

# Autoinjector Misconceptions – A Review of the Evidence

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Since the introduction of the “patient-friendly” autoinjector formulation, millions of doses of EpiPen® and EpiPen® Jr. have been sold in the United States and throughout the rest of the world. Today there are a number of other autoinjectors available to deliver the life-saving medication epinephrine (AdrenaClick®, Epinephrine Injection® USP [Mylan], Epinephrine Injection® USP [Teva], and Auvi Q®), but the progenitor product EpiPen® has really become synonymous with epinephrine autoinjectors in the same that we use Kleenex® when referring to tissue paper. The question today is whether we have become so acclimatized to this product that we no longer question its safety and clinical effectiveness – two things which are paramount in-patient care.

Myth	Review of Evidence
<b>Safety</b>	
<p><b>The FDA approved design of autoinjectors provides easy and safe delivery epinephrine for anaphylaxis events</b></p> <p><b>Healthcare professionals are proficient in the use of autoinjectors</b></p> <p><b>Autoinjector’s needles always deliver lifesaving epinephrine and never are associated with failures</b></p>	<ul style="list-style-type: none"> <li>• <i>Device failure from spontaneous activation caused by using sideways force to remove the blue safety release</i><sup>1,3,5,6,7,9,10,20,22,23</sup></li> <li>• <i>Device failure from inadvertent or spontaneous activation due to a raised blue safety release</i><sup>1,9,10,20,22,23</sup></li> <li>• <i>Difficulty removing the device from the carrier tube</i><sup>1,9,10,20,22,23,27,</sup></li> <li>• <i>User errors</i><sup>1,2,3,4,5,6,7,9,10,11,12,13,14,15,20,22,23,26,28,29,30,31,33</sup></li> <li>• <i>One third of the user errors reported to the FDA Adverse Events are from healthcare professionals</i><sup>3,4,6,7,9,10,14,15,16,17,18,19,20,21,22,23,24,25,27,29,30,31,32,33</sup></li> <li>• <i>There have been additional autoinjector failures due to the short needle length and therefore the inability to deposit this lifesaving drug to the fine capillary bed below the vastus lateralis (thigh muscle) when administered</i><sup>21,22,28,29,32</sup></li> </ul>
<b>Efficacy</b>	
<p><b>Only one twin pack of autoinjectors needs to be stocked according to regulatory guidelines</b></p> <p><b>Autoinjectors always administers the right amount of epinephrine for the right patient</b></p>	<ul style="list-style-type: none"> <li>• <i>CDC through IAC guidelines calls for three doses of epinephrine which would require 2 adult twin packs for adults and/or 2 junior twin packs of pediatrics</i><sup>20,29,34</sup></li> <li>• <i>Other challenges have arisen from giving the wrong dose (strength) to the wrong patient (pediatric versus adult), since the autoinjector delivers the entire contents of the device when it is activated</i><sup>18,20,22,23,25,27,29</sup></li> </ul>
<b>Costs</b>	
<p><b>Only one twin pack of autoinjectors needs to be stocked</b></p> <p><b>Autoinjectors are the most the most cost-efficient method of complying with the epinephrine requirement</b></p>	<ul style="list-style-type: none"> <li>• <i>Autoinjectors are designed to deliver 0.3mg of 1:1000 epinephrine to adult patients while the Junior is designed to deliver half that amount, 0.15mg of 1:1000 epinephrine, to pediatric patients. The challenge with the autoinjectors is that they are single use only and you cannot give the adult formulation to pediatric patients and vice versa, so practitioners who treat both adults and children must have three autoinjector of each strength to comply with IAC guidelines</i><sup>34</sup></li> <li>• <i>The half-life of epinephrine is only two minutes so if patients need subsequent injections, or the EMTs are more than 10-15 minutes away, then some patients require a third injection</i><sup>34</sup></li> <li>• <i>Epinephrine convenience kits probably provide value beyond the safety and efficacy concerns listed above. They have the appropriate length needle, a vial of epinephrine to accommodate multiple doses of adult or pediatric injections, a longer shelf life, and all at a price point far below the average wholesale price of all autoinjectors currently available in the U.S.</i><sup>20,21,22,23,25,26,27, 34</sup></li> </ul>

## Summarizing Autoinjector Misconceptions

There is a plethora of evidence from the medical literature demonstrating that epinephrine autoinjectors are not as safe nor as clinically efficacious as we continue to trust and believe. The clinical pitfalls of the autoinjectors should convince practitioners that kits offer the additional advantage of a medical time out; not to slow the delivery of care, but to insure we maximize both the safety and efficacy of this life-saving drug. The use of an epinephrine kit may also be more desirable since it provides more than one dose of epinephrine in managing both pediatric and adult patients. Furthermore, the kit contains needles of appropriate length to overcome some of the failures seen with autoinjectors. Lastly, the shelf life of these kits is typically much longer than the autoinjectors so practitioners do not have to waste and re-purchase stock as often due to outdated products. All of these clinical benefits are significant, especially when considering the convenience cost and price of the autoinjector dosage form.

## References from the Peer-Reviewed Literature

1. FDA alerts patients and health care professionals of EpiPen auto-injector errors. March 23, 2020. Available at: <https://www.fda.gov/media/136389/download>.
2. Singer AJ. Accidental digital self-injection of epinephrine: debunking the myth. *Ann Emerg Med*. 2010;56(3):275-277.
3. Carrascosa MF, Gallastegui-Menéndez A, Teja-Santamaria C, Caviedes JR. Accidental finger ischaemia induced by epinephrine autoinjector. *BMJ Case Rep*. 2013;2013:bcr2013200783. Published 2013 Sep 18. doi:10.1136/bcr-2013-200783.
4. Schintler MV, Arbab E, Aberer W, Spindel S, Scharnagl E. Accidental perforating bone injury using the EpiPen autoinjection device. *Allergy*. 2005;60(2):259-260. doi:10.1111/j.1398-9995.2004.00620.x.
5. Walsh K, Baker BG, Iyer S. Adrenaline Auto-injector injuries to digits; a systematic review and recommendations for emergency management [published online ahead of print, 2020 Feb 8]. *Surgeon*. 2020;S1479-666X(20)30016-0. doi:10.1016/j.surge.2020.01.005.
6. Anshien M, Rose SR, Wills BK. Unintentional Epinephrine Auto-injector Injuries: A National Poison Center Observational Study. *Am J Ther*. 2019;26(1):e110-e114. doi:10.1097/MJT.0000000000000541.
7. Hardy SJ, Agostini DE. Accidental epinephrine auto-injector-induced digital ischemia reversed by phentolamine digital block. *J Am Osteopath Assoc*. 1995;95(6):377-378.
8. Schmid M, Weidenhoffer I, Udvardi A, Lomoschitz K, Volc-Platzer B, Wöhrl S. Adrenaline Autoinjector Needle Interlocking in the Thumb Due to Improper Injection. *Open Allergy J*. 2013;6:18-21.
9. Dennerlein JT. Anaphylaxis treatment: ergonomics of epinephrine autoinjector design. *Am J Med*. 2014;127(1 Suppl):S12-S16.
10. Edwards E, Kessler C, Cherne N, Dissinger E, Shames A. Human factors engineering validation study for a novel 0.1-mg epinephrine auto-injector. *Allergy Asthma Proc*. 2018;39(6):461-465. doi:10.2500/aap.2018.39.4171.
11. Brown J, Tuthill D, Alfaham M, Spear E. A randomized maternal evaluation of epinephrine autoinjection devices. *Pediatr Allergy Immunol*. 2013;24(2):173-177. doi:10.1111/pai.12048.
12. Gosbee LL. Nuts! I can't figure out how to use my life-saving epinephrine auto-injector!. *Jt Comm J Qual Saf*. 2004;30(4):220-223. doi:10.1016/s1549-3741(04)30024-9.
13. Robinson MN, Dharmage SC, Tang ML. Comparison of adrenaline auto-injector devices: ease of use and ability to recall use. *Pediatr Allergy Immunol*. 2014;25(5):462-467. doi:10.1111/pai.12261.
14. Schwirtz A, Seeger H. Comparison of the robustness and functionality of three adrenaline auto-injectors. *J Asthma Allergy*. 2012;5:39-49. doi:10.2147/JAA.S33688.
15. Kessler C, Edwards E, Dissinger E, Sye S, Visich T, Grant E. Usability and preference of epinephrine auto-injectors: Auvi-Q and EpiPen Jr. *Ann Allergy Asthma Immunol*. 2019;123(3):256-262. doi:10.1016/j.anai.2019.06.005.
16. Parish HG, Morton JR, Brown JC. A systematic review of epinephrine stability and sterility with storage in a syringe. *Allergy Asthma Clin Immunol*. 2019;15:7. Published 2019 Feb 21. doi:10.1186/s13223-019-0324-7.
17. Greenberger PA, Wallace DV, Lieberman PL, Gregory SM. Contemporary issues in anaphylaxis and the evolution of epinephrine autoinjectors: What will the future bring?. *Ann Allergy Asthma Immunol*. 2017;119(4):333-338. doi:10.1016/j.anai.2017.07.030.
18. Salter SM, Loh R, Sanfilippo FM, Clifford RM. Demonstration of epinephrine autoinjectors (EpiPen and Anapen) by pharmacists in a randomised, simulated patient assessment: acceptable, but room for improvement. *Allergy Asthma Clin Immunol*. 2014;10(1):49. Published 2014 Sep 19. doi:10.1186/1710-1492-10-49.
19. Bardou M, Luu M, Walker P, Auriel C, Castano X. Efficacy of a Novel Prefilled, Single-Use, Needle-Free Device (Zeneo®) in Achieving Intramuscular Agent Delivery: An Observational Study. *Adv Ther*. 2017;34(1):252-260. doi:10.1007/s12325-016-0452-0.
20. Simons FE, Lieberman PL, Read EJ Jr, Edwards ES. Hazards of unintentional injection of epinephrine from autoinjectors: a systematic review. *Ann Allergy Asthma Immunol*. 2009;102(4):282-287. doi:10.1016/S1081-1206(10)60332-8.
21. Goldman RD, Long KC, Brown JC. Hooked epinephrine auto-injector devices in children: four case reports with three different proposed mechanisms. *Allergy Asthma Clin Immunol*. 2020;16:19. Published 2020 Mar 14. doi:10.1186/s13223-020-00418-0.
22. Weinhold T, Del Zotto M, Rochat J, Schiro J, Pelayo S, Marcilly R. Improving the safety of disposable autoinjection devices: a systematic review of use errors. *AAPS Open*. 2018;4(7):1-14.
23. Brown JC, Tuuri RE, Akhter S, et al. Lacerations and Embedded Needles Caused by Epinephrine Autoinjector Use in Children. *Ann Emerg Med*. 2016;67(3):307-315.e8. doi:10.1016/j.annemergmed.2015.07.011.
24. Bakirtas A, Arga M, Catal F, Derinoz O, Demirsoy MS, Turkas I. Make-up of the epinephrine autoinjector: the effect on its use by untrained users. *Pediatr Allergy Immunol*. 2011;22(7):729-733. doi:10.1111/j.1399-3038.2011.01195.x.
25. Potera C. Misuse of autoinjectors and inhalers. *Am J Nurs*. 2015;115(3):17. doi:10.1097/01.NAJ.0000461799.44904.d3.
26. Collett G, Elhusseiny AM, Scelfo C, Whitman MC, VanderVeen DK. Ocular injury via epinephrine auto-injector [published online ahead of print, 2020 Jun 2]. *J AAPOS*. 2020;S1091-8531(20)30101-4. doi:10.1016/j.jaapos.2020.02.008.
27. Sinclair MD, Bailey MA, McAree BJ, Dewhurst D, Kent PJ. Images in vascular medicine: rapid epinephrine 'reversal' with phentolamine following accidental autoinjector inoculation. *Vasc Med*. 2011;16(3):215-216. doi:10.1177/1358863X11404281.
28. Duong M, Botchway A, Dela Cruz J, Austin R, McDaniel K, Jaeger C. Skin to Intramuscular Compartment Thigh Measurement by Ultrasound in Pediatric Population. *West J Emerg Med*. 2017;18(3):479-486. doi:10.5811/westjem.2016.12.32279.
29. Wright M. Treatment after Accidental Injection with Epinephrine Autoinjector: A Systematic Review. *J Allergy Ther*. 2014, 5:3. DOI: 10.4172/2155-6121.1000175.
30. Bodkin RP, Acquisto NM, Gunyan H, Wiegand TJ. Two cases of accidental injection of epinephrine into a digit treated with subcutaneous phentolamine injections. *Case Rep Emerg Med*. 2013;2013:586207. doi:10.1155/2013/586207.
31. Ibrahim M, Kim H. Unintentional injection to the bone with a pediatric epinephrine auto-injector. *Allergy Asthma Clin Immunol*. 2018;14:32
32. Posner LS, Camargo CA Jr. Update on the usage and safety of epinephrine auto-injectors, 2017. *Drug Healthc Patient Saf*. 2017;9:9-18.
33. Topal E, Bakirtas A, Yilmaz O, et al. When should we perform a repeat training on adrenaline auto-injector use for physician trainees?. *Allergol Immunopathol (Madr)*. 2014;42(5):472-475. doi:10.1016/j.aller.2013.07.008.
34. Preventing and Managing Adverse Reactions. General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). Available at: <https://www.cdc.gov/vaccines/hcp/acip-recs/general-recs/adverse-reactions.html>.