

EPINEPHRINE PROFESSIONAL

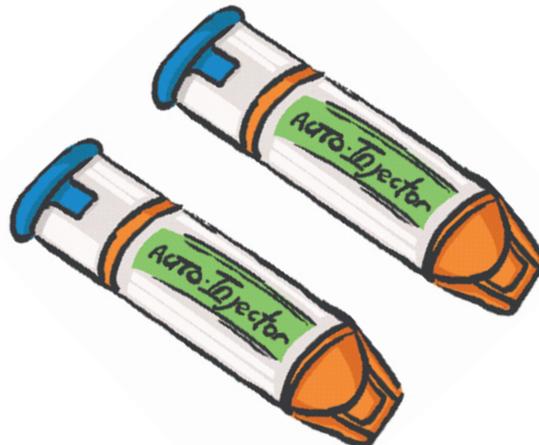
Autoinjector Comparison

EPINEPHRINE CONVENIENCE KITS



vs.

EPINEPHRINE AUTOINJECTORS



Challenging historical dogma: should you really have epinephrine autoinjectors in your emergency kit?

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What should the price for convenience be? Back in 2010, most of us were comfortable paying just over \$100 for the EpiPen 2-Pak (Mylan Specialty, LP) to stock our emergency kit. This was the most expensive drug and dosage form in our kit, but it gave us peace of mind that in an emergency situation we had access to the right lifesaving medication in an easy-to-administer formulation, even if the typical shelf life required us to purchase a replacement every 12-18 months. In 2015, when the price tripled to \$300 for the EpiPen 2-Pak—partly due to the American Heart Association's "endorsement" of autoinjectors in their updated cardiopulmonary resuscitation guidelines, the first time the guidelines referenced a particular dosage form

(autoinjector) and not just an active drug (epinephrine)—many practitioners began to question the value of these single-use applicators, as did social media, journals, and other publications.^{1,2} When the price for the EpiPen 2-Pak doubled to \$600 in 2016, and parents with at-risk children now had to decide between this dosage formulation and food on their tables, enough was enough.³

Hospitals, clinics, emergency responders, and even dental offices are beginning to question the historical dogma: Are epinephrine autoinjectors truly essential in emergency kits? Is the price for convenience really worth the value? Should it all be about price?

What should really be in your medical emergency kit?

There is general agreement among oral healthcare practitioners as to the essential medications in emergency medical kits: epinephrine, diphenhydramine, nitroglycerin, albuterol, glucose, aspirin, and oxygen.^{4,5} Furthermore, it is incumbent on all oral healthcare providers to keep up to date with the regulations of their licensing board regarding the specific emergency medications needed to remain compliant with the rules of the state or province in which they are licensed to practice. If the board states that practitioners must have a particular medicine available, then that medication must be available—and in date—if a medical emergency in which that medication may be appropriate arises.

A good example of an emergency medication that some oral healthcare practitioners

currently may be required to have available is smelling salts (ammonia inhalants). Despite their clear lack of safety and efficacy in addressing the underlying pathophysiology of syncope, ammonia inhalants remain part of medical emergency kits for some dental offices.⁶ This is just one example of historical dogma that is slowly changing in clinical and regulatory practice; indeed, there is a strong safety argument to be made for not exposing patients to this nonspecific respiratory irritant, because it can worsen the condition of a patient with airway edema or infection, can trigger acute asthma, and will increase intracranial pressure.⁷ According to the material safety data sheet, inhaled ammonia can cause a "[b]urning pain in the mouth and throat, constriction of the throat and coughing followed by nausea, vomiting or diarrhea when ingested or inhaled."⁸

The argument for putting patient safety first: Epinephrine is the most important medication in the minimal dental emergency kit. It is a true, lifesaving, α 1-adrenergic vasoconstrictor that reverses an immediate type 1, immunoglobulin E-mediated anaphylactic reaction by relieving upper airway obstruction, increasing blood pressure, and decreasing mucosal edema, thereby relieving and preventing shock. There are no absolute contraindications to epinephrine use in patients experiencing anaphylaxis, and most dental offices have 1:1000 epinephrine available in a very convenient autoinjector formulation that facilitates fast and easy administration.⁹ Since patient safety is always the primary concern, and the oaths of beneficence and non-maleficence that all dentists took upon graduation included "First, do no harm," it is necessary to validate whether autoinjectors are really the safest dosage form to administer life-saving epinephrine.

While autoinjector formulations have been designed for both the public and the trained healthcare worker to inject, this delivery mechanism is not entirely intuitive and has led to inadvertent lacerations and self-injections.¹⁰⁻¹⁴ Once the device is removed from the plastic case, the instructions are to first remove the cap (Fig 1). Removal of the cap exposes a hole that the cap had covered; one's instinct might suggest that this hole should be where the needle comes out (Fig 2). The opposite end of the auto-injector is a distinctly different color and has the appearance of a

button over which the user would naturally place the thumb to administer the injection (Fig 3). Unfortunately, because of this poor design, and especially during a stressful event such as a life-threatening medical emergency, autoinjector self-injections occur because the "button" end is actually where the needle comes out (Fig 4). Every year there are multiple reports of inadvertent self-injections in the literature, enough to enable a meta-analysis (the highest level of medical evidence) on this topic, raising questions about the safety of this dosage formulation.¹⁵⁻¹⁷

Another significant concern about the safety of autoinjectors is that they are all equipped with a 28-gauge, 0.5-inch needle. Several studies have shown that this needle length may be inadequate to deposit epinephrine into the rich capillary bed beneath the vastus lateralis (thigh) muscle so that systemic epinephrine levels rise fast enough and high enough to save the patient's life.¹⁸⁻²⁰ It would appear that some manufacturers of epinephrine autoinjectors are aware of this design flaw, since, rather than change their production to include a needle of appropriate length, they ask patients to continue to press and hold the autoinjector in place for an additional 3-10 seconds, depending on the product.²¹⁻²⁵ This is something that is difficult to do for anyone suffering an immediate and accelerated anaphylactic reaction and certainly not an appropriate response to overcome a potential design flaw.

The argument for efficacy: Given the design challenges of all currently available epinephrine autoinjectors, the efficacy of these products is also being called into question. Needle length inadequacy was the primary reason for the recent removal of one epinephrine autoinjector (Auvi-Q, Sanofi US) from the market, as the company had received 26 reports of device malfunctions from patients in the United States and Canada as of October 26, 2015. No one died as a result, but patients continued to experience symptoms of hypersensitivity reaction.²⁶

Another challenge related to efficacy has to do with the shelf life of all autoinjectors, which is consistently between 12 and 18 months. This contrasts with the more than 2 years of best-use dating for most ampules and vials of 1:1000 epinephrine. This shorter shelf life can sometimes mean that expired medication,

which may not be as potent or efficacious and could lead to poor patient outcomes, is being administered in an emergency situation.

In addition, because epinephrine has a half-life of around 2 minutes, many patients may require a second dose of this lifesaving medication if emergency medical personnel cannot reach the patient within 10 to 15 minutes of the initial dose. To be best prepared, most dental offices should carry at least 2 adult and 2 pediatric epinephrine autoinjectors, in date, at all times. This is the reason that most autoinjectors are available for purchase in a twin pack.²⁷ Since up to 16% of the general population are considered to be hyporesponders, it may even be prudent for more remote locales to have 3 adult and 3 pediatric autoinjectors at all times, should the patient require a third dose.²⁸

What about the price?

Since safety and efficacy concerns do not always make as eye-catching headlines as monumental price hikes, publicity has focused more on the geometric increase in price of these autoinjectors. The price of a 1-mL ampule of 1:1000 epinephrine has remained stable at around \$1, and a 1-mL vial of the same drug costs about twice as much. Each of these dosage forms contains enough medicine for 3 adult doses, whereas the adult single-dose EpiPen autoinjector—with its shorter shelf life, poor design, and inadequate needle length—has an average wholesale price of \$730.33 for the 2-pack at the time of writing. Recently, the manufacturer has decided to introduce an “authorized generic” version of EpiPen for approximately \$300.29. Meanwhile, the Adrenaclick epinephrine autoinjector

(Amedra Pharmaceuticals, LLC) is sold in a 2-pack for approximately \$500.30

Perhaps a better alternative from a safety, efficacy, and cost perspective would be for dental practitioners to make their own anaphylaxis kits: a 1-mL vial or ampule of 1:1000 epinephrine; a 1-mL syringe; a 25-gauge, 1.0- to 1.5-inch needle; any other needed supplies (eg, alcohol wipe, labels); and step-by-step instructions with pictures. This would certainly offer a better alternative than the historical dogma and at a price point that allows for frequent practice to demonstrate competency. While oral healthcare providers may be reluctant to access medication in vials or ampules, given the increased complexity inherent to these dosage forms compared to the more convenient autoinjector formulations, this lack of understanding or training can be overcome with regular practice to ensure competency.

Alternatively, clinicians could consider a similar, commercially available kit that retails for just over \$100.31

Conclusion

There are many longstanding dogmas in medicine that deserve review as new data, techniques, devices, and evidence come to light. Epinephrine autoinjectors have undergone such significant price increases over the last few years that an investigation into their relative value compared to the convenience they provide is warranted. Based on current evidence, additional safety and efficacy concerns with this dosage form indicate that preparing your own anaphylaxis kit may be a better approach to keeping patients safe.

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Disclaimer

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EPI NEPHRINE PROFESSIONAL

Autoinjector Comparison

	 EPI NEPHRINE PROFESSIONAL NDC 24357-011-13	Epinephrine Autoinjector 	Epinephrine Autoinjector Junior 
Cost	<\$100	>\$200	>\$200
Epinephrine	1 mL Vial	Pre-filled Dose	Pre-filled Dose
Number of Doses	3	2	2
Adult & Pediatric	YES both Adult and Pediatric	Only persons weighing greater than 30 kg. (60 lbs.)	Only persons weighing greater than 15-30 kg. (33-60 lbs.)
Dating	Up to 24 Months	?	?
Availability	YES	?	?
Intuitive	YES	NO	NO
FDA Status	Registered	Registered	Registered
Manufacturing	FDA Licensed Repackager	FDA Licensed Manufacturer	FDA Licensed Manufacturer

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