm Or Conjunctival • Erythema, pruritus, or tearing Or Other • Nausea • Metallic taste	Symptom(s)/sign(s) from ≥2 organ symptoms listed in grade 1	Lower airway • Mild bronchospasm, eg, cough, wheezing, shortness of breath which responds to treatment And/or Gastrointestinal • Abdominal cramps* and/or vomiting/diarrhea Other • Uterine cramps • Any symptom(s)/sign(s) from grade 1 would be included	Lower airway • Severe bronchospasm, eg, not responding or worsening in spite of treatment And/or Upper airway • Laryngeal edema with stridor • Any symptom(s)/sign(s) from grades 1 or 3 would be included	Lower or upper airway • Respiratory failure And/or Cardiovascular • Collapse/hypotension^ And/or Loss of consciousness (vasovagal excluded) • Any symptom(s)/sign(s) from grades 1, 3, or 4 would be included

Notes: The final grade of the reaction is not determined until the event is over, regardless of the medication administered to treat the reaction. The final report should include the first symptom(s)/sign(s) and the time of onset after the causative agent exposure and a suffix reflecting if and when epinephrine was or was not administered: a, ≤5 min; b, >5 min to ≤10 min; c, >10 to ≤20 min; d, >20 min; z, epinephrine not administered. Final report: Grade 1-5; a-d, or z; First symptom(s)/sign(s); Time of onset of first symptom(s)/signs(s). Case example. Within 10 min of receiving an AIT injection, a patient develops generalized urticaria followed by a tickling sensation in the posterior pharynx. Intramuscular epinephrine is administered within 5 min of symptoms(s)/sign(s) resulting in complete resolution of the reaction. The final report would be: Grade 2; a; Urticaria; 10 min. *Application-site reactions would be considered local reactions. Oral mucosa symptoms, such as pruritus, after SLIT administration, or warmth and/or pruritus at a subcutaneous immunotherapy injection site would be considered a local reaction. However, tingling or itching of the lips or mouth could be interpreted as a SAR if the known allergen, eg, peanut, is inadvertently placed into the mouth or ingested in a subject with a history of a peanut-induced SAR. Gastrointestinal tract reactions after SLIT or OIT would also be considered local reactions, unless they occur with other systemic manifestations. SLIT or OIT reactions associated with gastrointestinal tract and other systemic manifestations would be classified as SARs. SLIT local reactions would be classified according to the WAO grading system for SLIT local reactions.[33] A fatal reaction would not be classified in this grading system but rather reported as a serious adverse event. ^Hypotension is defined per the National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Expert Panel criteria[34]: "Reduced blood pressure after exposure to known allergen for that subject (minutes to several hours). A) Infants and children: low systolic blood pressure (age-specific) or greater than 30% decrease in systolic blood pressure. Low systolic blood pressure for children is defined as follows: 1 mo to 1 y: <70 mm Hg, 1–10 y: <70 mm Hg + [2 × age], 11–17 y: <90 mm Hg. B) Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline. Reprinted from The Journal of Allergy and Clinical Immunology: In Practice, Volume 5(1), Cox LS, Sanchez-Borges M, Lockey RF, World allergy organization systemic allergic reaction grading system: is a modification needed? Pages 58–62.e55, Copyright 2017, with permission from Elsevier.[4]

Abbreviations: AIT, allergen immunotherapy; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; WAO, World Allergy Organization.

Use of the AWP is controversial, but it is often used as a proxy for societal cost in cost-effectiveness analyses.[9] An economic analysis published in 2011 utilized the 2006–2007 AWP of the EpiPen to estimate the annual cost of EAIs for food-induced SARs.[10] According to the International Society for Pharmacoeconomics and Outcomes Research good research practices guidelines from 2010:

> Pharmaceutical prices used in the vast majority of cost-effectiveness analyses are either based on AWPs in the USA or government-negotiated prices in Europe. The former are not only imperfect measures of actual prices paid (e.g., ignoring discounts and rebates), but may also greatly overestimate societal opportunity costs because of the implicit inclusion of producer surplus created through patent-protected monopoly pricing.[11]

In summary, AWP is used as an approximation for societal drug costs, despite its limitations. The United States Department of Veterans Affairs (VA) Health Economics Resource Center (HERC) discusses the challenge of determining medication costs for research purposes. The HERC states, "We recommend using 121% of the drug costs reported in the Federal Supply Schedule, 152% of the VA cost, or 64% of

Table 2 Average wholesale prices for epinephrine autoinjectors in the USA

Manufacturer	Drug name	NDC number	Package size	Dose	AWP package price (US$)	Effective date
Mylan	EpiPen®	49502-0500-02	2 ea	0.3 mg/0.3 mL	730.33	5/16/2016
Mylan	EpiPen Jr.	49502-0501-02	2 ea	0.15 mg/0.3 mL	730.33	5/16/2016
Mylan	Epinephrine injection, USP autoinjector	49502-0102-02	2 ea	0.3 mg/0.3 mL	375	12/15/2016
Mylan	Epinephrine injection, USP autoinjector	49502-0101-02	2 ea	0.15 mg/0.3 mL	375	12/15/2016
Impax Generics	Epinephrine injection, USP autoinjector	54505-0101-02	2 ea	0.15 mg/0.15 mL	494.01	10/1/2015
Impax Generics	Epinephrine injection, USP autoinjector	54505-0102-02	2 ea	0.3 mg/0.3 mL	494.01	10/1/2015
Kaleo	Auvi-Q®	60842-0022-01	2 ea	0.15 mg/0.15 mL	5400[a]	n/a
Kaleo	Auvi-Q	60842-0023-02	2 ea	0.3 mg/0.3 mL	5400[a]	n/a

Notes: [a]Accurate AWP for Auvi-Q was not available because it is distributed through a single specialty pharmacy network.
Abbreviations: AWP, average wholesale price; ea, each; NDC: national drug code.

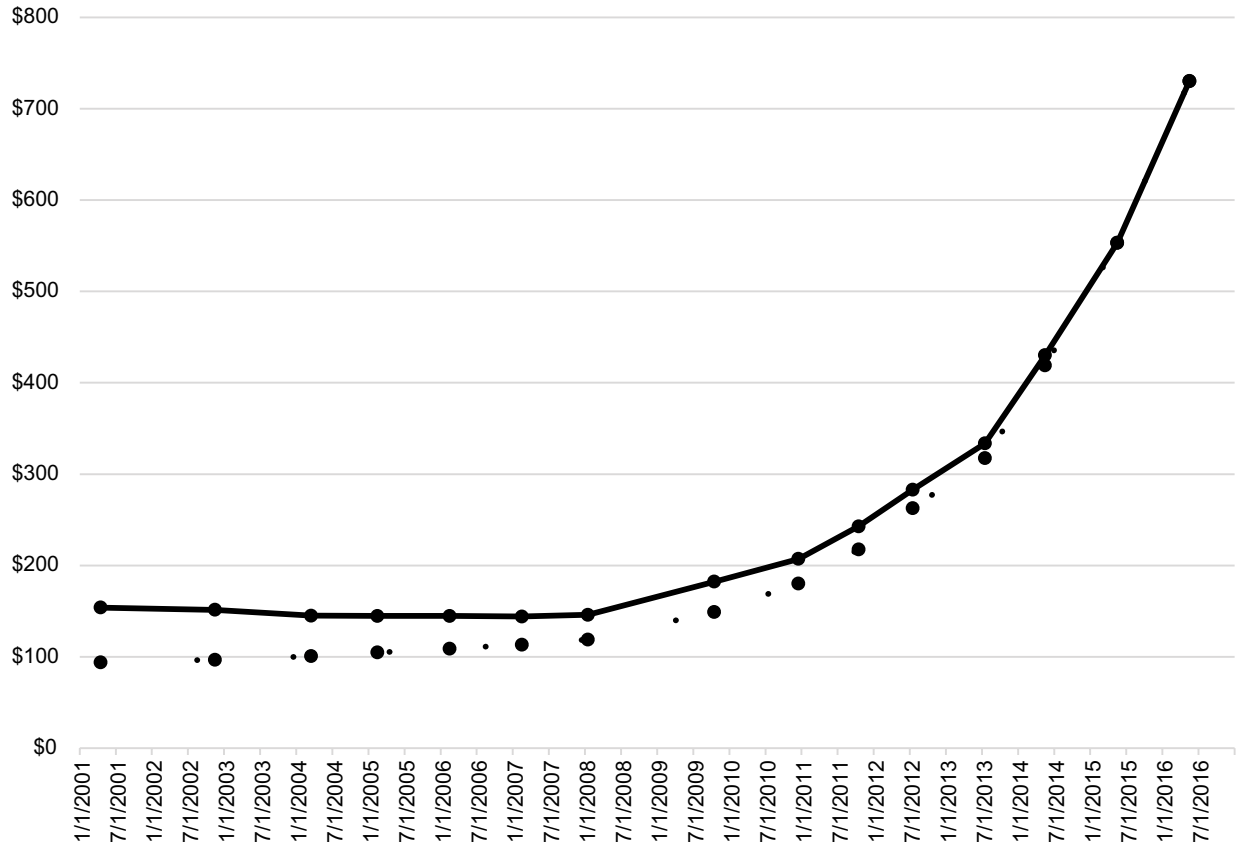

Figure 1 AWP for the EpiPen® 2001–2016.
Notes: AWP of an EpiPen 2-pack, or AWP of two EpiPens when sold individually, 2001–2016. The dotted line represents AWP in actual US dollars. The solid line represents AWP in constant year 2016 US dollars to adjust for inflation. Data were obtained from the Red Book Online System[7] and converted into constant US dollars using the Consumer Price Index for medical care from the US Bureau of Labor Statistics.[32] The most recent AWP available was effective date 5/16/16.
Abbreviation: AWP, average wholesale price.

AWP. To find the cost of a generic label prescription drug, we recommend using 27% of AWP."[9] Federal Supply Schedule prices are publicly available.[12]

Several factors limit the ability of newer products to garner and maintain a better market share versus Mylan's EpiPen. First, the EpiPen has name recognition. Second, training for the use of each device is different. To illustrate, the epinephrine injection, USP autoinjector from Impax Generics requires the removal of two caps rather than just one. Although learning to use a new device can be challenging, novel design elements can improve safety and usability. An example is that the Auvi-Q has unique features including its rectangular shape intended to fit into a pocket, a retractable needle, and voice instructions. Third, insurance

coverage differs for each EAI. According to the Managed Markets Insight and Technology database, the EpiPen has unrestricted access for 61% of commercial lives among 4624 commercial health plans.[13] In contrast, Auvi-Q has unrestricted access for "19% of commercial lives in all locations" among these same commercial health plans.[8] Even though Auvi-Q is not covered by many commercial insurance plans, the manufacturer offers it with $0 copayment to all commercially insured and Medicaid patients through a specialty pharmacy network distributor. Fourth, EAIs are rated "BX" by the FDA indicating that "data that have been reviewed by the Agency are insufficient to determine therapeutic equivalence" and when ordered may not be substituted by a pharmacist, one for another.[14]

The impact of copayments, coupons, and patient assistance programs on prices that subjects pay at the pharmacy counter requires further research. Pourang et al found that copayments did not affect the likelihood of an EAI being dispensed once it was prescribed in the Kaiser Permanente Health Maintenance Organization.[15] However, while the authors indicate that nearly 30% of copayments exceeded $30, they did not consider higher copayments. Data are not available on prescription:dispense ratios for subjects with exceedingly high copayments or for uninsured and underinsured subjects who may pay retail prices. More than 50% of EpiPen prescriptions are abandoned or not filled when the cost exceeds $300 for a 2-pack.[5] Two generic EAIs manufactured by Mylan have an AWP of $375. Two generic EAIs manufactured by Impax Generics have an AWP of $494.01. Patients with any commercial insurance plan or Medicaid receive Auvi-Q for $0 copayment through the specialty pharmacy network, ASPN Pharmacies LLC (200 Park Avenue, Suite 300, Florham Park, NJ 07932, 973-295-3289). All uninsured subjects who make <$100,000 annually have no copayment for Auvi-Q; uninsured subjects whose incomes exceed $100,000 pay no more than $360 for Auvi-Q.

Socioeconomic factors impact access to EAIs. Children from high-income versus low-income homes are 8.35 times more likely to be prescribed EAIs.[16] Medicaid-enrolled children are less likely to receive EAIs prior to arrival at an emergency department.[17] In another study, Caucasian versus non-Caucasian children were more likely to receive epinephrine early during an SAR.[18] Early use of epinephrine was defined as epinephrine administered before arrival to the emergency department. Owning an EAI greatly increased the odds of early epinephrine treatment (odds ratio 12.67, 95% CI: 4.46–35.96). The authors did not assess insurance status but indicate that this finding suggests that there might be an economic influence on access to EAIs.[18] Fleming et al examined the out-of-pocket costs for medications associated with food allergy and found higher costs for Caucasian and higher-income subjects.[18] They hypothesize that Medicaid-enrolled children may have lower out-of-pocket costs, that is, lower copayments. To reduce or eliminate insurance copayments, Fromer suggests that epinephrine be classified as a preventive medicine by the US Preventive Services Task Force (USPSTF).[5]

Decision analysis software (TreeAge Pro, Williamstown, MA, USA) has been used to evaluate the cost of generic EAIs versus the EpiPen using a model that tracked spending for individual subjects over 20 years, with the assumption that each subject needs two 2-packs yearly, one each for home and school or work.[19] The cost for the EpiPen over a 20-year model duration totals $58,667 (95% CI: $57,745–$59,588) versus $45,588 for the generic EAI (95% CI: $44,873–$46,304). The model also incorporates other food allergy-related costs, such as specialist visits, grocery costs, and loss of work time for parents of food-allergic children. These costs are assumed to be the same for all subjects regardless of the type of EAI prescribed.

The price of EAIs also affects school districts and communities. The Michigan legislature mandated that all public schools stock EAIs. It estimated the cost for two EAI 2-packs, one adult and one pediatric, at $140, while the "recently reported costs for commercial sources" was $1200, according to the authors of the article. The annual calculated cost to Michigan public schools based on these two cost estimates ranges from $565,460 to $4,846,800.[20]

A 2007 WAO survey of its House of Delegates indicates that EAIs are available in 59% of 44 countries surveyed.[21] Those without EAIs employed other methods for the self-administration of epinephrine.[22] These include the use of ampules of epinephrine 1:1000 (1 mg/mL) with an empty 1 cc syringe to be drawn up as needed or prefilled syringes containing various amounts of epinephrine. Both options are much less expensive than EAIs; for example, a vial of epinephrine 1:1000 (1 mg/mL) (Hospira, Lake Forest, IL, USA) had an AWP of $2.52 and retail price of ~$12 in 2016.[7] Epinephrine ampules may not be available in all countries. Both options also allow for tailored dosing of epinephrine, above or below the standard 0.15 or 0.3 mg doses contained in most FDA-approved EAIs. This may be beneficial for children weighing <15 kg (33 pounds) or for large or obese subjects. Of note, in November 2017, the FDA approved an

infant version of the Auvi-Q, Auvi-q 0.1mg, for children weighing 7.5–15 kg (16.5–33 pounds). It has a shorter needle and a smaller dose of epinephrine (0.1 mg versus 0.15 mg contained in other "junior" products).

Market forces appear to influence the cost of EAIs. For example, some US companies are offering low-cost alternatives. Symjepi™ (Adamis, San Diego, CA, USA) is an epinephrine prefilled syringe (EPS) that contains 0.3 mg of epinephrine, with a user-friendly design. It was approved by the FDA in June 2017 for subjects 30 kg (66 pounds) or more and is expected to be available at a lower cost than the current EAIs. A "junior" version is expected to follow. The concept of prefilled syringes is not new. The Ana-Kit® (Hollister-Stier Laboratories, Spokane, WA, USA) consisted of a syringe filled with 1 mL of epinephrine 1:1000 (1 mg/mL) housed in a protective case for subcutaneous injection before it was removed from the US market.[23,24] The Ana-Kit syringe had 0.1 mL graduations so that smaller doses could be administered depending on the subject's age. The instructions recommended the following doses: "Adults and children over 12 years: 0.3 mL; 6–12 years: 0.2 mL; 2–6 years: 0.15 mL; infants to 2 years: 0.05–0.1 mL."[25] An appropriate dose could be administered by pushing the syringe plunger until it stopped. A second dose could be administered as appropriate, after rotating the rectangular plunger ¼ turn to the right, to line up with a rectangular slot in the syringe.[25] An advantage of the prefilled Symjepi syringe is that it is housed in a dark blue plastic encasement to protect the epinephrine from ultraviolet light degradation. Epinephrine degrades with exposure to ultraviolet light, oxygen in ambient air, and excessive heat.[26–28] EPSs stored at room temperature in a pencil box maintain acceptable US Pharmacopeia concentrations (90%–115% of label claim), pH, and sterility for 3 months.[22] The stability is limited to 2 months in high-temperature and low-humidity climates.[22,29] In addition, some physicians and other health care professionals provide subjects with prefilled syringes wrapped in aluminum foil.[28,30] These can be transported in a crush-resistant eyeglass case.

Snap Medical Industries (Dubin, OH, USA) has developed EpinephrineSnap-V® (a kit containing a vial of epinephrine 1:1000 [1 mg/mL] and empty syringes) and the EpinephrineSnap convenience kit (a kit containing an ampule of epinephrine 1:1000 [1 mg/mL] and empty syringes). The Focus Health Group, located in Knoxville, TN, USA, has been contracted to commercialize these products. The AWP of this product is $156[7] although information from company officials states that the average price of EpinephrineSnap is $80 and the EpinephrineSnap-V is $130, with discounted group purchasing organization pricing available (Personal communication, November 1, 2017). Use of these options may not be as practical as is an EAI. The reason is that an epinephrine ampule or vial with an empty syringe requires more skill to properly draw up the epinephrine and administer it under emergency circumstances. Parents of individuals with a history of an SAR take longer to draw up epinephrine from an ampule (average 142±13 seconds) compared to emergency department nurses (29±0.09 seconds; $p<0.05$).[31] The epinephrine dose drawn up by parents also ranged 40-fold as compared to twofold for emergency department nurses.[31] The EpinephrineSnap products are geared toward use by emergency medical technicians and other health care professionals rather than individual subjects.

The rising cost of EAIs has made self-administered epinephrine potentially unavailable to some subjects. There are no data on deaths attributed to inability to afford EAIs. Lower-cost alternatives such as EPSs and epinephrine kits are entering the US market. EAIs have advantages, such as ease of use, but they are expensive. More research is needed on the complexity of drug pricing and on the optimal methods to determine individual and societal costs. Classifying EAIs as USPSTF preventive medicines could improve access by reducing or eliminating copayments.

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