Multicenter, Randomized Crossover Preference Study of Bidose Epinephrine Nasal Spray vs EpiPen®: Patient Perspective

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ABSTRACT

› **Purpose:** Medical devices that are easier to use are typically safer and more effective at delivering their intended therapies. Usability is especially pivotal in emergency situations, when lay users are under stress, for example during anaphylaxis when epinephrine is needed. In particular for patients with severe allergies, portability is very important for emergency epinephrine devices, because fast accessibility impacts overall treatment. Considering the importance of timely administration of epinephrine, devices that are more usable, portable, and preferred by patients may support earlier use of a lifesaving drug, mitigate the worsening of symptom progression, and reduce the incidence of anaphylactic deaths.

In this study, we investigated patient preferences between two medical devices that could be used in anaphylactic emergencies: the EpiPen® autoinjector and the Bidose epinephrine nasal spray. The EpiPen autoinjector functions by removing the safety cap, pushing the tip that houses the needle into the outer thigh until it clicks, holding for three seconds, and then removing the needle. The needle-free Bidose epinephrine nasal spray functions by inserting the nozzle in the nostril, pushing the plunger, and then removing the nozzle. Each EpiPen autoinjector contains one dose so patients are instructed to carry two EpiPen autoinjectors with them to ensure adequate treatment, while the Bidose epinephrine nasal spray contains two equivalent doses so patients will only carry one device.

› **Methods:** Preference in this study was evaluated via an eight-question survey that was validated through a pilot study in advance of the pivotal testing. Fifty-six participants with severe allergies (27 pediatric patients and 29 adult patients), distributed in six states across the United States, were each engaged in a one-on-one moderated session. All participants had been prescribed EpiPen but were only characterized as EpiPen-experienced if they had used an EpiPen autoinjector previously. Participants were presented with the EpiPen trainer and an empty Bidose epinephrine nasal spray device and simulated use of each one with counterbalanced presentation order between participants. Participants then responded to the survey questions.

Each question was analyzed separately for EpiPen-experienced participants (n = 24) and EpiPen-inexperienced participants (n = 32) with an exact binomial test using the binomial test function in R. For statistical significance, $p = .05$ was used.

› **Results:** The results indicate a significant preference for the Bidose epinephrine nasal spray over the EpiPen autoinjector on various metrics including portability, ease of learning, ease of use, overall preference, likelihood of recommending to others, safety, size, and comfort.

› **Conclusion:** Considering that the most common cause of death from food allergies is delayed epinephrine administration, prescription and use of a small, portable, easy to use device like the Bidose epinephrine nasal spray device might decrease the incidence of anaphylactic deaths.

INTRODUCTION

› The standard of care in the treatment of a severe allergic reaction (anaphylaxis) is epinephrine, most commonly delivered via intramuscular or subcutaneous injection with an epinephrine autoinjector like the EpiPen® (epinephrine injection, USP, Mylan Specialty LP, Canonsburg, PA)[1]

› Several patient concerns or anxiety related to autoinjector use (e.g., laceration injuries, accessibility, etc.) may impede epinephrine administration in the event of anaphylaxis[1,2]

› Delayed epinephrine treatment during anaphylaxis may increase the risk of hospitalization and potentially fatal outcomes[3-5]

› Recent studies have demonstrated that portability, safety, and ease of administration are preferred by patients with allergies when choosing a treatment device[4,6,7]

› Because timely administration of epinephrine is a critical factor for treating anaphylaxis, devices that offer both portability and ease of epinephrine administration are needed

› The purpose of this study was to evaluate patient preferences between the Bidose epinephrine nasal spray (ENS) and EpiPen autoinjector for severe allergies

AIM

› To investigate patient preferences between two medical devices that could be used in anaphylactic emergencies: the Bidose ENS and the EpiPen

METHODS

› This was a multicenter, randomized, crossover preference study of Bidose ENS versus EpiPen

Study devices (Figure 1)

Figure 1. Bidose ENS device (left) and the EpiPen (right) used in the study[a]

[a]Image depicts equivalent doses (1 Bidose ENS device = 2 EpiPens)
ENS, epinephrine nasal spray

› Using empty but fully functional Bidose ENS devices, study participants simulated dose administration into their nostril
- Users operate the Bidose ENS by inserting the nozzle into the patient's nostril, pushing the plunger, and then removing the nozzle from the nostril
- Each Bidose ENS device contains two equivalent doses; therefore, users only have to carry one device

› Using EpiPen training devices, which do not contain the drug or a needle, study participants simulated dose administration into their thigh
- Users operate the EpiPen by removing the blue safety cap, pushing the orange tip that houses the needle into the patient's outer thigh until it clicks, holding the device in that position for 3 seconds, and then releasing the pressure to remove the needle
- The EpiPen contains one dose; therefore, users have to carry two devices

Questionnaire development

› To assess preference, an eight-item, forced-choice questionnaire was designed based on differences between the Bidose ENS and the EpiPen for epinephrine administration
- Preference was assessed based on the following metrics: portability, ease of use, overall preference, willingness to recommend device, safety, size, use in a real emergency, and comfort using in public

› Three answer choices were provided: Bidose ENS, EpiPen, or no preference

› This questionnaire was iteratively refined in a pilot study of 13 participants (patients and healthcare professionals) and finalized in advance of pivotal preference testing

Pivotal preference study

› Two user groups participated in this preference study:
- Patients with severe allergies aged ≥ 11 years
- Healthcare professionals who treat patients with severe allergies
  - Results from the healthcare professional participants will be presented elsewhere

› Patients from New York, Massachusetts, Georgia, Texas, California, and Pennsylvania participated

› Each patient provided written consent before their session and were compensated for their time with an honorarium

› All patients enrolled in the study had been prescribed an EpiPen for their allergies and were subsequently classified as EpiPen-experienced (based on experience previously using an EpiPen in an emergency) or EpiPen-inexperienced (no previous experience using an EpiPen in an emergency)

› Patients attended a one-on-one session with a Moderator to learn how to use both devices
- Patients observed a demonstration of the first device and then used the first device on their own. They then observed a demonstration of the second device and then used the second device on their own. Presentation of the devices was counterbalanced across patients
- After using both devices, patients completed the eight-item questionnaire

› This study was reviewed and approved by the Core Human Factors, Inc. Independent Review Board, which is registered with the US Department of Health and Human Services

Statistical analysis

› Each question was analyzed separately for EpiPen-experienced and EpiPen-inexperienced patients with an exact binomial test using the binomial test function in the statistical software "R" (The R Foundation, Vienna, Austria)

› A probability value (p-value) of $p = .05$ was used to evaluate statistical significance

RESULTS

› Fifty-six patients with severe allergies participated in the study (**Table 1**)

› Out of 56 participants, 24 (43%) were EpiPen-experienced (**Table 1**)

› Patients reported being diagnosed with a range of allergy types, including food (n = 43), insect (n = 16), and medication (n = 8)
- Some patients had multiple allergy types

Table 1. Number of EpiPen-experienced and EpiPen-inexperienced patients by age group

User Group	N
EpiPen-experienced pediatrics (aged 11–17 years)	11
EpiPen-inexperienced pediatrics (aged 11–17 years)	16
EpiPen-experienced adults (aged 18+ years)	13
EpiPen-inexperienced adults (aged 18+ years)	16
Total	**56**

› For all but one parameter, at least 60% of patients indicated a statistically significant preference for the Bidose ENS (**Table 2**; **Figures 2, 3 and 4**)

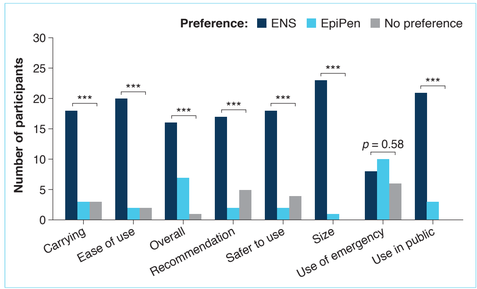
Table 2. Patient preference for Bidose ENS by experience

Question	EpiPen-experienced Patients n=24		EpiPen-inexperienced Patients n=32	
	Preference for Bidose ENS, n (%)	p value	Preference for Bidose ENS, n (%)	p value
Which device do you think you would be more likely to carry with you in daily life?	18 (75.0%)	<.001	27 (84.4%)	<.001
Which device is easier to use?	20 (83.3%)	<.001	26 (81.3%)	<.001
Which device do you prefer overall?	16 (66.7%)	<.001	27 (84.4%)	<.001
Which device would you recommend to others?	16 (66.7%)	<.001	24 (75.0%)	<.001
Which device do you think would be safer for you to use?	18 (75.0%)	<.001	20 (62.5%)	<.001
Which device do you prefer based on the size of the device?	23 (95.8%)	<.001	28 (87.5%)	<.001
Which device do you think you would be more likely to use in a real emergency?	8 (33.3%)	.58	20 (62.5%)	<.001
Which device would you feel more comfortable using in a public space?	19 (79.2%)	<.001	26 (81.3%)	<.001

ENS, epinephrine nasal spray

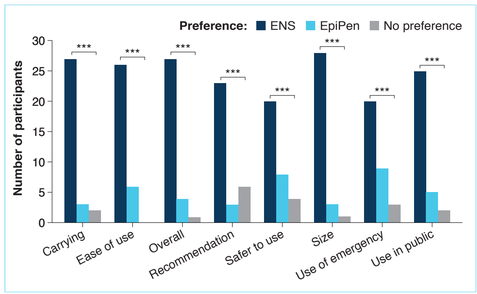
- Regarding device portability or the likelihood of carrying the device in daily life, 75% of EpiPen-experienced patients and 84% of EpiPen-inexperienced patients indicated preference for Bidose ENS (both $p < .001$).
- For ease of administration, 83% of EpiPen-experienced and 81% of EpiPen-inexperienced patients indicated preference for Bidose ENS (both $p < .001$)
- For perceived device safety, 75% of EpiPen-experienced patients and 63% of EpiPen-inexperienced patients indicated preference for Bidose ENS (both $p < .001$)
- Regarding device size, 96% of EpiPen-experienced and 88% of EpiPen-inexperienced patients indicated preference the Bidose ENS (both $p < .001$)
- EpiPen-experienced patients did not have a significant preference between EpiPen and Bidose ENS for use during an emergency ($p = .58$), while most EpiPen-inexperienced patients (63%) preferred the Bidose ENS ($p < .001$)

Figure 2. Device preference of EpiPen-experienced patients



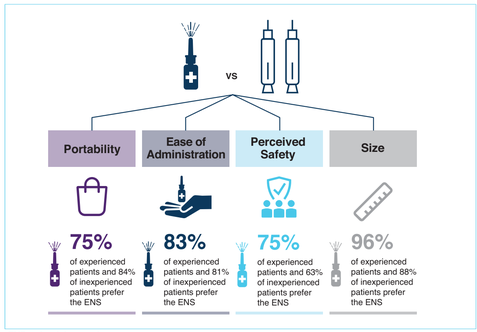
***$p < .001$
ENS, epinephrine nasal spray

Figure 3. Device preference of EpiPen-inexperienced patients



***$p < .001$
ENS, epinephrine nasal spray

Figure 4. Preference of patients for the ENS over the EpiPen



ENS, epinephrine nasal spray

CONCLUSIONS

1. **Both EpiPen-experienced and EpiPen-inexperienced patients preferred the Bidose ENS** over the EpiPen autoinjector for several parameters, including portability, ease of learning, ease of use, overall preference, likelihood of recommending to others, safety, size, and comfort using in public

2. **EpiPen-experienced patients did not have a significant preference between EpiPen and Bidose ENS for use during an emergency**, while EpiPen-inexperienced patients preferred Bidose ENS. This difference may have been due to past positive EpiPen experience during an emergency

3. **Bidose ENS may provide important advantages over the EpiPen**, which could result in a decrease in the incidence of delayed epinephrine treatment and, potentially, deaths resulting from anaphylaxis

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