Epinephrine and Anaphylaxis: The Evolution of Current Management

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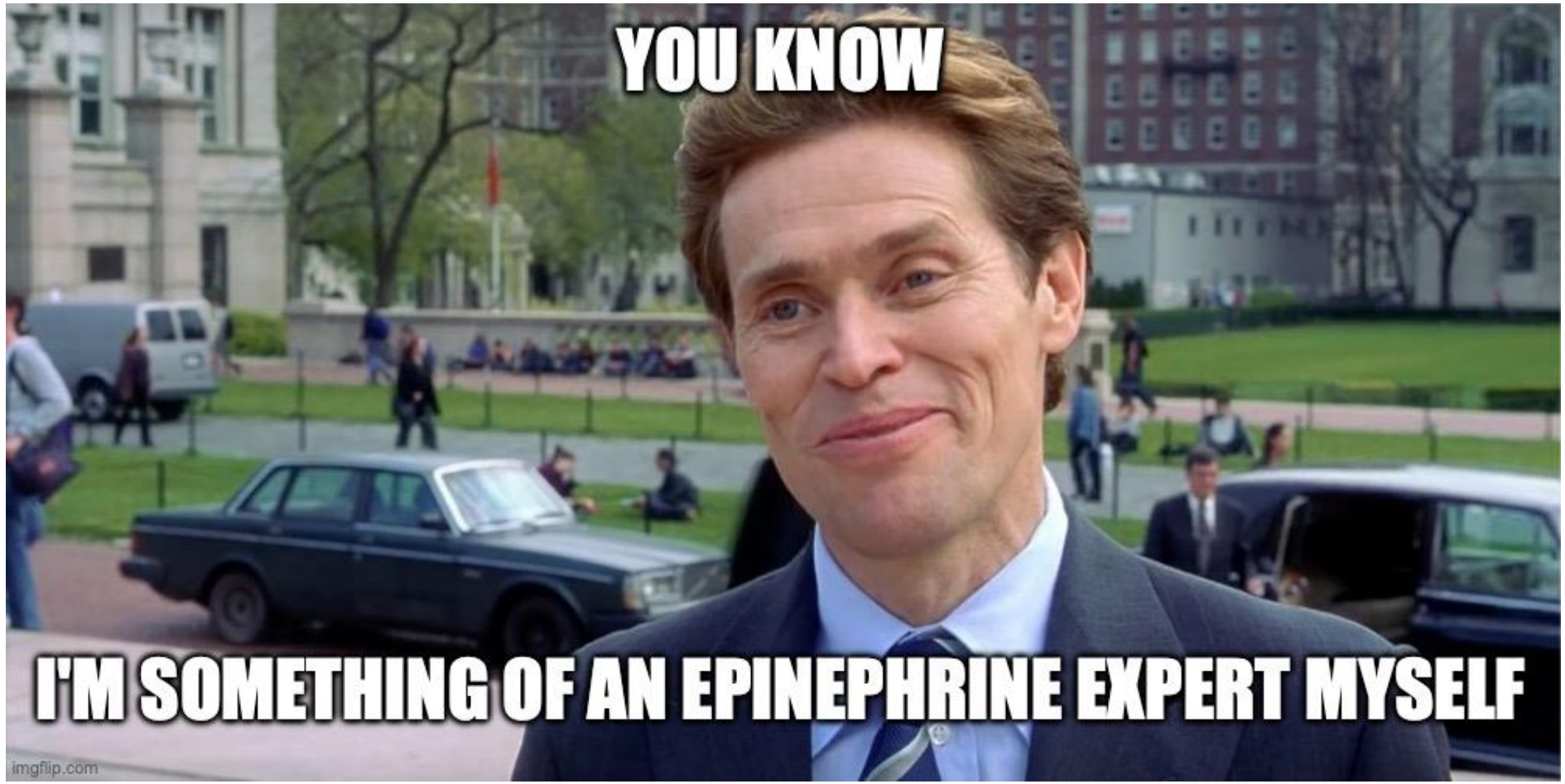
Learning Objectives

Upon completion of this session, you should be able to

- Describe how epinephrine works to stabilize the mast cell
- Detail anaphylaxis epidemiology, PK/PD, and describe how route of administration affects absorbance and hemodynamics
- Discuss current evidence gaps and updated practice guidelines


YOU KNOW
I'M SOMETHING OF AN EPINEPHRINE EXPERT MYSELF
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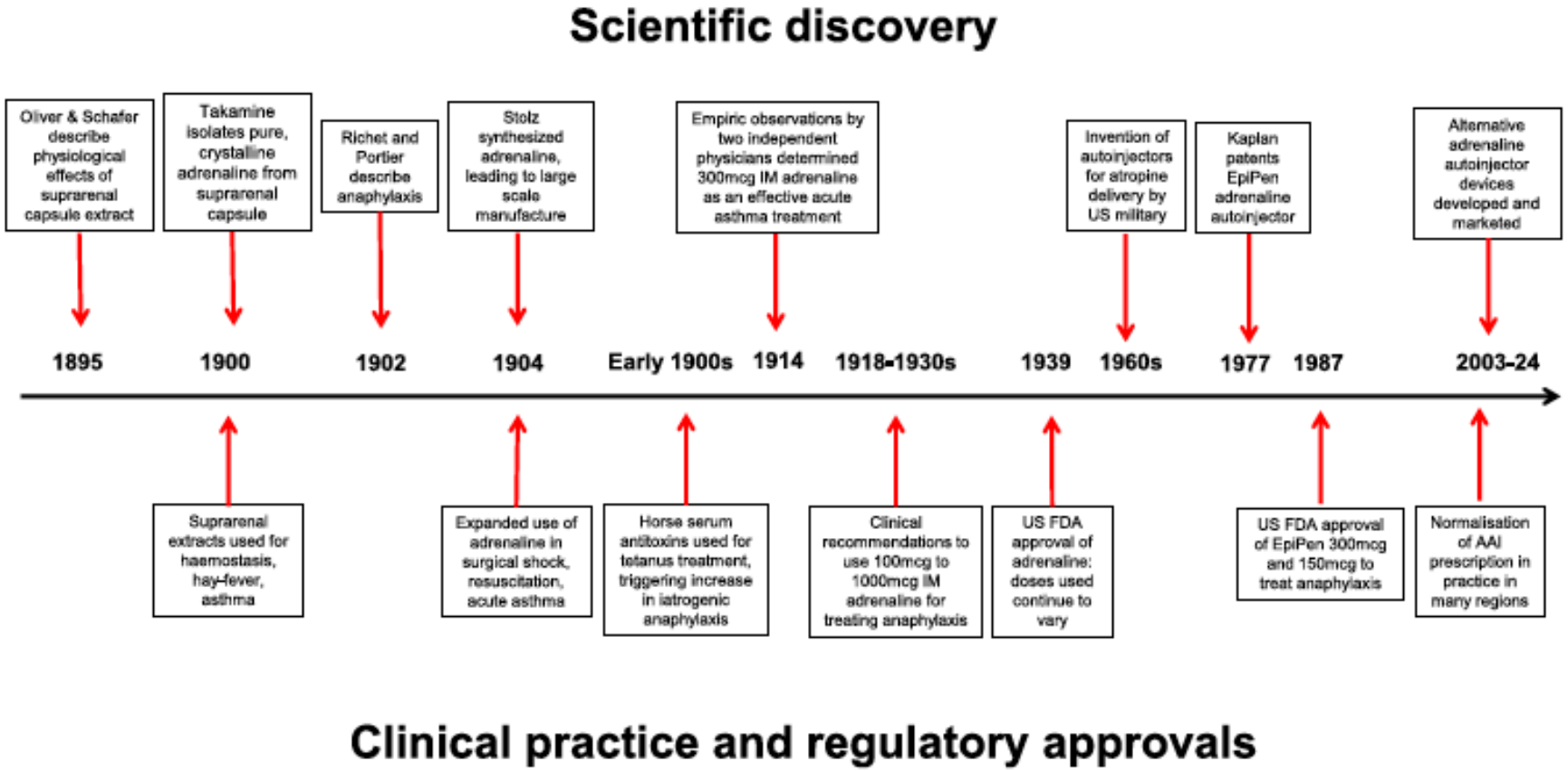
Epinephrine Is An Old, Reliable, Trusted Friend….



Sim et al Clin Exp Allergy. 2025 Jan;55(1):19-35.

…Without Solid Evidence of Efficacy (Beyond the Eye Test)

Allergy 2009: 64: 204–212

DOI: 10.1111/j.1398-9995.2008.01926.x

Review article

Adrenaline for the treatment of anaphylaxis: cochrane systematic review

Results: We found no studies that satisfied the inclusion criteria.

Conclusions: On the basis of this review, we are unable to make any new recommendations on the use of adrenaline for the treatment of anaphylaxis. In the absence of appropriate trials, we recommend, albeit on the basis of less than optimal evidence, that adrenaline administration by intramuscular injection should still be regarded as first-line treatment for the management of anaphylaxis.

Practice parameter

Anaphylaxis—a 2020 practice parameter update, systematic review, and Grading of Recommendations, Assessment, Development and Evaluation (GRADE) analysis

Check for updates

Additional good practice statements

Good practice statement 1. Administer epinephrine as the first-line pharmacotherapy for uniphasic and/or biphasic anaphylaxis.

Good practice statement 2. Do not delay the administration of epinephrine for anaphylaxis, as doing so may be associated with higher morbidity and mortality.

Ann Allergy Asthma Immunol 132 (2024) 124–176

Contents lists available at ScienceDirect

ELSEVIER

Annals

Practice Parameters

Anaphylaxis: A 2023 practice parameter update

Check for updates

CBS 25

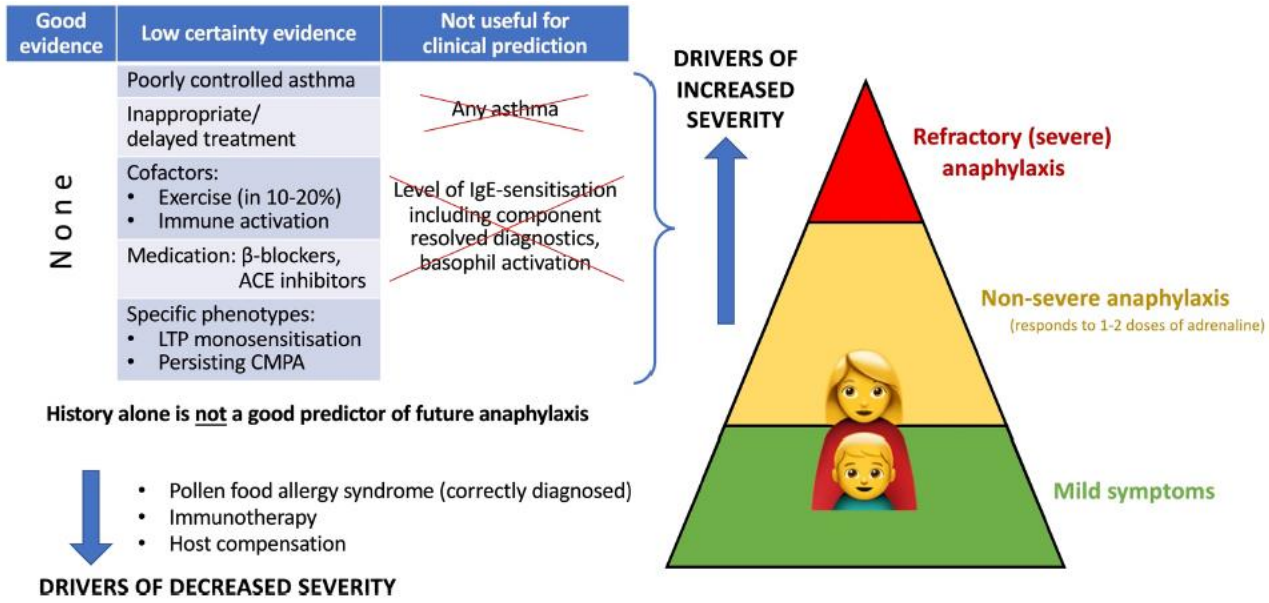
We suggest that clinicians counsel patients and caregivers to give epinephrine at the first sign of suspected anaphylaxis.

Strength: Conditional
Certainty of Evidence: **Very low**

Sheikh A et al Allergy. 2009 Feb;64(2):204-12
Shaker et al J Allergy Clin Immunol. 2020 Apr;145(4):1082-1123

Thus, Most Guidance is Opinion, Not Evidence

- Guidelines aim to prevent severe reactions, including anaphylaxis-related fatality
- Most recommendations are ***unevidenced***
  - Prior anaphylaxis poorly predicts future reaction severity
  - Severity is multi-factorial, severe reactions may not replicate
  - Asthma is not a consistently clear risk factor for severity
  - Carriage of twin-pack was an *advocacy* recommendation
  - Optimal dose, Tmax and Cmax are not established
  - No data support epinephrine use reduces fatality
  - Some countries risk-stratify epinephrine prescribing
  - Patients overwhelmingly survive despite lack of use
- We see this drug works, and there is no better option

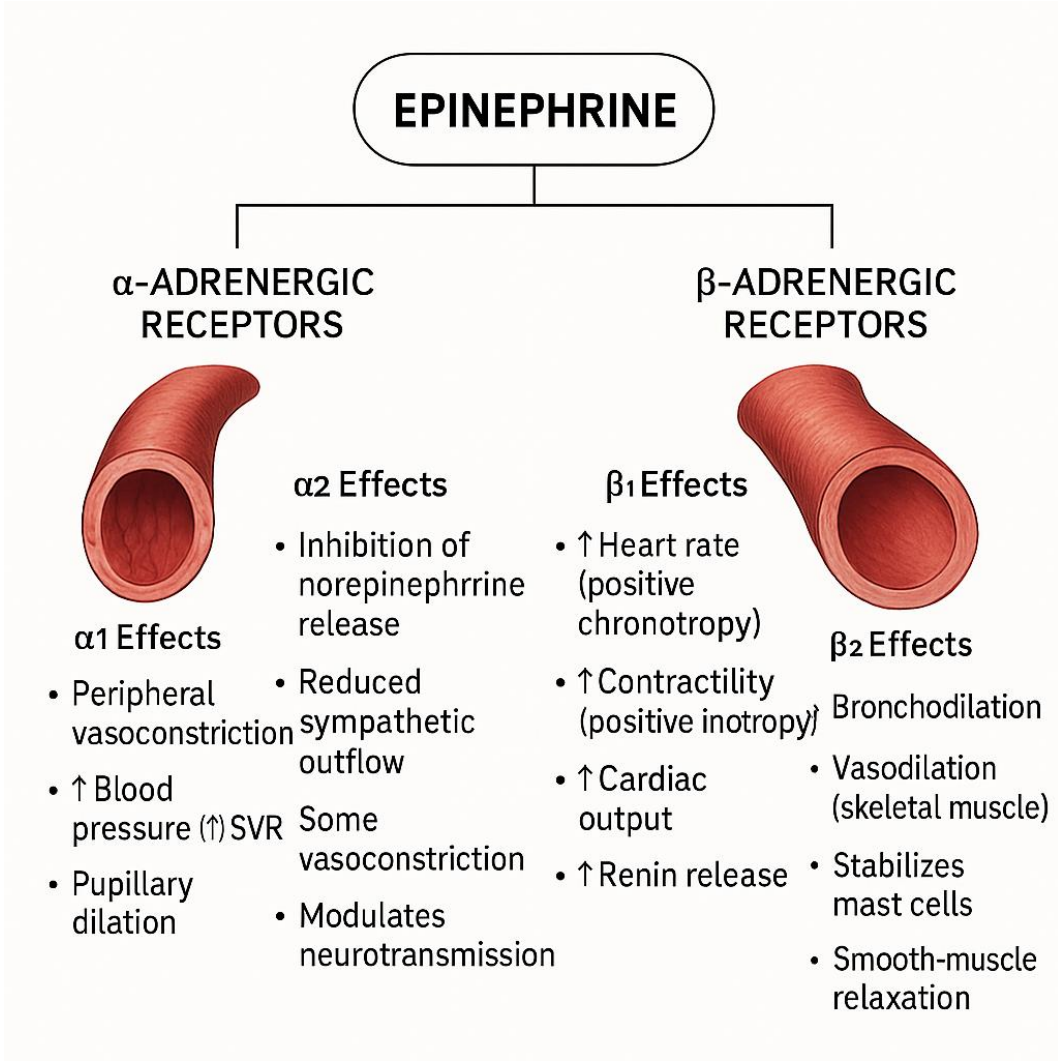


Turner et al Allergy 2022; 77: 2634-52
Greenhawt et al Ann Allergy Asthma Immunol. 2023;131(2):279-282

How Does Epinephrine Work? Very Well, Thank You….

Epinephrine Mechanism of Action

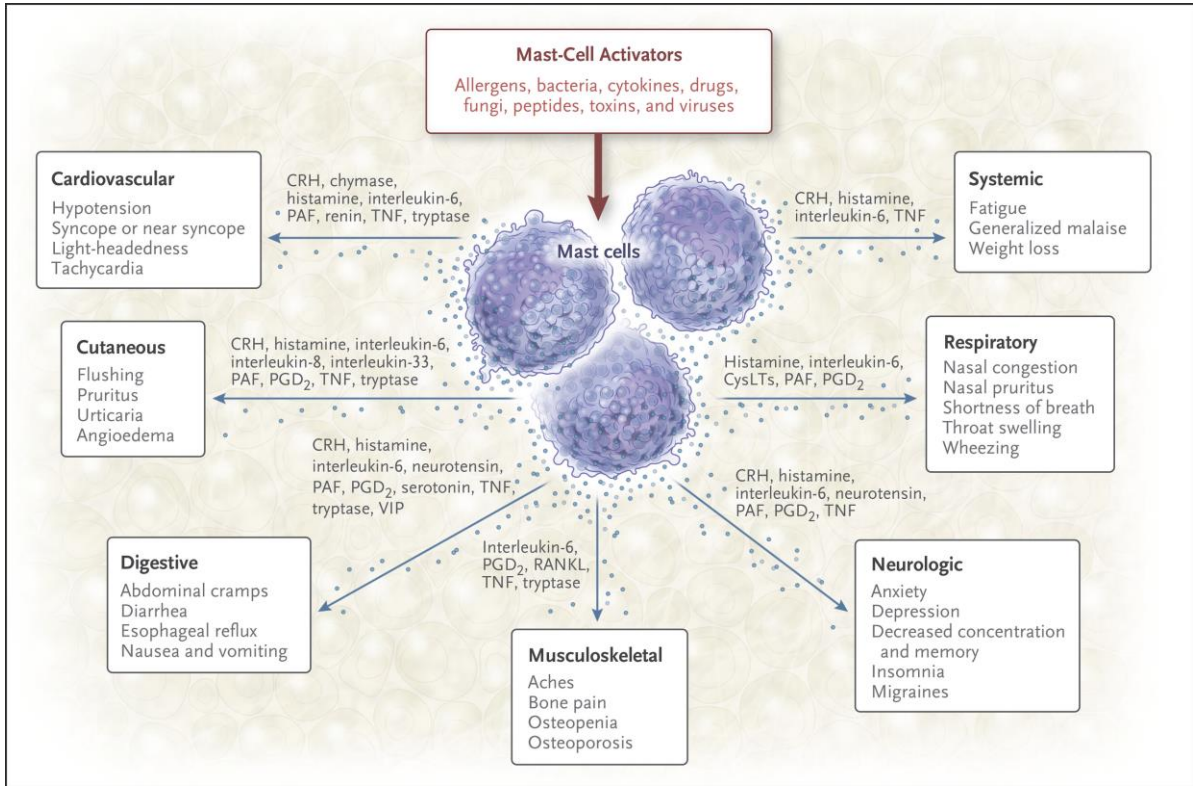
- Mediates effects through activating α and B adrenergic receptors
- α -1 receptors: increase SBP and SVR through vasoconstriction
  - Clinical effect relieves edema, counteracts hypotension, some relief of bronchoconstriction
- β_1 receptor: increase SBP, HR and cardiac output through inotropic effects
  - Clinical effect to relieve hypotension, increase coronary perfusion
- β_2 receptors: mast cell stabilization, bronchodilation/smooth muscle relaxation, vasodilation, nausea/vomiting (D_2 and D_3 dopamine receptor stimulation)
  - Clinical effect to allow respiration, inhibit wheezing and clinical effects of mediator release
- In theory these should reverse and stabilize anaphylaxis and allergic reactions



Simons et al J Allergy Clin Immunol 2011;127:587-93
Lieberman et al. J Allergy Clin Immunol 2010;126:477-80
Hsu E, Bajaj T. Beta2-Agonists. 2023 Jun 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025
Abosamak NR, Shahin MH. Beta2 Receptor Agonists and Antagonists. 2023 Jul 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025

Why We Give Epinephrine: Mediators and Their Actions

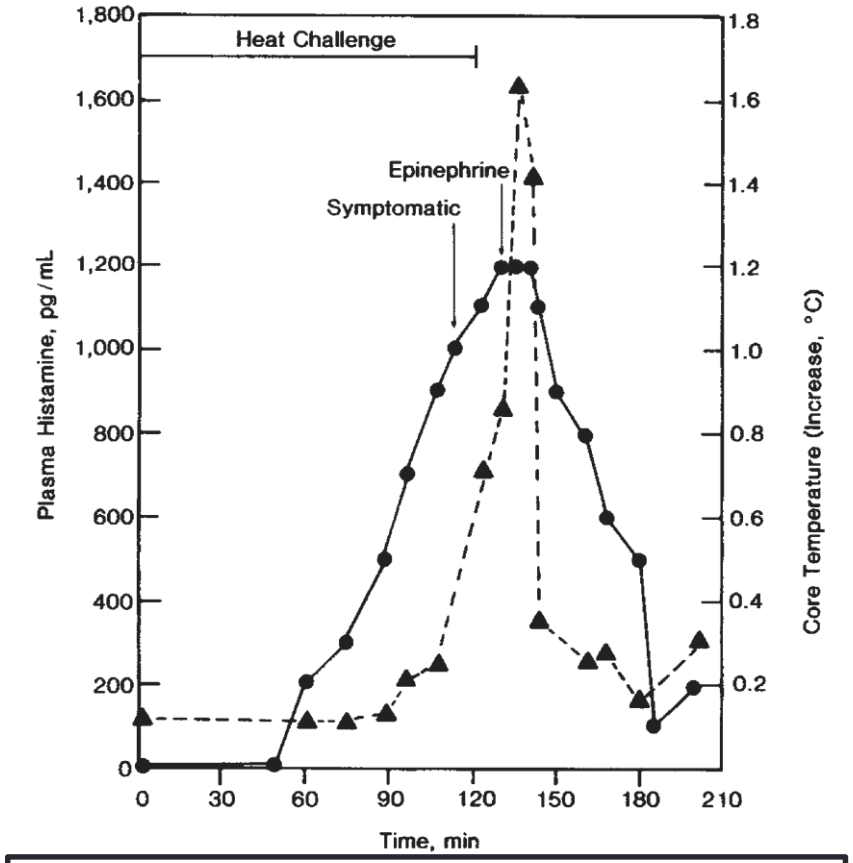
Mediators	Activity	Patient Effects
Histamine leukotrienes, thromboxane, prostaglandins, PAF	Smooth muscle spasm, mucus secretion, vasodilation, increased vascular permeability, activation of nociceptive neurons, platelet adherence, eosinophil activation/ chemotaxis	Wheeze, urticaria, angioedema, flush, itch, diarrhea, abdominal pain, hypotension, rhinorrhea, bronchorrhea
Proteases: tryptase, chymase, carboxypeptidase, cathepsin G	Cleaves complement, recruit eosinophils and neutrophils, further activation and degranulation, conversion of angiotensin I to angiotensin II	Increase BP and vascular resistance, coronary artery vasoconstriction.
Proteoglycans: heparin, chondroitin sulfate	Anticoagulation, inhibit complement, recruit eosinophils, inhibit cytokines, activate kinin	Prevent clotting, worsen reaction severity
Chemoattractants: chemokines, eosinophil chemotactic factors	Summons cells to site	May be partly responsible for recrudescence of symptoms in late phase reaction or extension and protraction of reaction
TNF alpha	Produces PAF	Vascular permeability and vasodilation;



Simons et al J Allergy Clin Immunol 2011;127:587-93
Theoharides TC, Valent P, Akin C. N Engl J Med. 2015 Jul 9;373(2):163-72.

Key Property: Epinephrine Stabilizes Mast Cells

- Epinephrine works so well in anaphylaxis because it inhibits mast cell histamine release
- Primary effect is via β2-adrenergic receptor via adenylyl cyclase activation and increased intracellular cAMP and activates protein kinase A
  - Inhibits FCεR1-mediated Ca release and degranulation
- Is a non-selective adrenergic receptor agonist but has different effects based on concentration
  - High: β1 mediated cardiac effects; α-1 mediated vasoconstriction
  - Low/moderate: β1 mediated cardiac effects; β2 mediated vasodilation of small arterioles/arteries
  - With IM thigh injection, the β2-mediated vasodilation causes dip in DBP, which recovers as higher levels reach
  - β2 is double-edged—stabilizes mast cells but vasodilation decreases SVR



1986 NIAID study of exercise challenges shows histamine levels rapidly decrease following epinephrine administration, showing its mast cell stabilization effect

Ellis et al Pharmaceutics. 2024 Jun 14;16(6):811.
Barisione et al *Pharmaceuticals* **2010**, *3*, 1016-1044
Casale et al JAMA 1986; *55:2049-2053*
Hsu E, Bajaj T. Beta2-Agonists. 2023 Jun 20. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025
Abosamak NR, Shahin MH. Beta2 Receptor Agonists and Antagonists. 2023 Jul 3. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025

Histamine Mediates Clinical Effects

- Histamine is a major pre-formed mediator that is immediately released from the mast cell
  - Responsible for vasodilation, flushing and decreased peripheral resistance
  - Net effect: decrease systolic blood pressure, vasodilation (H1/H2) increase vascular permeability
- H1 activation: tachycardia, coronary artery vasospasm, smooth muscle contraction, uterine contraction, GI contraction
- H2 activation: tachycardia, increased atrial and ventricular contraction, increased myocardial oxygen demand, uterine contraction
  - Combined H1 and H2 receptor blockade is required to counter flushing, headaches, hypotension, and tachycardia.
- Epinephrine does not reverse H1 and H2 activation but it antagonizes its activation through alpha- and beta-adrenergic receptor activation, and histamine release diminishes as mast cell stabilizes

Simons et al J Allergy Clin Immunol 2011;127:587-93
Lieberman et al. J Allergy Clin Immunol 2010;126:477-80

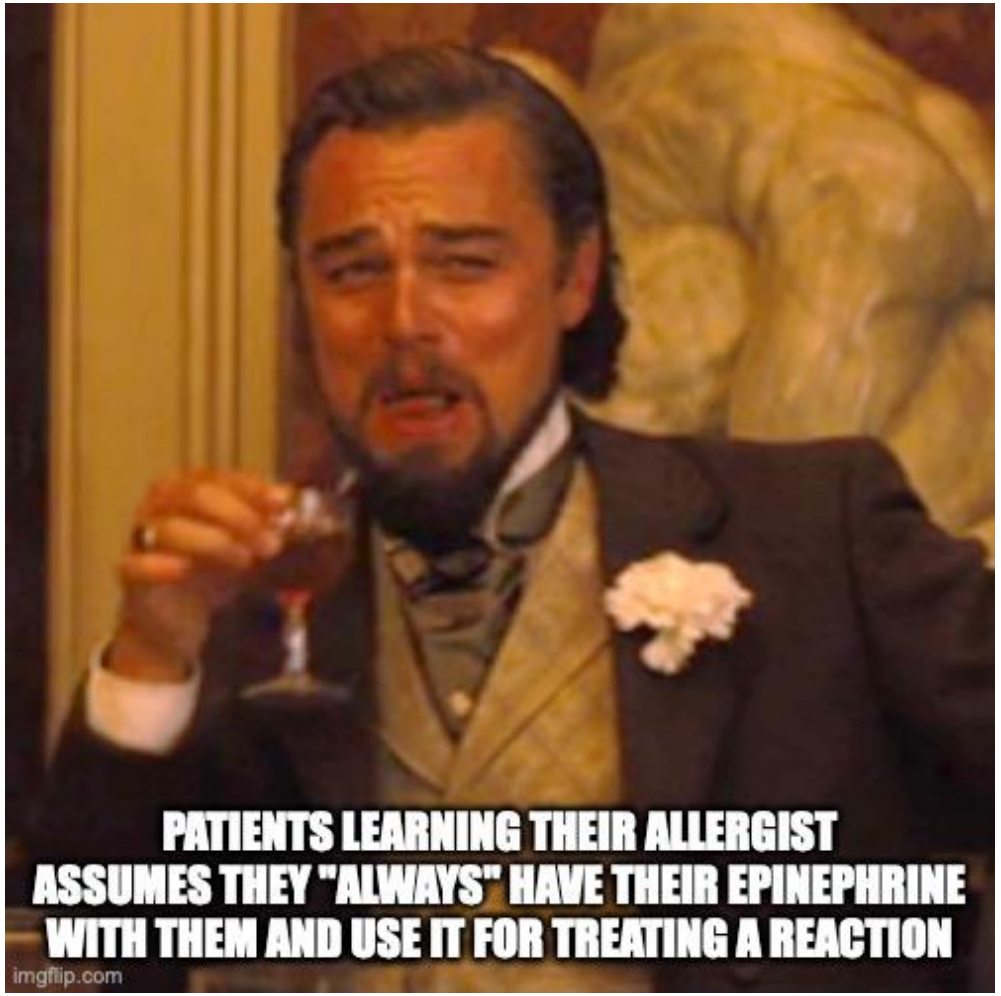
Understanding The Systemic Responses In A Reaction

At Onset of Reaction	Early Stage (Minutes) with No Treatment	Prolonged Shock
Blood pressure	↓	↓↓
Pulse	↑	↑
Cardiac output	↑	↓
PVR	↓	→↓(*)
Intravascular volume	→↓	↓

- Paradoxical bradycardia reported as a common feature of traumatic hypotension in humans.
- Upright posture has been associated with fatal anaphylaxis by reducing venous return to the heart
- ***Underscores the importance of prompt epinephrine administration to reverse these effects***

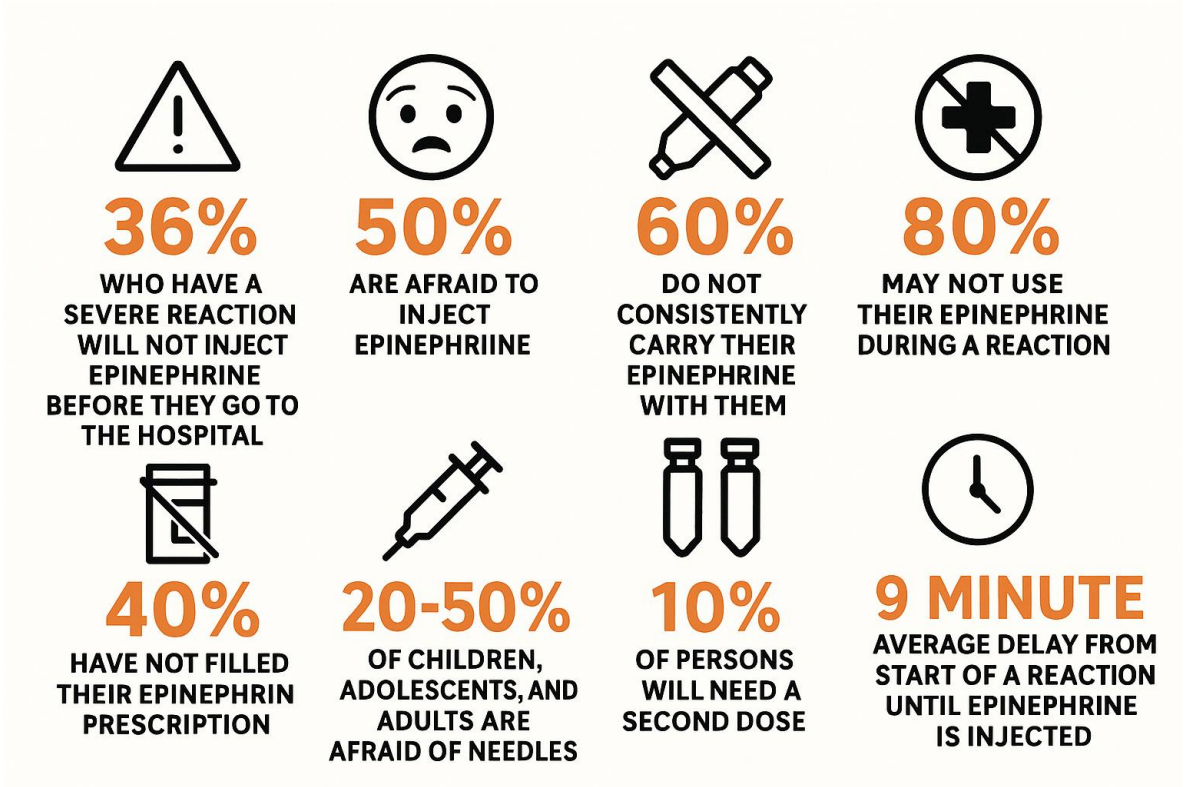
Simons et al J Allergy Clin Immunol 2011;127:587-93
Lieberman et al. J Allergy Clin Immunol 2010;126:477-80

Overcoming Human Tendencies….



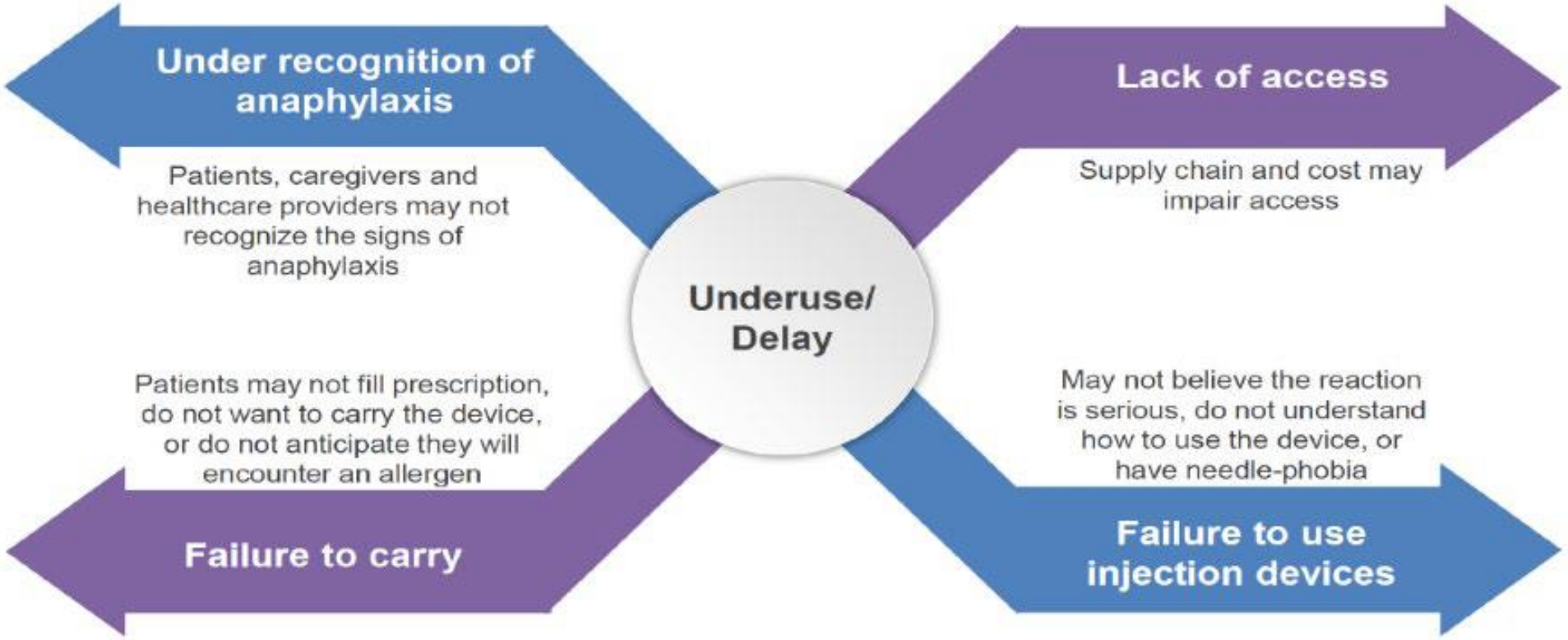
What Patient Factors Are We Up Against As Prescribers?

- Not filling or refilling their prescription
- Not carrying their epinephrine on them
- Not using epinephrine before hospital arrival
- Delayed use of epinephrine when used
- High rates of needle-phobia
- Devices considered bulky and too big
- Device shortages and reliability issues
- High prices and access issues



Lieberman et al. Ann Allergy Asthma Immunol 2023; 131: 185−193

Barriers As Recognized By The FDA



- This slide comes directly from the FDA's presentation during the May 2023 Pulmonary-Allergy Drugs Advisory Committee meeting regarding intranasal epinephrine
- The FDA clearly recognizes there are issues that validate an unmet need for needle-free delivery forms

https://www.fda.gov/media/168055/download. Presented by FDA May 11, 2023

Patients Are Not Using Their Epinephrine

- What happens to patients in anaphylaxis who do not use epinephrine?
  - Registry of 10 years of 7,964 European Anaphylaxis Registry patients with complete treatment data
  - Only 23.2% received epinephrine. 10.5% received no treatment, >75% received anti-histamines
  - % receiving epinephrine varied by country, more did if treated by a healthcare person vs. self-treated
  - Trend in time improved for epinephrine use in the healthcare setting but not for patients self-treating
  - Getting epinephrine was not influenced by reaction elicitor, patient, or severity (all grade II-IV)
- **If 75% of cases survived without epinephrine, do they actually need it?**
- **Is there more that we can do to understand WHY patients underuse epinephrine?**

Grabenheinrich et al J Allergy Clin Immnol Pract 2018; 6: 1898-1906.e1

European Anaphylaxis Registry Data

	Professionally treated		Lay- or self-treated	
	OR [95% CI]	*P* value	OR [95% CI]	*P* value
Female sex	0.83 [0.72; 0.97]	**.016**	1.01 [0.69; 1.46]	.976
Age (vs 18-64 y)				
Children	0.86 [0.64; 1.14]	.130	1.37 [0.60; 3.12]	.691
Elderly	1.17 [0.92; 1.49]	.094	1.31 [0.60; 2.88]	.795
Cardiovascular comorbidity	1.10 [0.89; 1.36]	.387	**2.01 [1.05; 3.85]**	**.036**
Elicitor (vs unknown)				
Insect	0.87 [0.60; 1.26]	.356	1.03 [0.44; 2.41]	.980
Food	0.82 [0.59; 1.15]	.108	0.80 [0.38; 1.69]	.983
Drugs	0.94 [0.65; 1.36]	.782	0.63 [0.17; 2.34]	.985
Allergen immunotherapy	1.19 [0.56; 2.51]	.497	*	
Reacted before to the same allergen	1.00 [0.84; 1.18]	.973	**2.50 [1.70; 3.66]**	**<.001**
Stress (as cofactor)	1.20 [0.88; 1.64]	.241	1.08 [0.45; 2.63]	.860
Immediate-type reaction (<10 min)	**1.22 [1.05; 1.42]**	**.010**	1.05 [0.72; 1.55]	.791
Organ system involved†				
Skin	0.91 [0.73; 1.15]	.441	**0.58 [0.34; 0.96]**	**.036**
Gastrointestinal	0.90 [0.77; 1.05]	.178	0.86 [0.58; 1.28]	.463
Respiratory	1.15 [0.96; 1.38]	.120	1.07 [0.65; 1.76]	.793
Cardiovascular	**1.74 [1.43; 2.11]**	**<.001**	**1.70 [1.07; 2.71]**	**.026**
Severity (vs grade II)				
Grade I	**0.59 [0.36; 0.96]**	**<.001**	0.56 [0.17; 1.86]	.163
Grade III	1.57 [1.33; 1.85]	.918	1.02 [0.68; 1.55]	.728
Grade IV	**6.38 [3.91; 10.39]**	**<.001**	*	

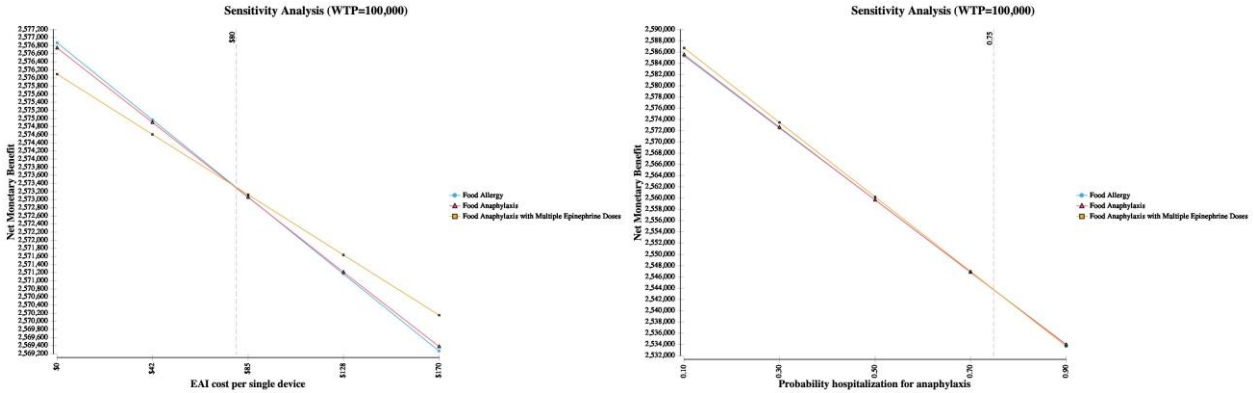
CI, Confidence interval; *OR*, odds ratio.
Predictive multivariate logistic model (mutual adjustment), conditioned on study center (individual center), location of reaction (medical setting, home, work/school, restaurant, or outdoors), and person treating (emergency doctor, general practitioner, allergy specialist, self, family member, or teacher).
*Less than 30 cases in the stratum. *P* value for contribution to model, <.05 highlighted bold.
†In reference to those with no signs/symptoms in this organ system.

- Few significant predictors of epinephrine use in either group
- None were consistent except for cardiovascular symptoms
- Patients, but not professionals had higher odds for epinephrine use for repeat reactions to the same allergen
- Professionals, not patients, had higher odds of administering epinephrine for reactions with short onset from exposure
- Use patterns do not impact fatality

Grabenheinrich et al J Allergy Clin Immnol Pract 2018; 6: 1898-1906.e1

Does Carrying Multiple Devices Help Patients?

- Dogma is to always have 2 epinephrine autoinjector devices at all times
  - Since 2010, only epinephrine twinpacks have been sold in US
  - < 10% of food reactions require 2nd epinephrine
  - Few people carry 1 device let alone 2 devices….
- Is universally prescribing 2 devices the most cost-effective strategy? Markov model of 3 scenarios:
  - 1) Everyone gets 2 devices (universal approach)
  - 2) 2nd device only given with a prior history of anaphylaxis
  - 3) 2nd device only with prior history of anaphylaxis requiring multiple epinephrine doses (multi-epi)
  - Presumes the 2nd device reduces fatality risk by 10-1000 fold
  - Consdered additional risks of asthma, obesity, or rural residence



- The universal approach was not cost-effective
- Exceeded incremental cost-effectiveness threshold by 100-170x
- The net monetary benefit (value of the strategy at a specific cost effectiveness threshold) of the multi-epi approach was greater for past hx of anaphylaxis or a universal approach
- No difference when considering asthma, obesity, or living rural

Shaker, Turner, Greenhawt. J Allergy Clin Immunol Pract 2021;9: 2440-2451.e3.

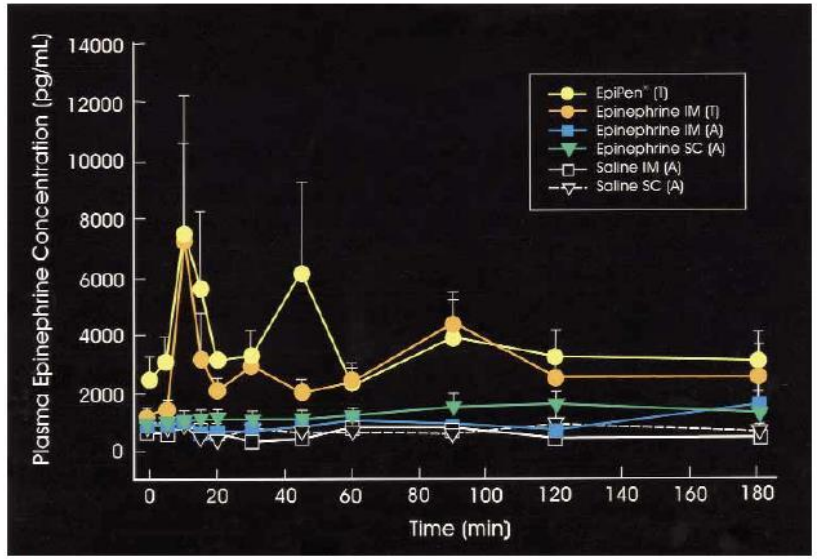
PBL Tie In

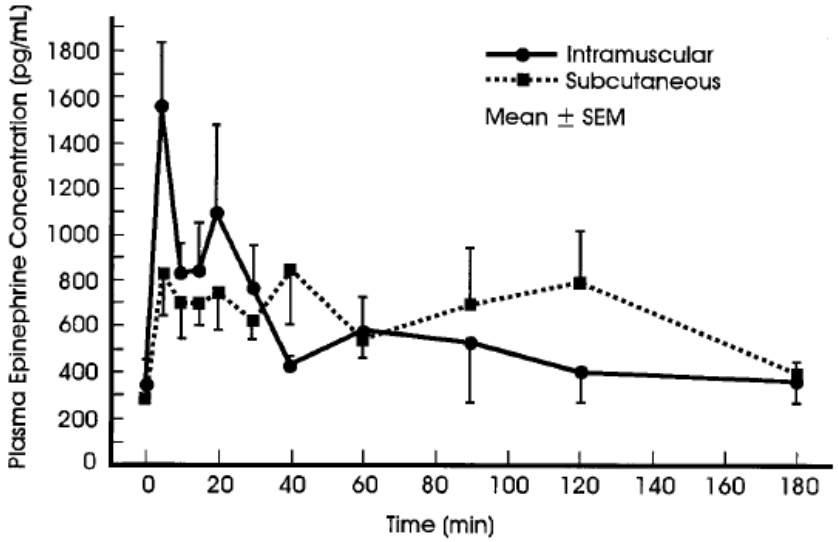
- Multiple accidental exposures since childhood, some “severe” (has required 2 doses of epi)
- Prior reactions variable; some required ED care and epinephrine (not self-administered)
- New issue being misattributed to milk allergy vs worsening disease control
  - Increased ED utilization
  - Recurrent “cross-contamination” being claimed is a huge red flag
- Stereotypical preparedness & risk taking which is aligned with the data I just presented
- Often forgets epinephrine, poorly confident in how to use it, hesitant to self-inject
  - While fatality is exceptionally unlikely outcome, these pre-dispose to increased morbidity
  - Has he been asked about needle-phobia, reasons for hesitancy, or preference for a form of epinephrine
- Can his epinephrine preference be tailored? Would you prescribe a newer form?

PK/PD, Route of Delivery, and Bioequivalence

What Is The Optimal Route/Placement for Injection?

- Small n data in "...healthy adult males with BMI 36.6 ± 4.6 [e.g. obese} not in anaphylaxis support a faster mean time to peak plasma concentration in IM route in the thigh"
  - Former standard was SQ deltoid injection
- Levels are much higher (for both routes) than more recent studies
- Same effect shown in children and adults
- No study has shown what the adequate plasma concentration is or the time to peak onset is
  - Unclear if the Tmax or Cmax is the crucial aspect
- Sentinel data suggesting route/location can optimize PK
  - This study help prompted SQ to IM change, as well as switch location of administration from deltoid to mid-anteriolateral thigh
  - This was not shown to influence PD or clinical efficacy, however



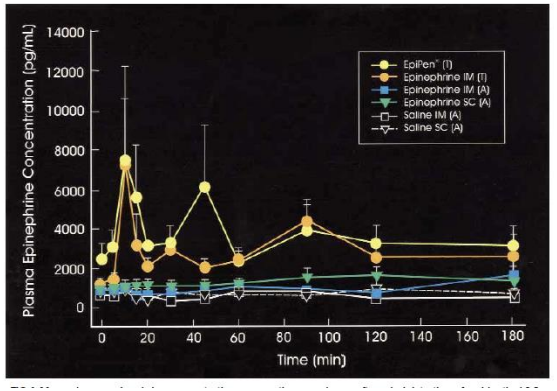


Simons FER. *J Allergy Clin Immunol.* 1998;101:33-37
Simons FER J Allergy Clin Immunol 2001; 108:871-3.

But Did We Get This Right?

- Simons et al data very limited (sample, scope)
  - Adult males, deltoid SQ vs lateral thigh IM (not thigh SQ)
  - Both routes work, no difference in outcomes
- C_{max} 2877 pg/mL (SQ deltoid) vs.1821 pg/mL (IM thigh)
  - Known that autoinjector not “IM” in all patients/circumstances
  - Varies based on needle length and BMI
- Per Simons, SC space poorly vascular, retains material
  - Didn’t test QQ thigh because “not recommended” clinically
  - Notes thigh Cmax higher with IM vs autoinjector (variability)
  - Postulates needle length a bigger issue than BMI
- FDA challenged if IM was optimal route in editorial
  - More data needed, Simons et al studies ”important milestones”

13 adult men



8 children

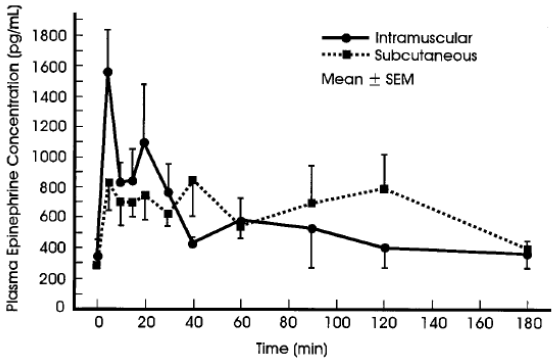


TABLE I. Mean maximum plasma epinephrine concentrations

Injection route	EpiPen IM	Epinephrine IM	Epinephrine IM	Epinephrine SC	Saline IM	Saline SC
Injection site	Thigh	Thigh	Arm	Arm	Arm	Arm
C_{max}: mean ± SEM (pg/mL)	12,222* ± 3,829	9,722* ± 4,801	1,821 ± 426	2,877 ± 567	1,458† ± 444	1,495† ± 524

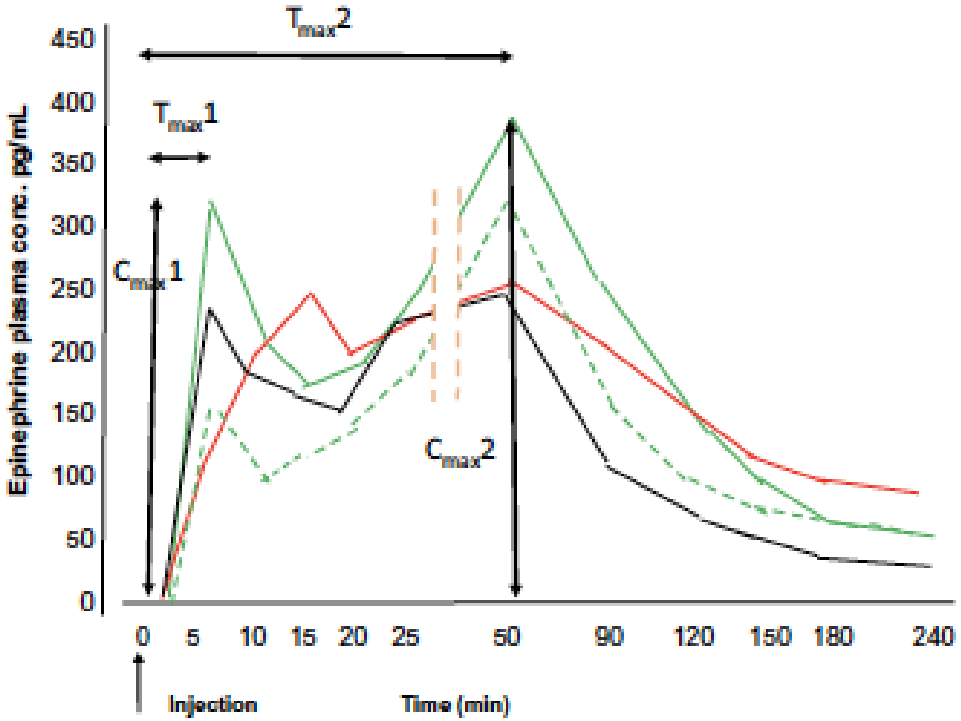
TABLE II. The pharmacokinetics of epinephrine

Mean ± SEM	Epinephrine solution (subcutaneous)	EpiPen Auto-injector (intramuscular)
Epinephrine dose (mg) ± SEM	0.27 ± 0.04*	0.3
$C_{baseline}$ (pg/ml)	285 ± 32	339 ± 115
C_{max} (pg/ml)	1802 ± 214	2136 ± 351
t_{max} (min)	34 ± 14†	8 ± 2†
$t_{1/2}$ (min)	—	43 ± 15
AUC (ng/ml/min)	67 ± 13	108 ± 18
Cl (ml/min/kg)	—	147 ± 38
Vd_{ss} (L/kg)	—	2.0 ± 1.5

Simons FER. *J Allergy Clin Immunol.* 1998;101:33-37
Simons FER J Allergy Clin Immunol 2001; 108:871-3.
Chowdhury BA, Meyer RJ.. J Allergy Clin Immunol. 2002; 109: 720.

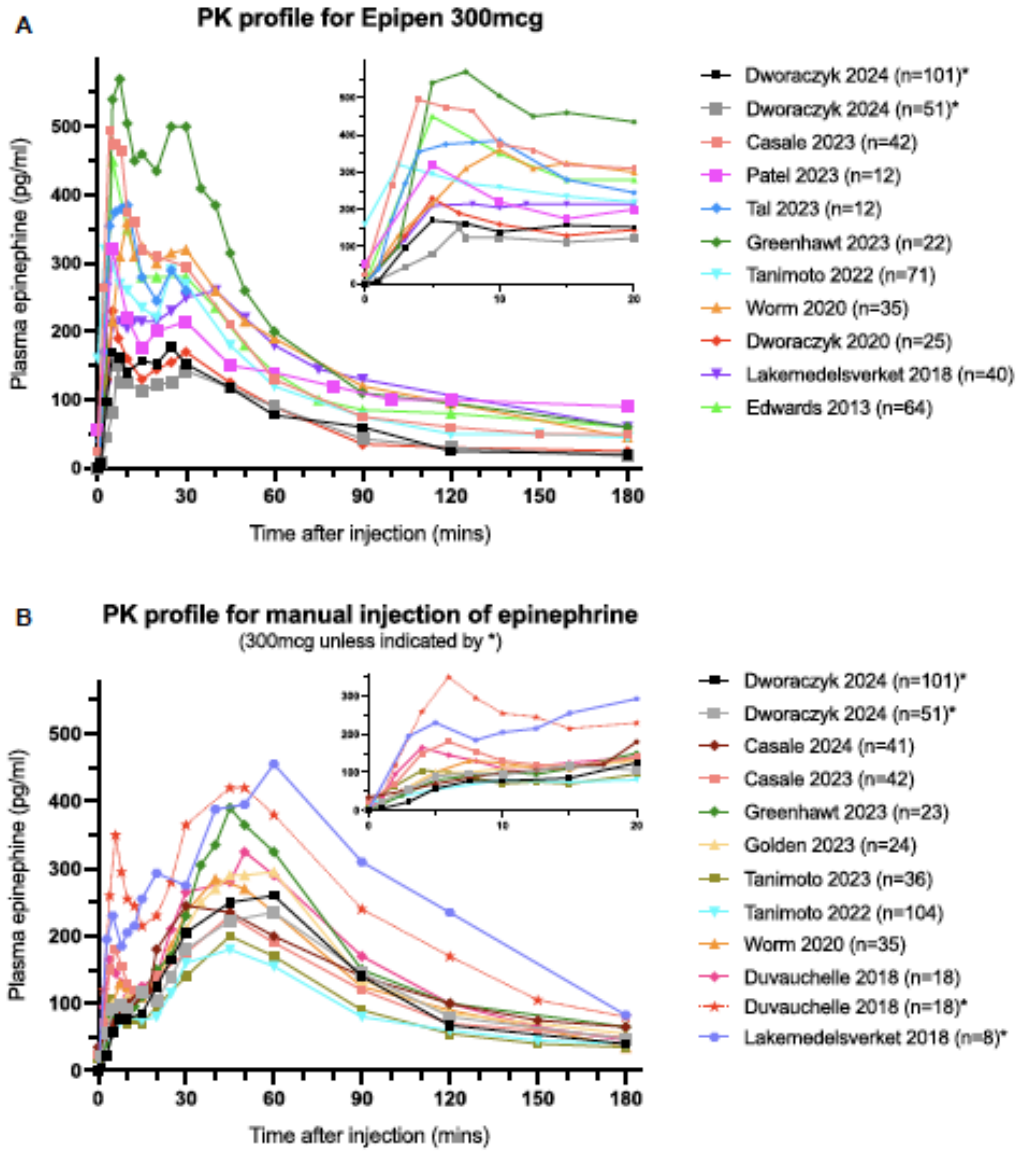
Historical Uncertainty Regarding IM Administration

- Cmax higher in obese vs. non-obese males, children, and females
- Is IM IM?—if obese, shorter needle, thick clothing, more likely SC
  - Longer needle even w/lower pressure more likely IM, but also in bone
  - Confirmed by ultrasound deposition by Duvauchelle et al and Worm et al
  - Earlier EAI approval data may have included SC deposition in some subjects
  - May explain why obese females w/rapidly progressing sx at higher fatality risk
- More spring pressure does not guarantee IM deposition
- 2 peaks seen for Tm/Cm
  - influenced by vasoconstriction then vasodilation, and possible SC deposition
  - Higher dose can proportionally influence the 1st Tm/Cm
  - Edwards et al: EAI deliveries similar Tm/Cm but unclear it was IM deposition



…Which Recent PK/PD Studies Confirm

Medication and dose	N	Mean time to maximal plasma concentration (min)	Mean plasma concentration (pg/mL)	Mean systolic blood pressure change (mmHg)	Diastolic blood pressure change (mmHg)	Heart rate change (bpm)
Neffy study[8]						
Neffy intranasal 2mg	42	30	481	23.6	8.10	17.3
IM epinephrine 0.3 mg via syringe/needle	42	45	339	11.9	5.48	9.71
IM epinephrine 0.3 mg via autoinjector	42	7.5	753	18.2	5.62	12.3
Sublingual film AQST study[15]						
AQST-109 12 mg	22	15	497.9	26.3	12.5	16.8
IM epinephrine 0.3 mg via syringe/needle	27	50	391	10	-4.5	12
IM epinephrine 0.3 mg via autoinjector #1	27	10	669.9	13.5	-9.5	14
IM epinephrine 0.3 mg via autoinjector #2	29	30	688.4	11	-6	17.5
Intranasal spray NDS1C study[7]						
NDS1C intranasal 13.2 mg (same nostril)	75	20.1	332	NR	NR	8.8
IM epinephrine 0.3 mg via autoinjector	215	20	285.7	NR	NR	5.9



Lieberman and Greenhawt Curr Opin Allergy Clin Immunol. 2025 Oct 1;25(5):309-314
Patel et al J Allergy Clin Immunol 2025;155:418-20.

So,Why Might IM Injection Studies Differ?

- Poiseuille's law: flow rate is proportional to needle radius to 4th power, so smaller bore needles have slower flow
- However, when looking at PK with needles < 21ga vs ≥22ga, such an effect is not apparent
- Is variation between subjects within the same study using the same needle size/device

  --External force applied by the user may explain variability

  --Some data suggest dose is more critical than force
- **Why is this important**--this can affect the bracket used for establishing bio-equivalence

  --This is why cross-over study design is essential
- Any real-world PK variability is not affecting outcomes
- Needle-free forms may have more consistency

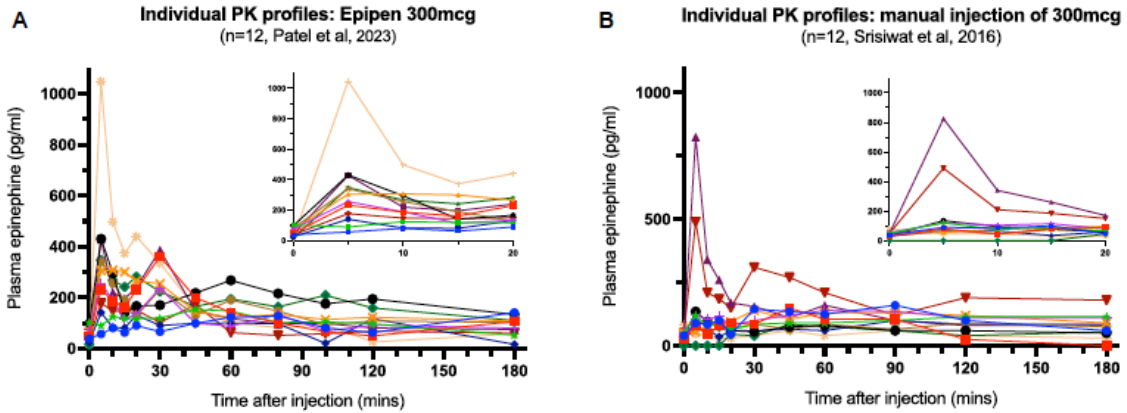
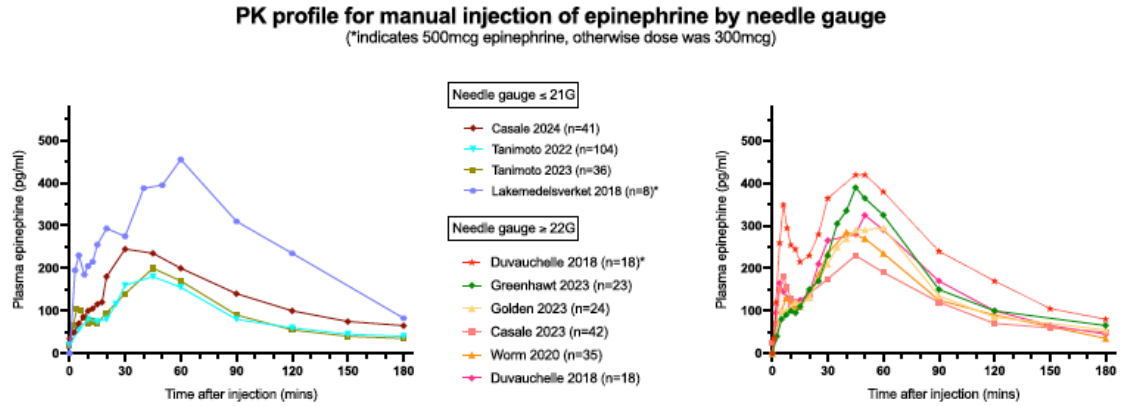


FIG 2. Plasma epinephrine levels at an individual participant level, following administration of epinephrine, 300 μg, by Epipen in Patel et al[4] **(A)** or manual injection with a syringe/needle in Srisawat et al **(B)**.[5]



Patel et al J Allergy Clin Immunol 2025;155:418-20.
Turner et a Clin Exp Allergy. 2022;52:18–28

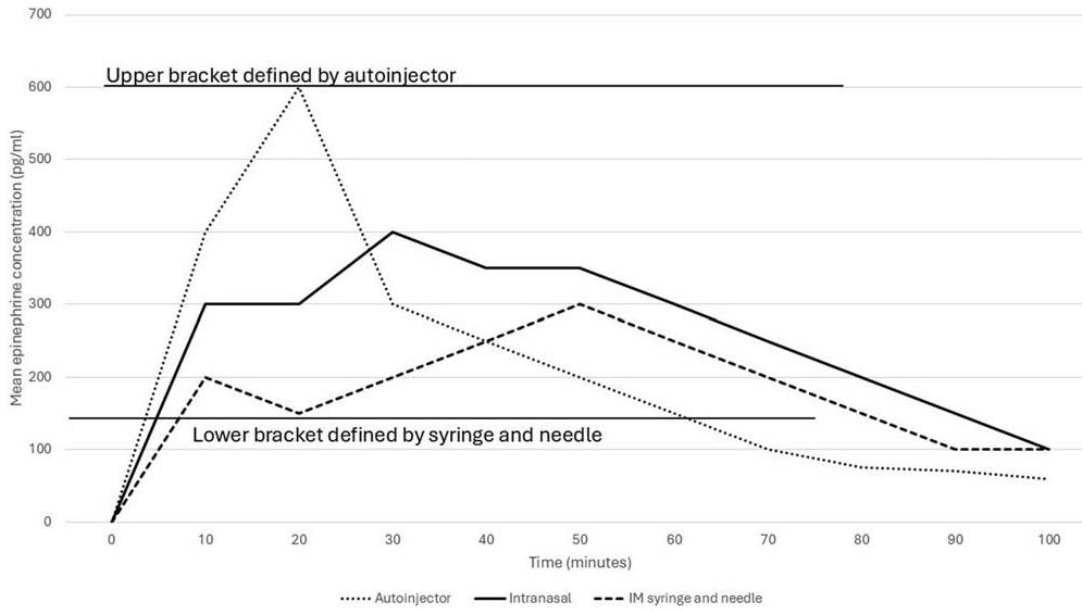
FDA 505 (b)(2) Pathway For New Epinephrine Forms

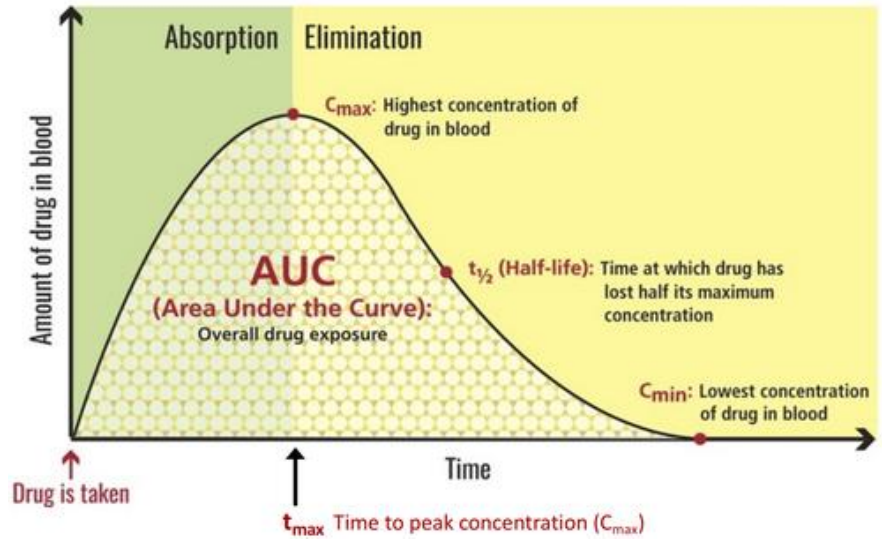
- 505 (b)(1)—full NDA w/new data; 505(j)—generic equivalence abbreviated NDA
- 505 (b)(2) is a hybrid pathway allowing use of existing published data for a drug with safety and efficacy that is well understood (epinephrine meets this standard)
  - New epi forms are not 505(j)—these are modified forms but are not therapeutically equivalent (or substitutes)
  - Saves developmental time/money on largely redundant data while allowing post-approval exclusivity
  - Sponsor must form scientific safety/efficacy bridge via PK/PD studies showing uncompromised performance
  - For epi, this bridge is the PK bracket
- Use of this pathway has to be approved by the FDA in pre-IND meetings
- Must show baseline-corrected AUC and Cmax between 80-125% of the reference within pre-agreed upon time points to satisfy the bracket
- Aim is biocomparability to establish the bridge, not necessarily bioequivalence

https://www.accessdata.fda.gov/drugsatfda_docs/psg/PSG_214697.pdf#:~:text=In%20addition%2C%20prospective%20applicants%20should%20submit%20partial,(AUC0%2D10min)%20and%2030%20minutes%20(AUC0%2D30min)%20after%20administration.

Biocomparability: Bracketed Approach for Approval

- Approach is to show PK equivalence
  - Lower bracket is marker of efficacy
  - Upper bracket is marker of safety
  - Sponsor chooses the 2 reference comparators
  - EpiPen and manual IM epinephrine most common
- Markers for comparison
  - Time to maximal plasma concentration (T_m)
  - Maximal plasma concentration (C_{max})
  - 100 pg/mL may be considered physiologically ”active”
- EpiPen approved 1987, without known PK
  - All the other IM/IN products were approved with PK studies alone

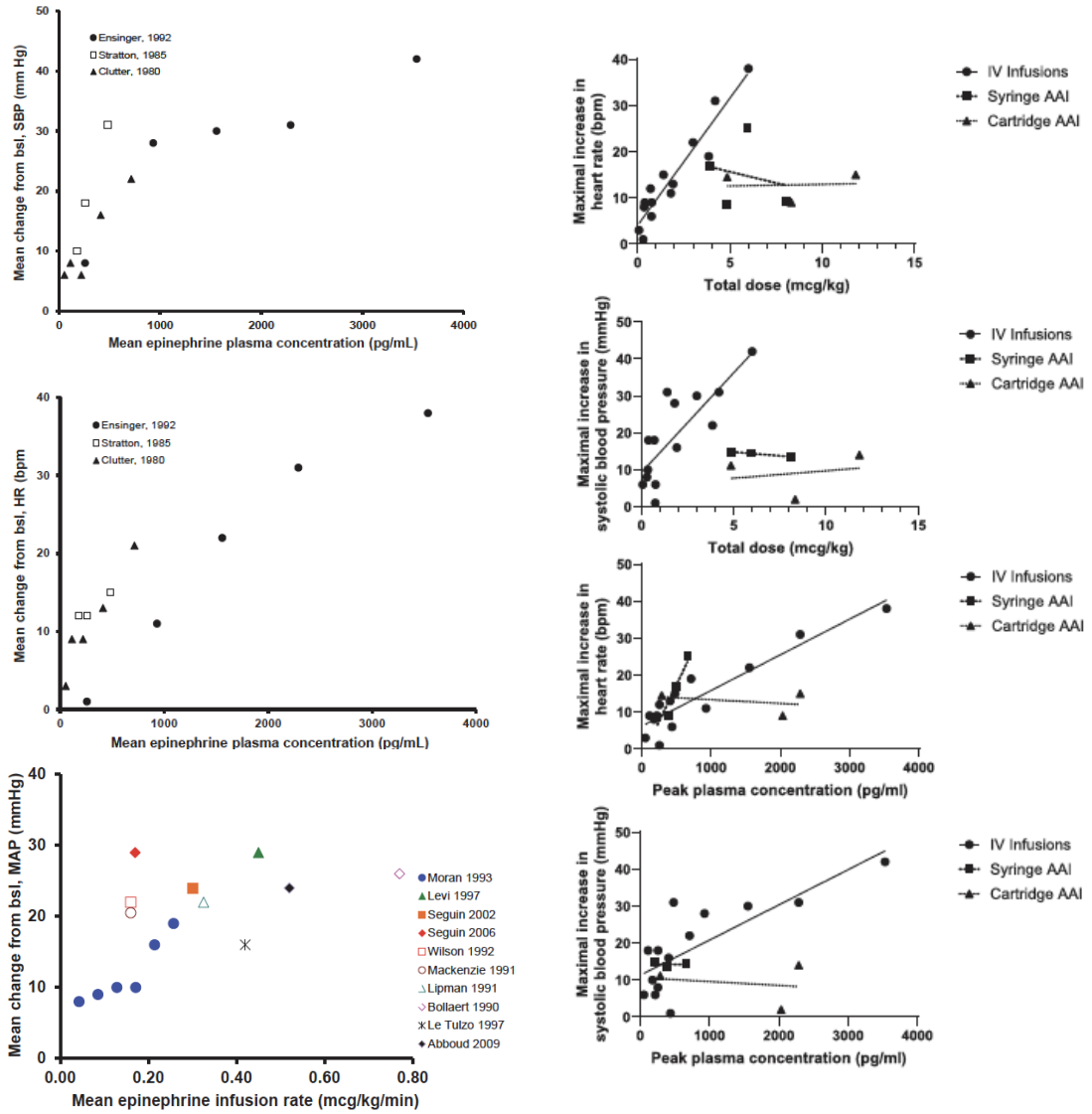




Lieberman and Greenhawt Curr Opin Allergy Clin Immunol. 2025 Oct 1;25(5):309-314
Turner et a Clin Exp Allergy. 2022;52:18–28

PD Effects Proportional to Concentration

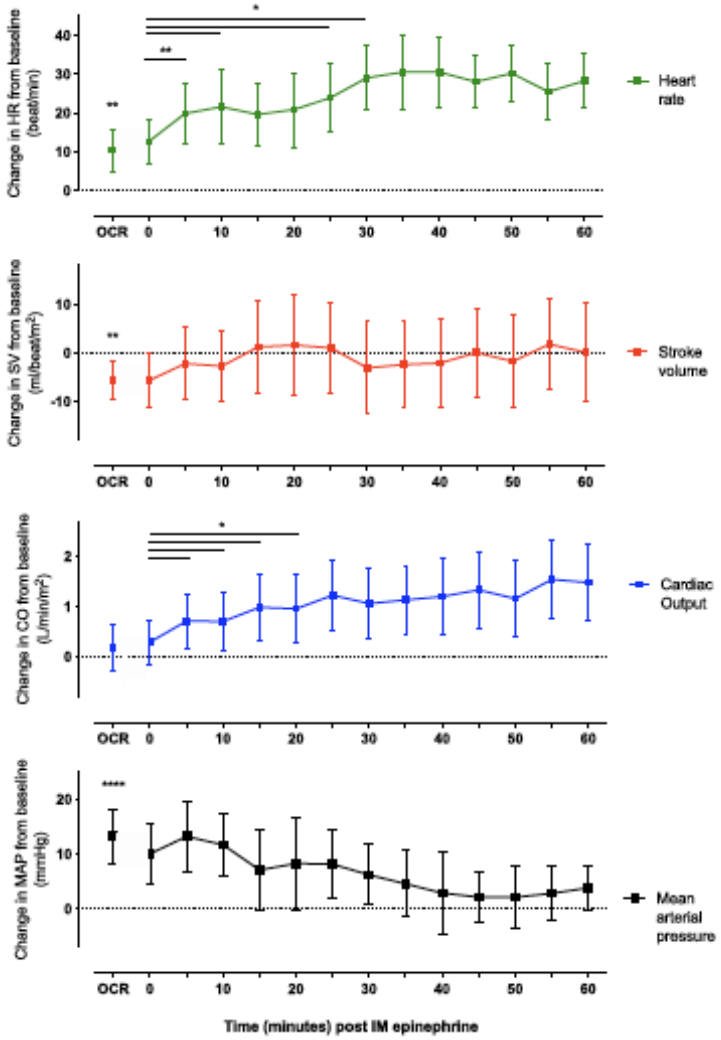
- Multiple data show PD response is proportional to plasma concentration, regardless of route
  - This is a key FDA assumption for 505b2
- Still a poor relationship between PK/PD with either new or existing forms
- PK of IM needle/syringe appears to have smallest Cmax, most delayed Tmax, and lower increases in HR/BP, but clearly works
- It remains unclear if PK/PD optimization has an impact on clinical outcomes
- Dose may have the most impact on PD

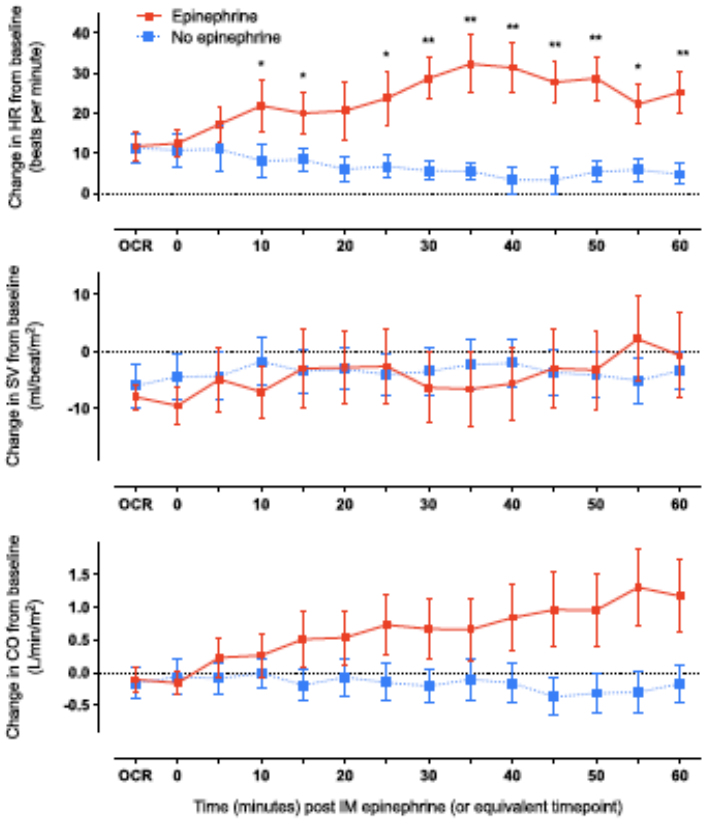


Sim et al Clin Exp Allergy. 2025 Jan;55(1):19-35.

What We Aim For In Resuscitation

- In distributive shock, must preserve MAP
- Alpha adrenergic effects increase SVR and HR to preserve stroke volume (inotropy)
  - Cardiac output= SV x HR
  - Are more alpha 1 than beta 2 receptors which is why BP may respond faster than HR
- Rapid rise in DBP maintains coronary perfusion and bolsters MAP
  - MAP=arterial pressure in single cardiac cycle
  - MAP = DBP + 1/3(SBP – DBP)
  - Perfusion requires minimum MAP 60mmhg
  - With IM injection, local beta 2 receptor activation in the skin and small arteries/arterioles is associated with vasodilation, and observed temporary DBP dip

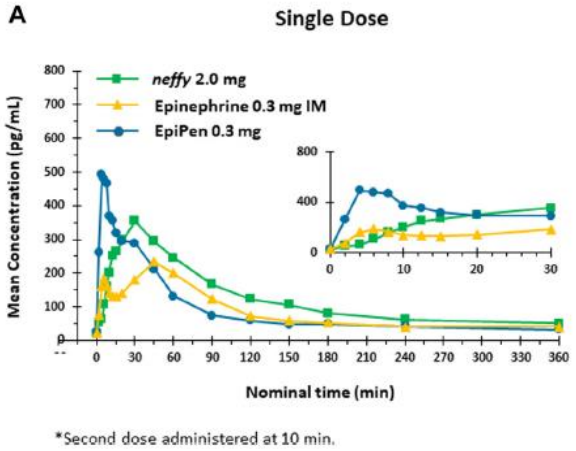


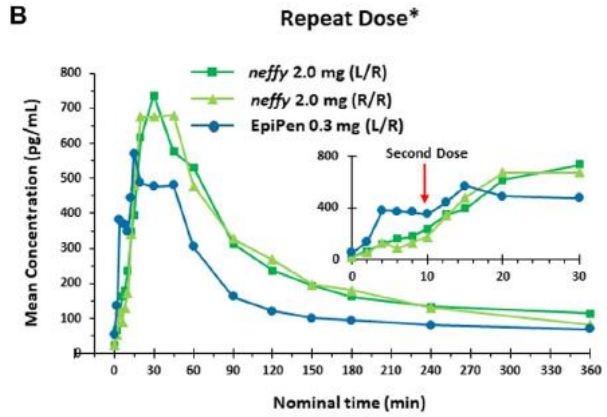


DeMers D, Wachs D. Physiology, Mean Arterial Pressure. 2023 Apr 10. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025
Patel et al Allergy. 2023 Jul;78(7):1997-2006

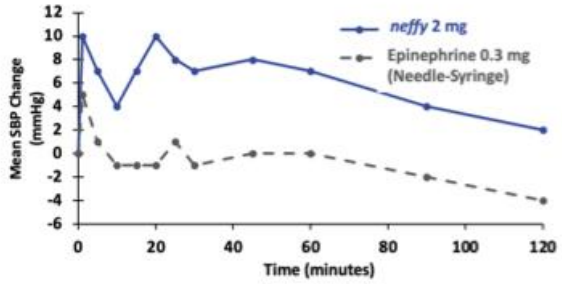
Intranasal Epinephrine Spray (ARS-1, neffy®)

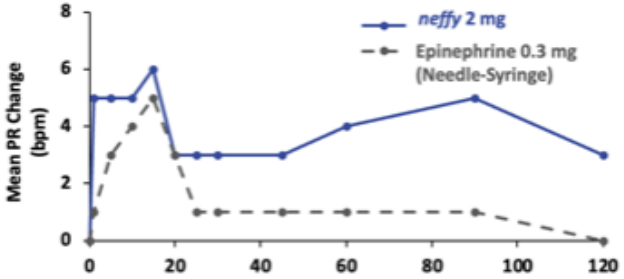
- Bracketed in single dose vs comparators:
  - Tm slower but Cmax larger (AUC_{0-10} slower)
  - Faster PD than IM epinephrine comparator
  - Peds PK proportional with adult dosing
  - PD faster than IM with self-dosing and nasal obstruction
  - HR, BP response noted to rise around a minute after administration in healthy volunteers
- Robust rise with second dose (same nostril)
- Exceeded comparator with 2nd dose

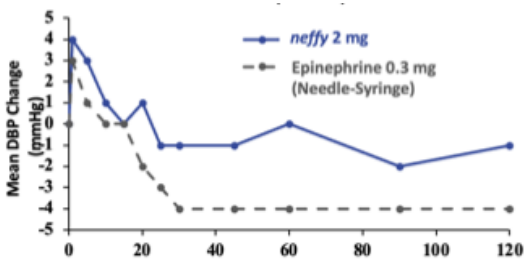




*Second dose administered at 10 min.



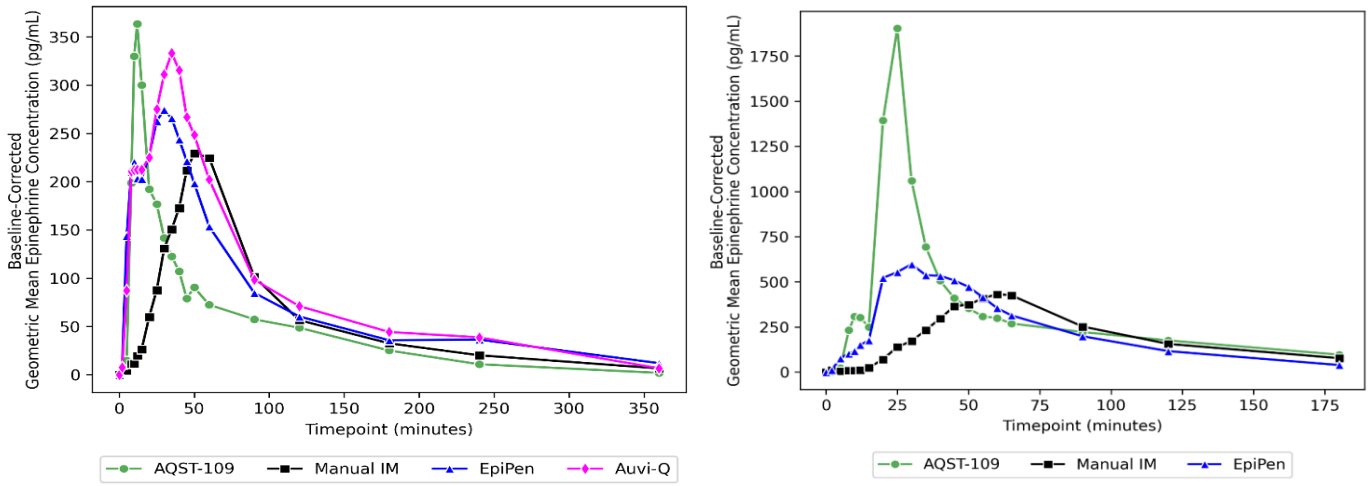


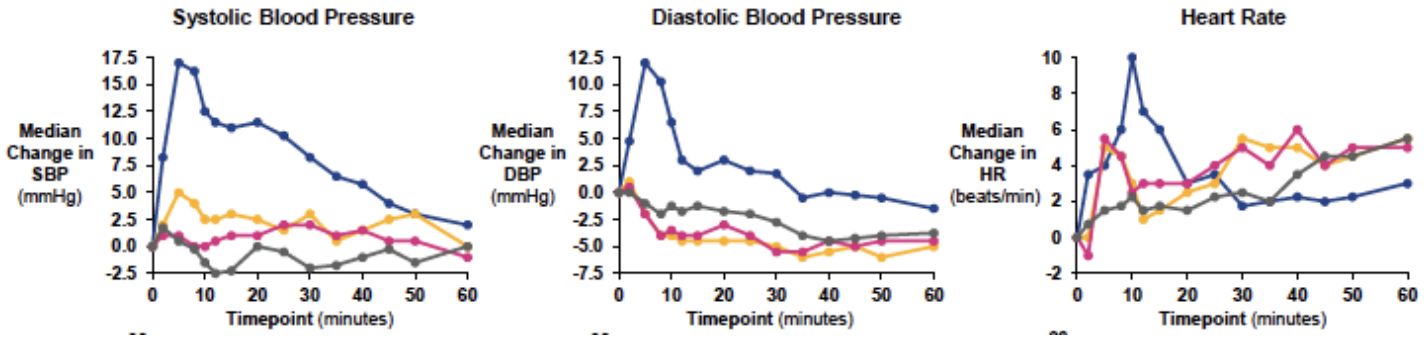


Casale et al. J Allergy Clin Immunol . 2023 Dec;152(6):1587-1596
Ellis et al Pharmaceutics. 2024 Jun 14;16(6):811

Sublingual Epinephrine Film (AQST-109)

- Bracketed through 60min vs comparator:
- Higher PK vs EpiPen/AUVIQ
  - Tm and Cmax better
  - Faster PD vs EpiPen
  - No diastolic BP dip
  - Peds PK is proportional to adult
  - PK/PD unaffected by placement or food/liquid presence
- 2nd dose PK much higher
  - PD not higher in subjects with highest PK's



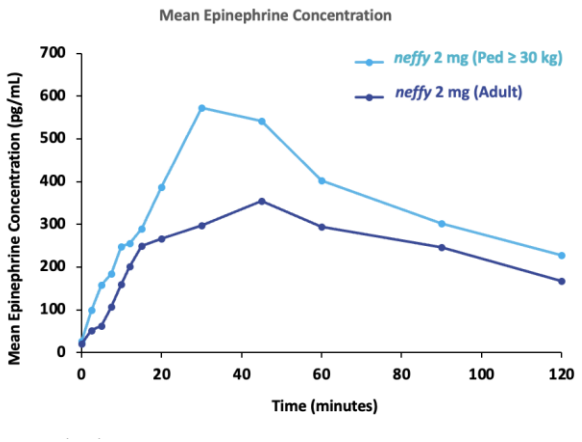


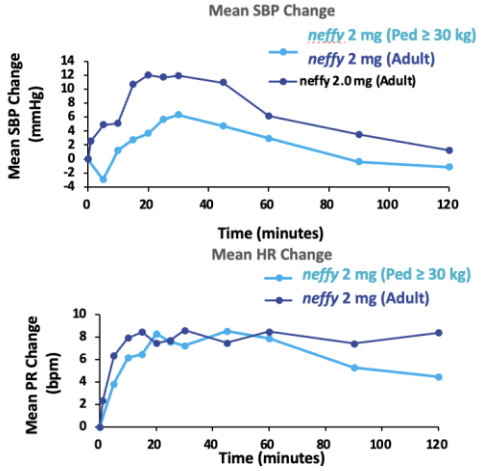
Golden et al. Ann Allergy Asthma Immunol 2025; Nov 24:S1081-1206(25)01363-8..

Pediatric Dosing for Needle-free Forms

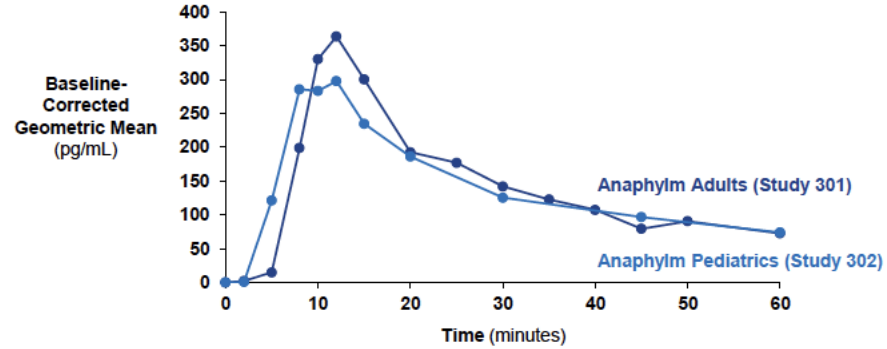
- Peds approval does not require bracketing and nor considers PD—only PK proportionality
- Peds PK levels higher than adult levels, PD responses are lower but proportional
- Both studies achieved “bridge” to adult data that the FDA accepted for filing

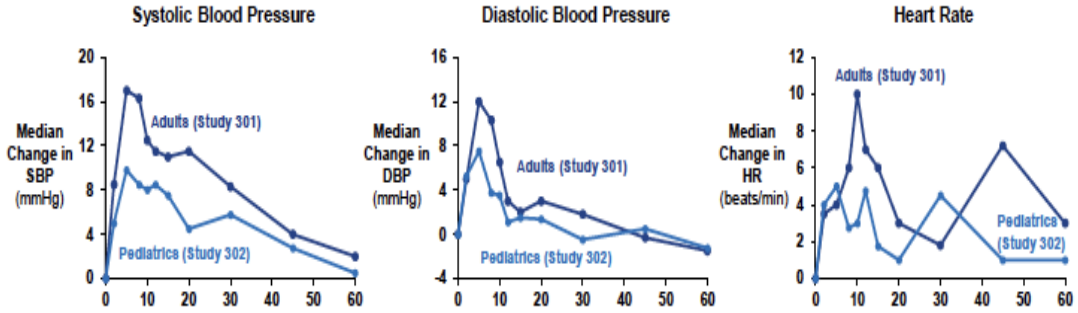
Intranasal Spray





Sublingual Film

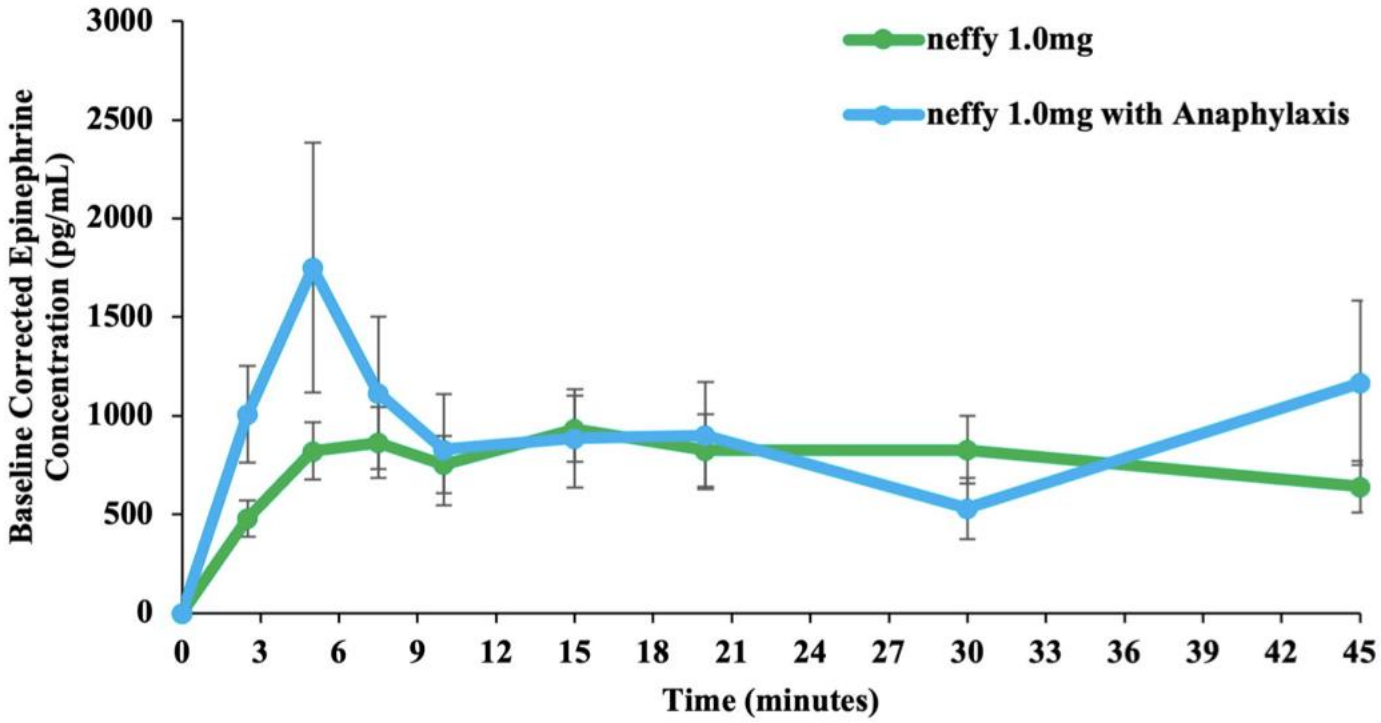




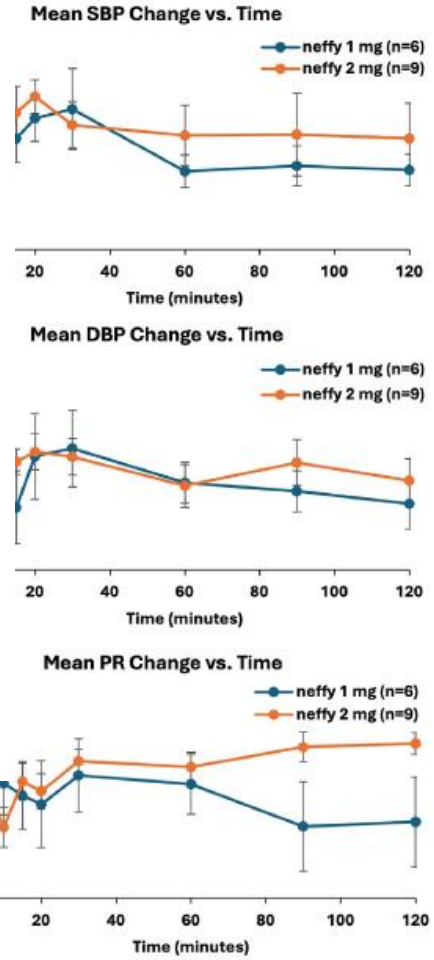
Greenhawt et al 2025 ACAAI Meeting; manuscript submitted and under review
Fleisher et al J Allergy Clin Immunol Pract 2025; 13:1335-41

Intranasal Spray Data In Anaphylaxis

- Real-use study required for regulatory approval in Japan
- N=15 (of 85) childrer
  receive intranasal ep
  anaphylaxis (per JSA
- N=6 received 1mg, 9
  median resolution of
- 1/15 had cardiac syn
  persist and resolve a
- N=7 required additio
- N=1 had biphasic rea
  epinephrine
- N=2 had AE
- Transient decrease in DBP (1mg) and HR/SBP (2mg) seen
- Of course this worked—did we expect something different?



PD Response

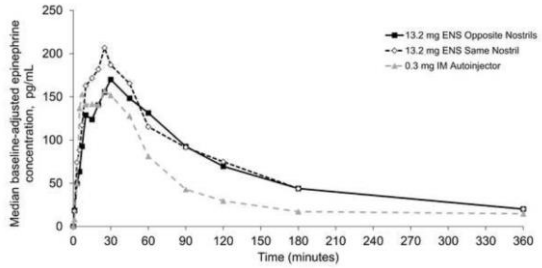


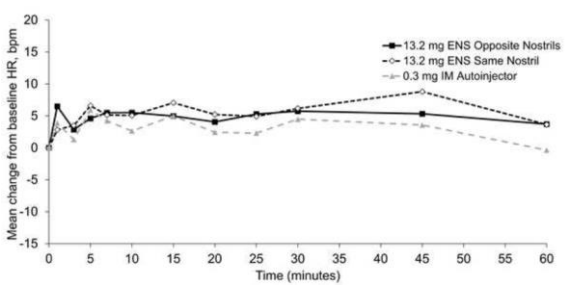
Ebisawa et al J Allergy Clin Immunol Pract 2025; 13: 2787-94
Ellis et al Pharmaceutics. 2024 Jun 14;16(6):811

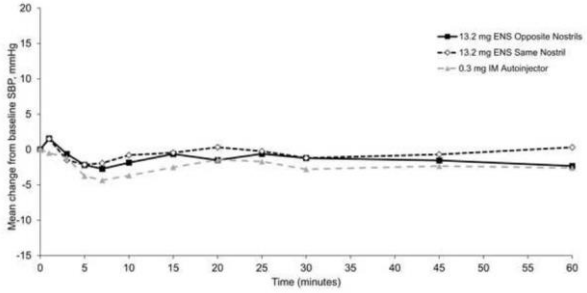
Other DPI Intranasal Forms With Late-Stage Development

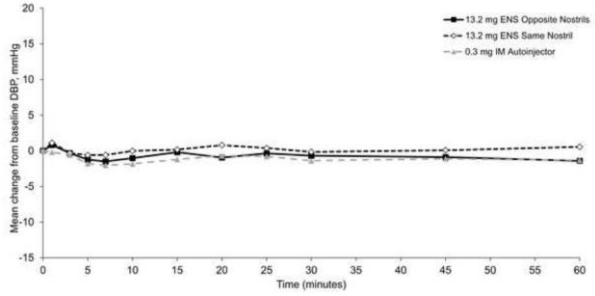
Bryn

- 13.2mg delivered as 2 x 6.6mg doses



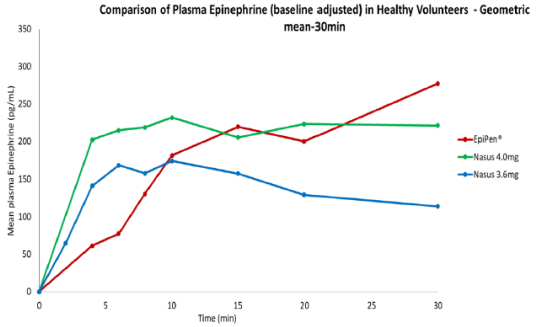


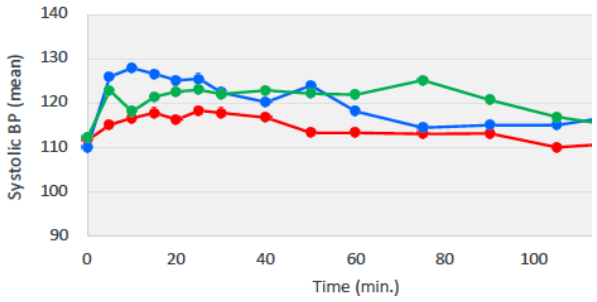


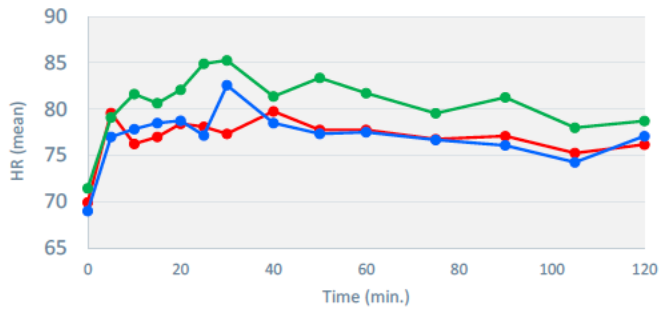


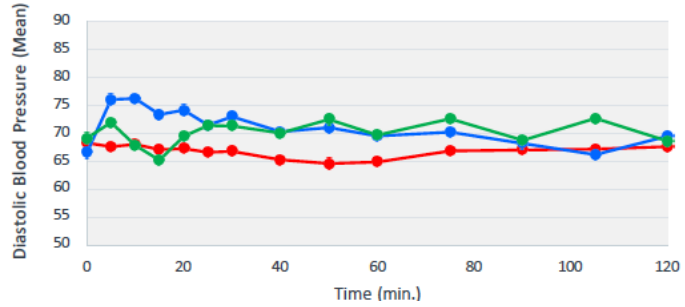
Nasus

- 3.6mg (blue) and 4mg (green) dose









Greenhawt et al J Allergy Clin Immunol Pract 2024; 12:3274-3282.
https://www.nasuspharma.com/wp-content/uploads/2025/11/Nasus_Pharma_Company_Presentation_November_2025_new.pdf

Needle-free Developmental Pipeline

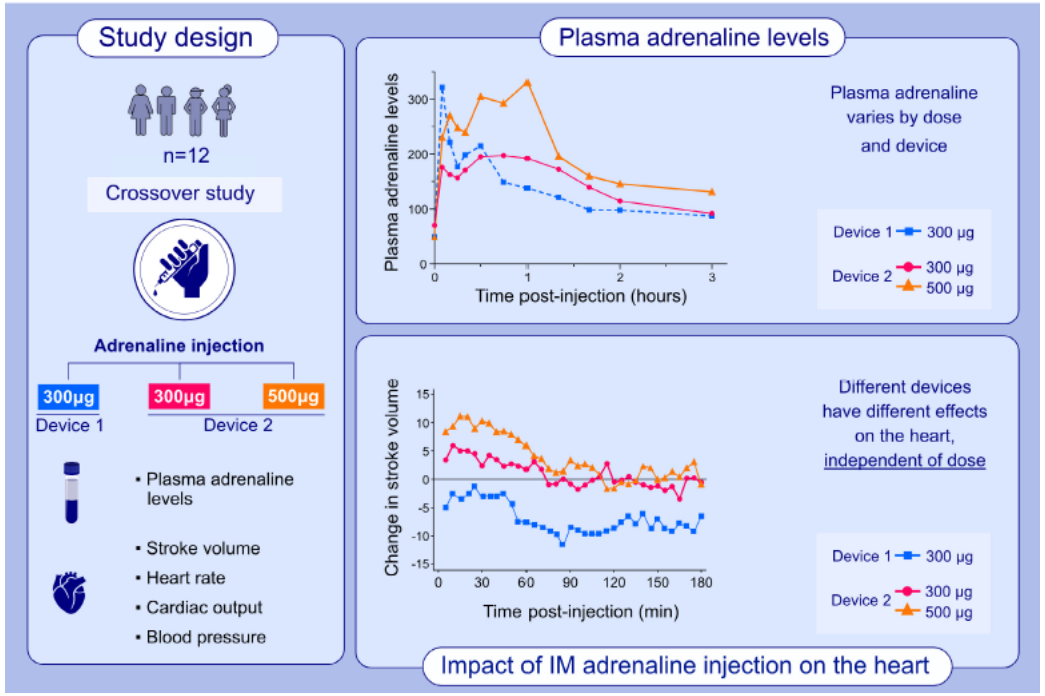
Company	Product (dose)	Current Status
AQST-109 (Aquestive)	sublingual flim (12mg)	Phase 3 (awaiting approval)
NDS1C (Bryn)	Nasal spray	Phase 2 (company folded?)
Hikma (former Insys)	nasal stpray	Phase 2
AMP-019 (Orexo)	nasal DPI (1mg)	Phase 2
NS-002 (Nasus)	nasal DPI (1mg)	Phase 2
Nasdepi (Bellhaven)	nasal DPI (3.5/5.5mg)	Phase 3 (ongoing)
IN-001 (Insignis)	sublingual spray (4.5/9mg)	phase 1 (ongoing)
DMC-1H1 (DeMotu Cordis)	oral DPI	phase 1
KL-01401 (Imbrium/Klaria)	transmucosal film	phase 1
Epinephrine Cyclops (Pureims)	oral PDI	phase 1

PK Parameters	ARS Pharma[1] (Market Cap $885M) Neffy (nasal spray) Commercial	Orexo[3] (Market Cap SEK1.3B) OX640 (nasal powder) Clinical	Aquestive[4] (Market Cap $825M) ANAPHYLM (sublingual) NDA filed	EpiPen[5]	Nasus Pharma[5] (Market Cap $70M*) NS002 (nasal powder) Clinical
Cmax (Mean) (pg/ml)	341	377	497	360	477
Tmax (Median) (Minutes)	30	25	15	15	10
AUC 0-10 min (h/pg/ml)	712	912	1,074	966	1988
AUC 0-30 min (h/pg/ml)	4,901	5,796	6,900	4550	7228
T100** (pg/ml) (Median/Mean) (Minutes)	10/21	5	10	9	4/5
% of patients reaching 100pg	15% at 5 min 60% at 10 min 83% at 30 min		82% at 10 min 91% at 15 min	55% At 6 minutes	91% At 6 minutes

Courtesy Aquestive Pharmaceuticals
https://www.nasuspharma.com/wp-content/uploads/2025/11/Nasus_Pharma_Company_Presentation_November_2025_new.pdf

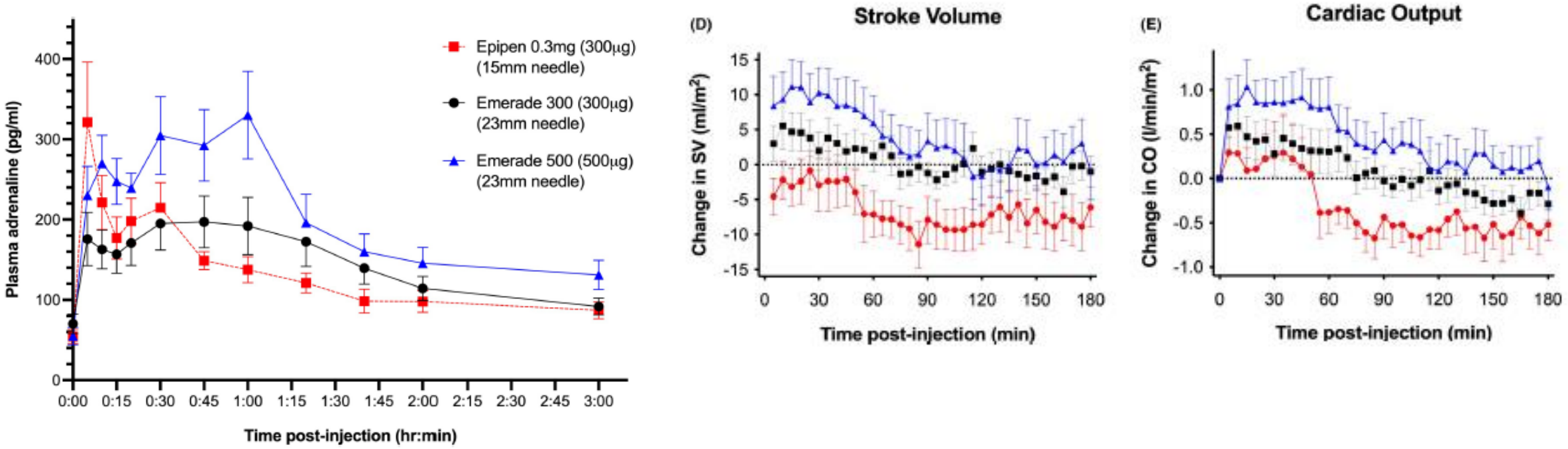
How Much May Dose or Device Impact Performance?

- Inconsistencies in PK/PD profiles seen between devices, and with PK/PD and Tmax/Cmax
- N=12 cross-over study of 2 devices
  - 300mcg of device 1, then 300mcg or 500mcg device 2
  - All teens >40kg with food allergy
  - First device 16mm needle, second device 23mm needle each
- 500µg greater & longer increase in HR, SV, CO vs 300µg
- One 300µg had increase in HR/SV, the other had fastest Tm but increased HR with decreased SV and CO
- Devices did not perform equally, had PK/PD disconnect
- Is optimal CV effect associated with Tm given a negative inotropic effect seen in one device brand?



Patel et al Allergy 2023; 78: 1997-2006

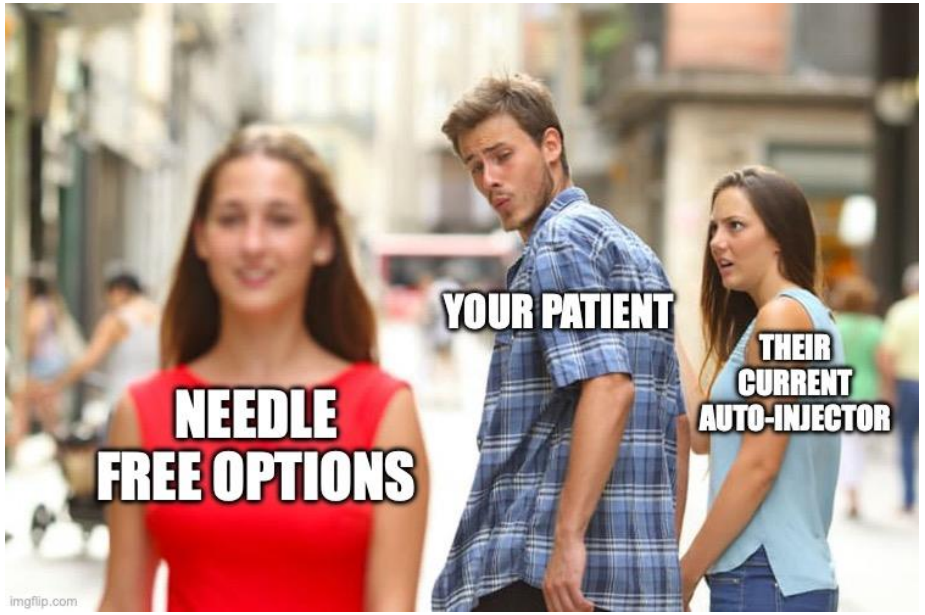
Does This Matter to the Patient?



- This suggest differences in SV and CO between 0.3mg devices and a superior PD performance for 0.5mg device
- Absolute clinical effect in anaphylaxis still unknown since all 3 forms “work”
- Tmax was not affected by the dose
- A higher dose can optimize the Cmax, but it is unclear what the optimal dose for treatment may be
- We have available PK and PD data, which patients should be made aware of when considering their choice

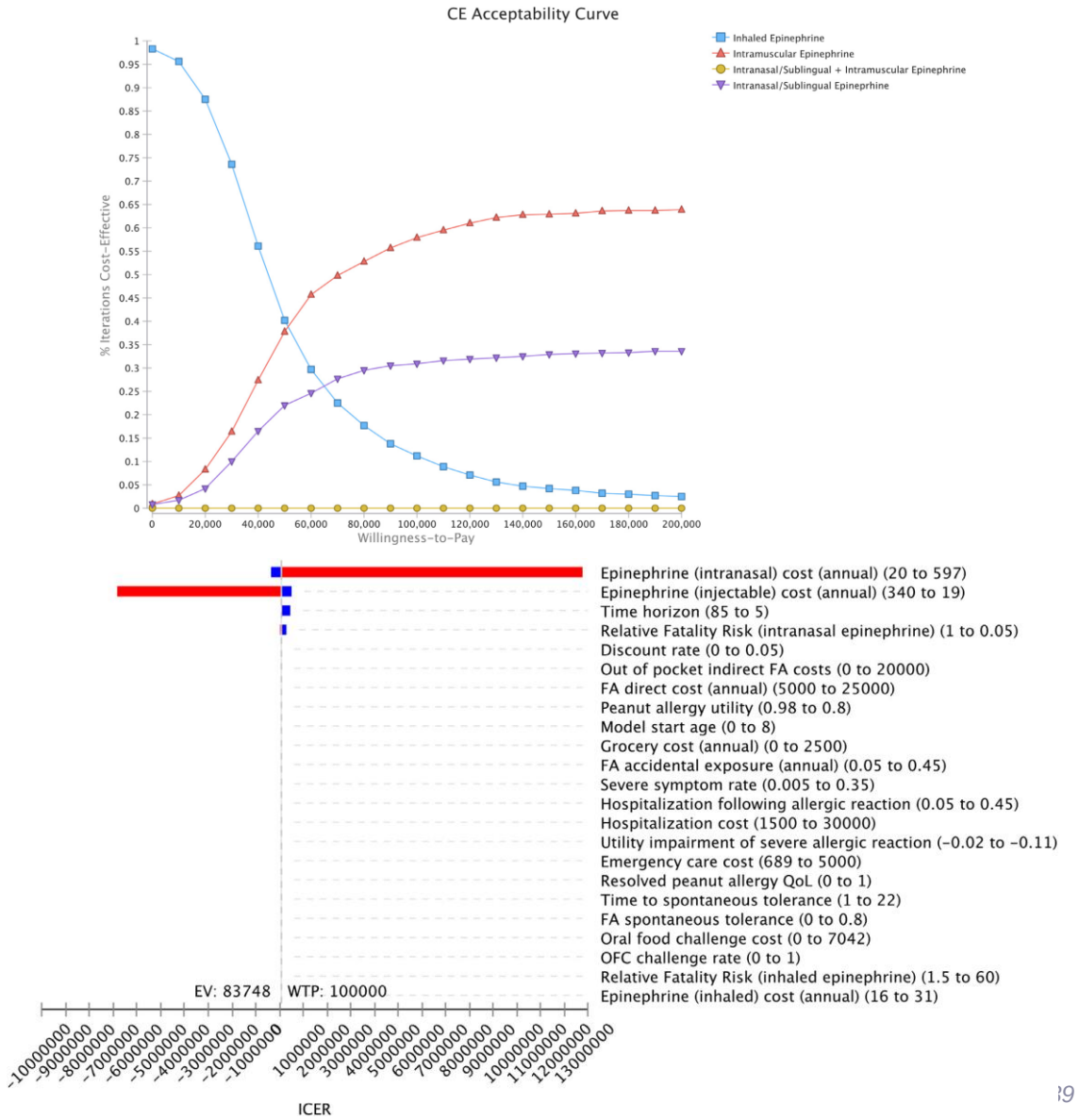
Patel et al Allergy. 2023 Jul;78(7):1997-2006

Choosing Wisely



Are Autoinjectors More Cost-effective?

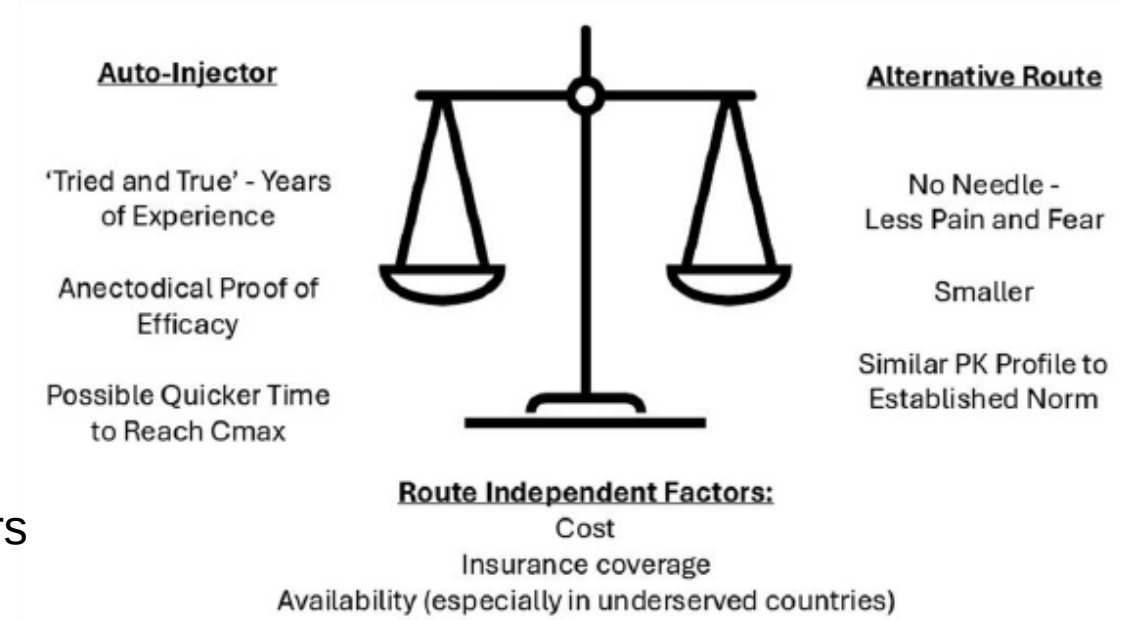
- 2018 study noted EAI's at then $700 price was not cost-effective, and true value-based price was ~$24 per single unit
- Analysis updated in 2024 to account for needle-free forms, reduced pricing b/c of generics, extended shelf life
- Needle-free forms were cost-effective vs. EAI based on price and if used with less delay leading to less need for care
- Difference is thin and favors needle-free forms if single device cost is ≤$4 greater than an EAI
- EAI cost-effective up to $233 per twin-pack.
- Not cost effective to have both EAI & needle-free
- EAI preferred in 58% of iterations, needle-free in 31%, and inhaled in 11%
- IM more cost effective if needle-free price >$41, EAI < $36, or risk reduction of the needle-free form was 27% or more than EAI



Shaker et al Ann Allergy Asthma Immunol 2025; 134: 587-93

Choosing A Form Of Epinephrine and PBL Tie In

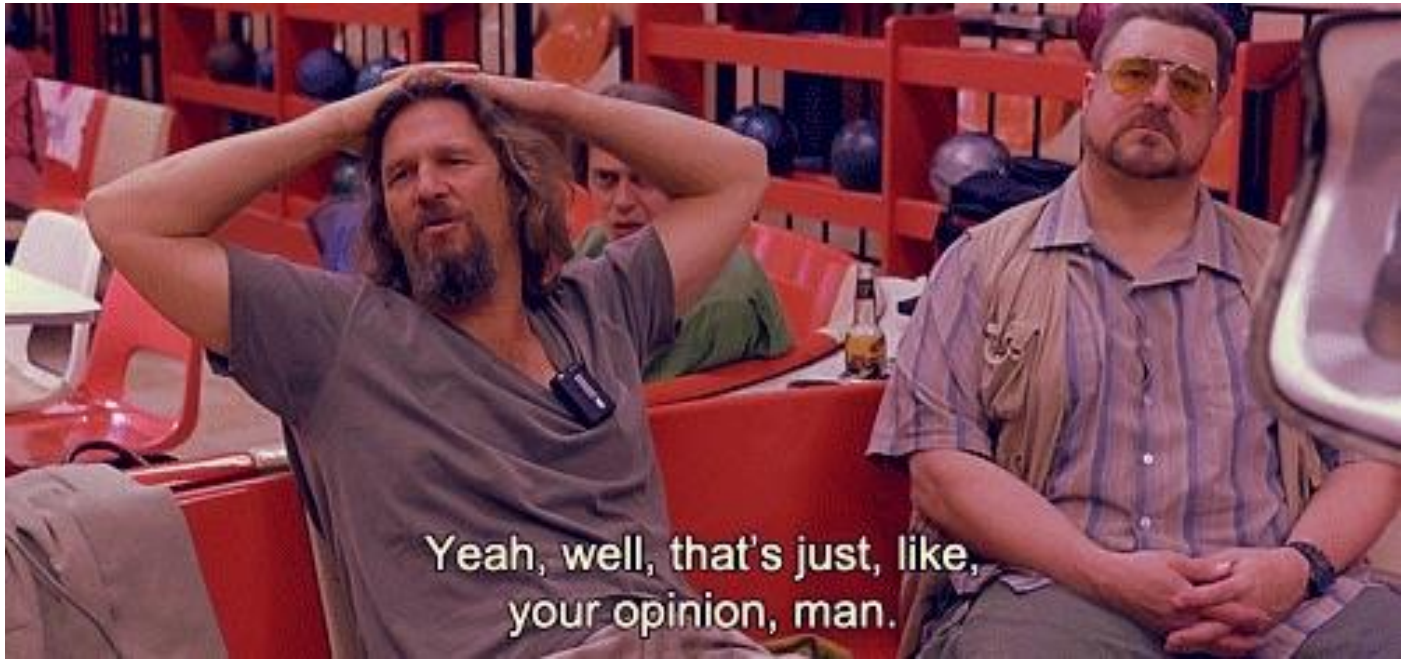
- Preferences for route/form still being elucidated
- No form is without side-effects, but these can be tailored
  - Trade injection for other local effects
  - Can eliminate issue of needle-phobia
- Portability may be better with needle-free forms
- Reliability of newly approved nasal device is high
- PK and PD are more optimized with certain forms vs others
- Shelf life and temp stability better with needle free forms
- Price is lower with most EAI forms because of generics
- All “work” equally to resuscitate a patient
- Decision-aid in late-stage development

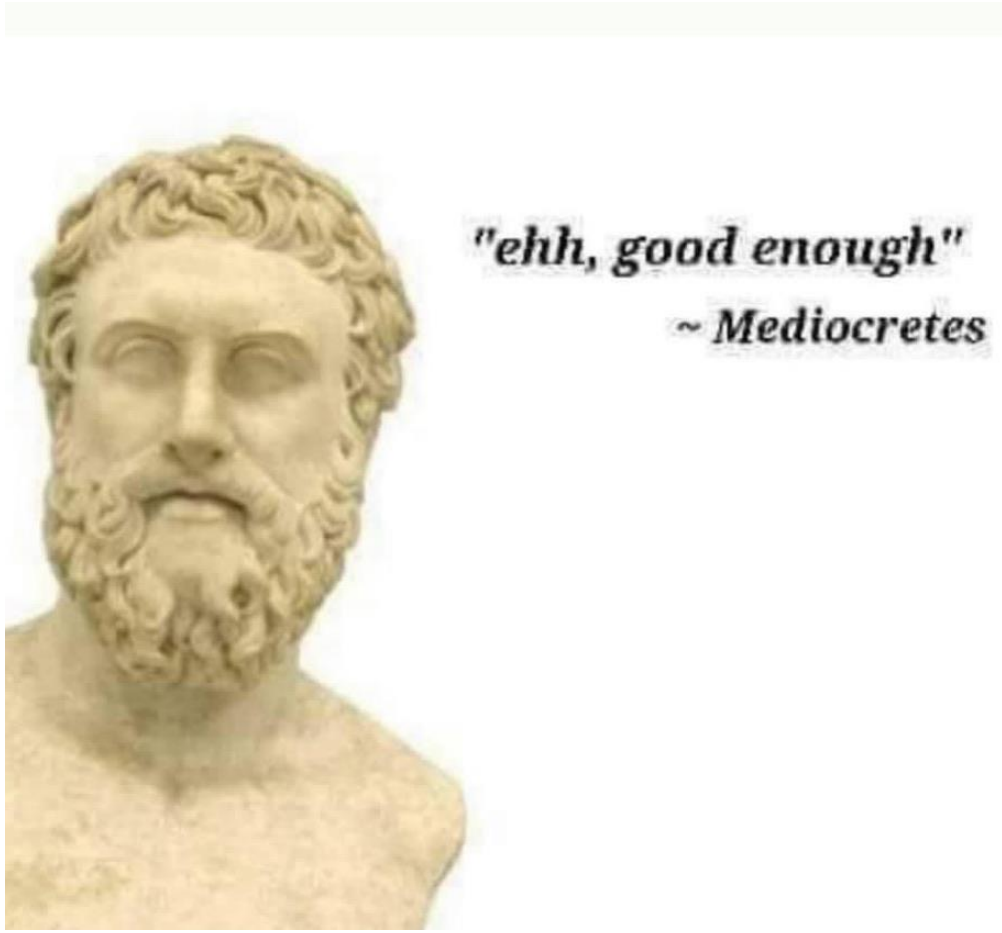


- **Be honest—how many of you would be comfortable prescribing a needle free form for the PBL patient?**
- **If you are, how many of you would prescribe some EAI as “backup”**

Lieberman and Greenhawt Curr Opin Allergy Clin Immunol. 2025 Oct 1;25(5):309-314

Any Questions?





So you have no frame of reference here, Donny. You're like a child who wanders into the middle of a movie and wants to know...