



Self-injectable epinephrine: doctors' attitude and patients' adherence in real-life

Ismael Carrillo-Martin^a, Marco Caminati^{b,c,d},
Luciana K. Tanno^{e,f,g}, and Alexei Gonzalez-Estrada^a

Purpose of review

Epinephrine is the only life-saving treatment of anaphylaxis. Prescription and administration rates of self-injectable epinephrine are generally low. It is unclear whether this is because of availability, low prescription rates, fear of using epinephrine, or a combination of these issues.

Recent findings

This review focuses on what self-injectable epinephrine devices (SIED), such as auto-injectors and prefilled syringes, are preferred by patients and healthcare professionals (HCP). Our findings suggest that a device's ease to use, proper and frequent training on its operability, and availability have an impact on preferences and adherence to treatment with SIEDs. After prescribing a patient with a SIED, clinicians should emphasize its use in anaphylaxis, educate patients/caregivers to identify anaphylaxis and on how to use the SIED, and encourage constant practicing with training devices.

Summary

Epinephrine is the sole recommended anaphylaxis treatment and SIEDs are of critical usefulness in the community setting. Further studying of these devices is needed to optimize education for HCPs and patients and their accessibility to SIEDs.

Keywords

anaphylaxis, auto-injector, epinephrine

INTRODUCTION

Anaphylaxis is an acute, potentially life-threatening systemic allergic reaction with an estimated prevalence between 1.6 and 5.1% [1^{••},2,3]. There are several anaphylaxis pathways depending on triggers; and phenotypes (type I IgE/non-IgE, cytokine release, mixed, and complement) and endotypes depending on involved cells (mast cells, basophils, T cells, macrophages, monocytes), molecules [immunoglobulin (Ig) E, IgG, or complement C5a and C4a] and released mediators [histamine, tryptase, TNF- α , interleukin (IL) 6, IL-1 β] [4]. Depending on the pathway by which anaphylaxis ensues, the symptoms can be several, and in many cases, may overlap; however, the main treatment regardless of the pathway is epinephrine [4]. The first-line of treatment for anaphylaxis is intramuscular epinephrine administered into the anterolateral thigh [1^{••}]. It has been shown that failure to promptly use intramuscular epinephrine in anaphylaxis is associated with higher rates of complications, hospitalizations, and deaths [5,6[•]]. Self-injectable epinephrine devices (SIEDs) in the form of epinephrine auto-injectors (EAI) are a useful

and preferred method of management of anaphylaxis, specially outside the hospital setting [7–9]. Despite all this, recent reports suggest that epinephrine for the treatment of anaphylaxis remains underutilized [10–12]. In this review, we focus on the current attitude and adherence of healthcare professionals (HCP) and patients to SIEDs, and the possible factors that may influence their use, such as patient education on anaphylaxis, and device

^aDivision of Pulmonary, Allergy and Sleep Medicine, Department of Medicine, Mayo Clinic, Jacksonville, Florida, USA, ^bSchool of specialization in Allergy and Clinical Immunology, University of Verona, ^cAsthma Center and Allergy Unit, Verona University Hospital, ^dDepartment of Medicine, University of Verona, Verona, Italy, ^eUniversity Hospital of Montpellier, Montpellier, ^fSorbonne Université, INSERM UMR-S 1136, IPLESP, Equipe EPAR, Paris and ^gWHO Collaborating Centre on Scientific Classification Support, Montpellier, France

Correspondence to Alexei Gonzalez-Estrada, MD, 4500 San Pablo Road, Jacksonville, FL 32224, USA. Tel: +1 904 953 2451; fax: +1 904 953 0017; e-mail: gonzalez.alexei@mayo.edu

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KEY POINTS

- According to current guidelines, epinephrine is the only recommended treatment for anaphylaxis.
- Epinephrine in the shape of self-injectable devices (SIEDs), such as EAls, is the best available option for treatment of anaphylaxis in the community setting.
- Although epinephrine is essential to treat anaphylaxis, commercial availability of EAls is limited to 32% of countries worldwide.
- The ability to identify cases of anaphylaxis, proper use of SIEDs, and cost and availability of these devices are all factors that may determine a patient's or HCP's preference and adherence to SIEDs to treat anaphylaxis.
- Thorough and constant training on how to properly operate a SIED has been shown to increase the use of these devices and improve the outcomes of patients with anaphylaxis.

differences, preferences, training, and accessibility to SIEDs.

PATIENT EDUCATION ON ANAPHYLAXIS

One of the key elements to promptly treat anaphylaxis is knowing how to recognize an episode. The diagnostic criteria proposed by the National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network (NIAID/FAAN) [13] are likely being increasingly used as the method to diagnose anaphylaxis [1[¶]]; however, there are still differences in diagnostic criteria depending mostly on geographically defined academic consensuses [14[¶]]. Although these criteria are mostly to guide clinicians to diagnose anaphylaxis, an attempt should be made to familiarize patients and their caregivers with manifestations of anaphylaxis.

Previous reports suggest that the low rates of patients' use of epinephrine during anaphylaxis are because of the inability to identify its manifestations, lack of emergency action plans, and fear of epinephrine side effects [10,15–17]. In that regard, current international and United States guidelines recommend that after a first episode of anaphylaxis, patients are prescribed an EAI and referred to an allergist [1[¶],18–20]. The aim of an allergy follow-up should include educating patients on anaphylaxis and its manifestations, avoidance of triggers, treatment with epinephrine, and use of EAls [1[¶]]. Despite these recommendations, a considerable number of patients are not referred to an allergist. As reported by Motosue *et al.* [21], out of 18 279

patients seen at an emergency department in the United States for anaphylaxis between 2005 and 2014, only 29% had an allergy follow-up within 1 year of emergency department discharge.

Patients need to be educated on the likelihood of anaphylaxis reoccurrence in order to understand the need for these follow-up visits. Roughly 10% of patients with history of anaphylaxis present a reoccurrence within 12 months after the initial episode, and reoccurrences appear to be more common in children, patients with allergic rhinitis or asthma, and an initial episode because of food allergens [22–24,25[¶]]. Stronger efforts are needed to encourage clinicians to refer patients with history of anaphylaxis to an allergist and for patients to seek such follow-up allowing them to identify new episodes and adequately manage them.

SELF-INJECTABLE EPINEPHRINE DEVICES NOWADAYS

EAls were first introduced in the 1980s with two alternative doses (0.15 and 0.3 mg) [7,26[¶]]. Since then, EAls have evolved in search for more user-friendly devices, better safety, increased ergonomics and even comfort to carry the device at all times; combined, these changes aim for higher prescription rates and better patient adherence.

EpiPen (Mylan Specialty L.P., Basking Ridge, New Jersey, USA) was approved by the US Food and Drug Administration (FDA) in 1987 and remained the only available EAI in the United States until 2005 when alternative devices started to launch [27].

There are different SIEDs available, some of which exist in brand and generic versions (Table 1). However, their commercial availability is restricted in over 65% of countries worldwide [28]. In the United States, there are pen-style EAls, such as EpiPen and its generic alternatives, authorized generic EAls of the discontinued Adrenaclick (Impax Laboratories, LLC), and a device named Auvi-Q (Kaleo, Inc. Richmond, Virginia, USA). Another SIED is SYMJEPI (Sandoz, a Novartis Division, Princeton, New Jersey, USA), which is not an EAI, but an epinephrine prefilled syringe (EPS) [29[¶]].

Pen-style EAls have similar functionality. There are three major differences between Adrenaclick and EpiPen devices mostly regarding needle gauge and injection technique. The decision regarding the best SIED for each patient should ideally be made during an open discussion between clinician and patient (or caregiver) taking these differences into consideration.

The design of devices and characteristics of individual patients may have an effect on the delivery of

Table 1. Main differences between EpiPen, Auvi-Q, Symjepi, Emerade, and generic devices

Characteristic	EpiPen	Auvi-Q	Symjepi	Emerade ^a	Generic ^a
Type of device	EAI	EAI	Prefilled syringe	EAI	EAI
Available doses ^b (mg)	0.15 ^c , 0.3	0.1 ^d , 0.15, 0.3	0.15, 0.3	0.15, 0.3, 0.5	0.15, 0.3
Devices included per package	2	2	1 or 2	1 or 2	2
Trainer included	Yes	Yes	No	No	Amneal: no Teva: yes
Injection technique ^{e,f}	Swing, push until click, and hold	Place, press, and hold	Manual injection, press on plunger until click, and hold	Place, press, and hold	Amneal: place, press, and hold Teva: swing, push until click, and hold
Hold against thigh after injection (seconds) ^f	3	5	2	5	Amneal: 10 Teva: 3
10-s massage of injected area ^g	Yes	No	Yes	Yes	Yes
Needle safety guard	Auto-retractable	Auto-retractable	Manual (sliding mechanism)	Auto-retractable	Amneal: manual (re-cap) Teva: auto-retractable
Audio instructions	No	Yes	No	No	No

^aIncludes authorized generics of EpiPen by Teva Pharmaceuticals USA, Inc. (North Wales, Pennsylvania, USA) and of Adrenaclick (discontinued) by Amneal Pharmaceuticals LLC (Bridgewater, New Jersey, USA).

^b0.1 mg dose for patients 7.5–15 kg (16.5–33 lb), 0.15 mg dose for patients 15–30 kg (33–66 lb), 0.3 mg dose for patients 30 kg (66 lb) or more, 0.5 mg dose for patients 60 kg or higher.

^cSold as EpiPen Jr.

^dSold as Auvi-q.

^eAll devices are intended for epinephrine injection to the anterolateral side of the thigh.

^fAs per instructions for patients provided by each device manufacturer.

^gNot available in the United States. Emerade Medeca Pharma AB, Uppsala (Sweden).

the medication and its ability to reach the desired intramuscular level. Needle lengths of EAI's range from 7.5 to 25 mm and the importance of this factor has been studied as it may affect an EAI's chances of adequate (intramuscular) or inadequate (subcutaneous, periosteal, and intraosseous) injection [30–34]. This is of particular importance when choosing SIEDs for pediatric or overweight and obese adults who may be at higher risk of periosteal/intraosseous and subcutaneous injections, respectively [30,33].

PATIENTS AND HEALTHCARE PROFESSIONALS: ADHERENCE AND PREFERENCES

The patients' perspective and its effect on adherence

Some studies have focused on the patients' perspectives of SIEDs and the factors that influence their adherence to epinephrine during anaphylaxis. Portnoy *et al.* [35^{***}] reported that out of 2000 patients prescribed with Auvi-Q ($n=1000$) or EpiPen ($n=1000$), those prescribed with Auvi-Q were

almost twice as likely to carry the EAI at all times, felt more confident about using the device correctly, found the instructions clearer, and found the trainer device more helpful than those prescribed with EpiPen. In that study, the patients reported seven reasons for why they did not carry their EAI (from most relevant to least relevant): they did not think they would be exposed to the allergen, they had not needed the device in the past, they forgot to carry it, their symptoms were not severe enough to warrant carrying the device, size of the device, shape of the device, and low confidence in correctly using the EAI [35^{***}]. This study emphasized the importance of devices' ergonomics and user-friendliness, as well as proper education as some of the criteria patients consider key to their adherence to EAI's for the treatment of anaphylaxis.

A study involving interviews of 15 patients who had been prescribed EpiPen found that public acceptability of EAI's, previous experiences, carrying the device, and device design were the five main issues affecting the likelihood of a patient adhering to the device in case of anaphylaxis [36]. Eleven of the 15 patients reported a reaction that required

treatment with epinephrine; however, only 7 of them had used the EAI [36]. The issues the patients had with the device involved inconsistent health professional advice, social perception of carrying/using the device in public, adequacy of the dose, access to the medication through emergency services, having not needed to use the device during previous episodes, outcomes of using the device previously, and doubts whether the benefits of carrying/using the device outweighed the potential risks [36].

Similarly, the way patients/caregivers perceive anaphylaxis, the life challenges posed by the condition (avoidance of triggers, and cost of alternative foods and EIAs), social/family isolation, constant anxiety and fear of anaphylaxis and of inflicting further pain through the EAI, guilt, influence of HCPs, and lessons learned; were the eight main topics that impacted 10 caregivers' experiences and knowledge of the use of epinephrine for anaphylaxis in a study by Chooniedass *et al.* [37]. HCPs may have an impact on a caregiver's likelihood of using the EAI when needed through attitudes and instructions. Caregivers reported that the fact that EIAs were not used in hospitals during anaphylaxis, discouraged them from using the devices in future potential episodes; stating that HCPs should be role models for caregivers of patients with anaphylaxis [37]. Furthermore, caregivers also mentioned that in some occasions, they had been berated by HCPs for not using the EAI before seeking medical attention at an emergency department and that this had impacted negatively the caregivers' perception of the device and the HCPs, and increased the sense of guilt already experienced because of hesitance to use EIAs [37]. Lastly, caregivers reported that having experienced episodes of anaphylaxis and recorded each episode, had led them to better ways of coping and more proactive management of later episodes [37]. Even though the studies by Money *et al.* [36] and Chooniedass *et al.* [37] were limited by their small samples, they elucidate some key points that need addressing in order to improve adherence, and they highlight the need to expand education not only to patients/caregivers but also to include HCPs in order to avoid having a negative impact on adherence to EIAs.

Adherence and preferences based on devices designs and operability

It is possible that patients will have better adherence to SIEDs if these are easy to carry and operate. EpiPen containers are 5.5" long and 1" in diameter compared with Symjepi's case, which is 4.1" long, 1.6" wide and 0.9" deep, and Auvi-Q's 3.5" long, 2" wide,

and 0.5" deep case [29[■]]. Auvi-Q was reportedly preferred over EpiPen and Twinject (discontinued in the United States) for its portability, shape, and smaller size [38,39]. Future studies could broaden the comparisons of portability between different EIAs and SIEDs.

Operability of SIEDs might play an essential role in patients' preferences. At first glance, EIAs could seem easier to operate than EPS, such as Symjepi as the latter requires knowledge of injection techniques. However, the ease of use of Symjepi and EpiPen devices was compared in 34 untrained individuals aged 12–17 years old, and no operating errors were found in the Symjepi cohort ($n=17$) compared with four use errors in the EpiPen trainer cohort ($n=17$) [40]. Further studies could focus on whether these error rates are significant between EPS and other EIAs, and whether such difference exists amongst alternative demographics.

After proper training by an HCP, understanding of EIAs operability can be reached through each device's information leaflets, labels, and other audio and/or visual instructions. One study reported that the design and label comprehension, as well as audio instructions of one EAI, were considered easy and helpful by patients who successfully completed simulated injections with the device [41]. Patients were found to be better at operating one EAI over others and preferred that device based on methods and clarity of instructions [38,39,42[■]]. A study found that out of 693 patients/caregivers aged 11–65 years of different demographics, experience with EIAs, and education level, 533 preferred Auvi-Q over EpiPen (77 versus 17%; $P<0.001$) based on the device's method of instruction and easier to follow instructions [38]. Furthermore, 521 individuals correctly completed all injection steps with Auvi-Q compared with 240 individuals with EpiPen (75 versus 35%; $P<0.001$) [38]. Similarly, Guerlain *et al.* [39] reported that the same device was preferred over EpiPen and Twinject devices based on clarity of instructions, and ease of use [39]. These factors can impact a patient's preference for one device over others and their adherence to treatment.

Reasons for patients' nonadherence could be multiple; from failure to fill a prescription to failure to carry the EAI at all times, lack of knowledge in its operability, and fear of adverse effects of epinephrine. Reported rates of EAI adherence are only as high as 76% and out of the few patients who fill their EAI prescription, the rates of errors in use is high and others do not use the EAI for fear of adverse effects; with adherence rates being generally higher in patients less than 18 years old [43,44[■],45[■],46,47]. It is important that HCPs and patients/caregivers have open discussions to choose the best SIED and

that patients receive education on its operation, its safety and the need to use it during anaphylaxis, helping the patient to feel confident and safe to use the EAI.

The healthcare professionals' perspective

Similar factors can determine an HCP's preference for a specific epinephrine administration method. A 2010 study reported that nurses from different settings (emergency department, pediatrics, school, allergy clinic, acute care, radiology, delivery, family practice, clinic, or public health) preferred an EAI over other methods after receiving proper training in its use, and that the safety features and easier instructions on the SIED had influenced their preference [48].

Reportedly, the use of epinephrine (drawn or in EAI) for anaphylaxis in the emergency department and prescriptions for EAI are low with some exceptions, such as the United Kingdom and Australia [10–12,21,49–54]. Recent interest has developed regarding the use of EAI in the hospital setting. In a survey completed by 182 HCPs, 82% preferred using an EAI over drawn epinephrine, with significant results based on time required for training, ease of use, convenience, dosing satisfaction, risk of dosing errors, and speed of administration [55]. However, in the same study, EAI was considered to increase the risk of HCP self-injury and to increase the cost for patients [55]. Another study found that HCPs using EPS had a higher rate of correct use than using EpiPen [56]. The use of drawn epinephrine has also been associated with a higher risk of potentially life-threatening errors [57].

EAI prescription rates after an episode of anaphylaxis are generally low [18,21] and it is possible that these rates are affected by factors, such as dosing issues, and needle gauge and length [26,58]. A 2017 study reported that 3622 (46.5%) out of 7790 patients had an EAI dispensed within 1 year after discharge from an emergency department for anaphylaxis [18]. This study reported that patients at least 65 years and patients with medication-induced anaphylaxis had lower likelihood of getting an EAI dispensed, whereas patients less than 5 years old and patients with food-induced anaphylaxis had higher likelihood of EAI dispensing [18]. Future studies could focus on comparing different SIEDs with drawn epinephrine in terms of usability, risk–benefit, and cost–benefit in the hospital setting.

EPINEPHRINE AUTO-INJECTOR TRAINING

There is evidence that knowledge on EAI use is not adequate in HCPs and patients/caregivers, leading

to frequent mistakes, misplaced injections, and accidents, such as doses injected on digits or received by someone other than the patient with anaphylaxis [59–62].

Properly training HCPs and patients/caregivers on the use of EAI is of the utmost importance for better adherence and outcomes. It has been suggested that regular and repeated training sessions can be of greater benefit than single sessions with an allergist [63]. In this regard, Topal *et al.* [64] showed that HCPs can benefit from frequent EAI training as these skills decrease more after 6 months posttraining than after 3 months posttraining. A study by Sirin Kose *et al.* [65] focused on the advantages of training caregivers of pediatric patients with anaphylaxis in the operability of an EAI. The study found that 47 (79.7%) out of 59 caregivers always carried an EAI and that they had practiced with an EAI training device after education in the hospital [65]. They also reported that the probability of properly using an EAI was higher when the caregivers received training every 6 months (96%) than when the training occurred in 12-month and 18-month intervals (70.1 and 18.6%, respectively) [65]. Another recent study showed that parents and patients did not use EAI properly because of a lack of training, and that training sessions on every follow-up visit could benefit the confidence to use EAI and treatment adherence [44].

Since a great number of anaphylaxis episodes occur outside the hospital setting, training sessions should be sought for in community settings. In recent years, there have been efforts to promote training of school nurses and staff to identify and manage anaphylaxis focused on EAI. The reports derived from these efforts show that in most cases, only nurses or selected staff receive this training and are allowed to administer epinephrine for anaphylaxis; and agree that broader and continuous training of staff are recommendable [66,67,68,69,70]. It is possible that if training of school staff on the use of EAI was broader and occurred more frequently, there would be better outcomes of anaphylaxis cases in that setting.

AVAILABILITY OF SELF-INJECTABLE EPINEPHRINE DEVICES

In general, access to SIEDs is difficult, and the obstacles go beyond the financial aspect; however, most of the studies that focus on SIED accessibility focus on this issue [71–74]. Being able to properly identify anaphylaxis and use SIEDs to treat it is only important if patients who get prescribed with EAI are also able to get the devices. EAI are expensive

(from \$250 to \$608) and have exponentially increased prices in recent years [29[■],75–78].

Whenever EAI is not available or affordable, physicians may recommend alternative formulations; however, there are some disadvantages to these options. Prescribing patients with 1 mg/ml ampules of epinephrine and empty syringes is an option; however, drawing the proper dose of epinephrine is more time-consuming and complicated than using EAI as it warrants more thorough training [75]. Another alternative is EPS, such as Symjepi, which is priced lower (\$250) than other SIEDs [29[■]]. The disadvantages of this alternative are the need for thorough training in intramuscular injections, and stability issues; however, the stability of epinephrine solutions appears to be well tolerated for up to 3 and 2 months in climates with extreme temperatures [75].

Since the US School Access to Emergency Epinephrine Act of 2013 [79], there have been efforts to make EAI more widely available in the United States. The reports resulting from the EIPEN4-SCHOOLS program (Mylan Specialty L.P. Canonsburg, Pennsylvania, USA) showed that the majority of anaphylactic episodes in schools happen to students and because of foods, and less than half of the cases are managed with EAI with some cases being managed with drawn epinephrine or medications different to epinephrine [66,68,80,81]. Similarly, a Chicago-based study showed that 38 district-issued EAI were administered in Chicago Public Schools to students (92%) and staff (8%) [82]. These studies suggest that having readily available EAI in schools can improve adherence to epinephrine for anaphylaxis and episode outcomes.

In the United States, the cost of stocking non-healthcare places with SIEDs could be significant and may present disadvantages compared with relying in already established emergency services, namely the emergency medical services (EMS). For example, the unsubsidized annual cost of providing Michigan public schools with EAI can be as high as \$4846800 without considering the cost of training school personnel to use the devices [83]. Furthermore, a 2019 report concluded that having stock EAI in Australia would be too expensive and EAI are limited to schools with at-risk students and/or supplied by parents [69[■]]. In contrast, some models, such as having universal stock epinephrine usable for all students instead of having individual students provide their own SIED to use exclusively at school, have been shown to be cost-effective in certain populations and to provide better health and economic outcomes [84[■]]. Similarly, having stock twin-pack EAI in commercial aircrafts was found to be cost-effective at a \$2470422 per year cost or \$0.08

per passenger-at-risk [85[■]]. The cost-effectiveness of having stock SIEDs in nonhealthcare environments warrants further study comparing all current options and in different populations.

CONCLUSION

Epinephrine remains the treatment of choice for anaphylaxis and SIEDs, such as EAI and EPS are essential options to manage anaphylaxis in the community. Recent government/healthcare efforts have made EAI more widely available in the community. The importance of training HCPs and patients/caregivers in use of SIEDs has been underlined by recent studies that suggest these measures will improve patients' adherence to treatment with epinephrine and EAI prescription rates by clinicians. Future studies could broaden our understanding of the benefits and cost-effectiveness of thorough training on recognition of anaphylaxis, use of SIEDs, and availability of these devices in different populations.

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- of special interest
- of outstanding interest

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