

et al. But for the reasons cited above, we caution against accepting the Diacano et al's data as *prima facie* evidence of the necessity of needle penetration of the fascia as a requirement for IM delivery of epinephrine. In addition, we disagree that there are no published data supporting evidence of a possible gender difference in the pharmacokinetics of epinephrine and their assumption that such baseline differences could not affect such pharmacokinetics. Finally, we feel that a role of compression in the depth of penetration cannot be excluded based on available data.

Perhaps the final take home from these exciting polemics is that dogmatic conclusions as to how we apply these studies to patient care should be avoided. The studies are sparse, and the numbers are small.

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REFERENCES

1. Dreborg S, Kim H. Tissue compression and epinephrine deposition. *J Allergy Clin Immunol Pract* 2019;7:2096-7.
2. Diacono D, Pumphrey RS, Sharma V, Arkwright PD. The deep fascia of the thigh forms an impenetrable barrier to fluid injected subcutaneously by autoinjectors. *J Allergy Clin Immunol Pract* 2015;3:297-9.
3. Stout R. Bioject Medical Technologies Inc. Announces FDA Market Clearance for the Zetajet Needle-Free Injection Therapy System. Portland, Ore: Bioject Medical Technologies Inc.; 2009.
4. Kumar RB. Needle free injection systems. *Pharma Innov* 2012;1:57-72.
5. Viegas EO, Tembe N, Nilsson C, Meggi B, Maueja C, Augusto O, et al. Intradermal HIV-1 DNA immunization using needle-free Zetajet injection followed by HIV-modified vaccinia virus ankara vaccination is safe and immunogenic in Mozambican young adults: a phase I randomized controlled trial. *AIDS Res Hum Retroviruses* 2018;34:193-205.
6. Ravi AD, Sadhna D, Nagpaal D, Chawla L. Needle free injection technology: a complete insight. *Int J Pharm Investig* 2015;5:192-9.
7. 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 observations study. *Adv Ther* 2017;34:252-60.
8. Song TT, Merrill NL, Cole JW. Delivery depth of epinephrine by auto-injector into the subcutaneous tissue of pig. *Ann Allergy Asthma Immunol* 2013;111:143-5.
9. Dreborg S, Kim L, Tsai G, Kim H. Epinephrine auto-injector needle lengths: can both subcutaneous and periosteal/intraosseous injection be avoided? *Ann Allergy Asthma Immunol* 2018;120:648-53.
10. Duvauchelle T, Robert P, Donazzolo Y, Loyau S, Orlandini B, Leher P, et al. Bioavailability and cardiovascular effects of adrenaline administered by Anapen auto-injector in healthy volunteers. *J Allergy Clin Immunol Pract* 2018;6:1257-63.
11. Lenders JW, De Boo T, Lemmens WA, Reijenga J, Willemsen JJ, Thien T. Comparison of blood pressure response to exogenous epinephrine in hypertensive men and women. *Am J Cardiol* 1988;61:1288-91.
12. Hinojosa-Laborde C, Chapa I, Lange D, Haywood JR. Gender differences in sympathetic nervous system regulation. *Clin Exp Pharmacol Physiol* 1999;26:122-6.
13. Soldin OP, Mattison DR. Sex differences in pharmacokinetics and pharmacodynamics. *Clin Pharmacokinet* 2009;48:143-57.

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The real world is not standardized



To the Editor:

The editorial by Wang¹ that accompanied the article on peanut oral immunotherapy (OIT) in clinical practice² notes the size of the reported cohort and the duration of observations of our clinical practice. However, the editorial criticizes the report for not being the randomized, controlled trial that it was never intended to be. Baseline food challenges were not performed in patients with a history of an IgE-mediated reaction within 2 years of starting OIT. Would it have been ethical to challenge patients with known peanut allergy? As we note in our article, no patient was excluded from OIT because of the severity of reaction history or the magnitude of peanut specific IgE. All patients, except for the 8 who refused consent, were reported. The only bias was the choice parents made in seeking care for their children. The editorial also criticizes the absence of prespecified clinical end points when, in fact, the end point of passing a 6000-mg peanut protein challenge (substantially higher than in most controlled trial reports) was clearly stated.

We are most concerned about the use of the editorial to promote a product. Although the editorial properly notes that there are no reports of adverse events occurring as a result of changing the source of peanut protein in our patients, it attributes the need for OIT practitioners to be prepared for and educate their patients about reactions solely to nonstandardized peanut. The editorial appears to conflate the use of nonstandardized peanut with the "lack of sufficient personnel and resources" as the reason allergy practices may not implement OIT. Most allergy practices do not outsource premade subcutaneous immunotherapy vaccines because of "lack of sufficient personnel and resources." The editorial implies that it is not possible to have a guideline or billing code without a commercial product. It seems to ignore the Learning Early About Peanut Allergy (LEAP) study that was based on the use of Bamba and the subsequent guidelines recommending Bamba, peanut butter, or peanut butter powder for the prevention of peanut allergy.

The insistence on the use of a "standardized" peanut product will be costly and will limit patients' access to care. Allergists have, for more than a century, safely and effectively used extracts for injected immunotherapy in which the allergen content may vary by as much as 10-fold. Cost-effective medicine requires balancing the risks and benefits of a therapy. Our reports^{2,3} along with the early published trials from academic medical centers,^{4,5} using readily available peanut foods, have demonstrated an efficacy and major adverse event rate comparable to that in studies that used a "standardized" product for a material cost of just "peanuts."

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REFERENCES

1. Wang J. Peanut oral immunotherapy: data from a real-world clinical practice. *J Allergy Clin Immunol Pract* 2019;7:427-8.
2. Wasserman RL, Hague AR, Pence DM, Sugerman RW, Silvers SK, Rolen JG, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. *J Allergy Clin Immunol Pract* 2019;7:418-26.
3. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. *Ann Allergy Asthma Immunol* 2018;121:272-5.
4. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in peanut allergic children. *J Allergy Clin Immunol* 2009;124:286-91.
5. Bird JA, Feldman M, Arneson A, Dougherty I, Brown LS, Burk CM, et al. Modified peanut oral immunotherapy protocol safely and effectively induces desensitization. *J Allergy Clin Immunol Pract* 2015;3:433-5.

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Reply



To the Editor:

In the opening paragraph, Wasserman et al¹ state that my editorial “criticizes the report for not being the randomized, controlled trial that it was never intended to be.” I am surprised that they interpreted the editorial to be a criticism as I simply pointed out that “the authors acknowledge certain limitations given the retrospective nature of their data,”² which is a reiteration of Wasserman et al’s³ own words in the discussion of their original report, “As a retrospective study, there are potential biases.” As the authors already present their report as being from real-world practice, the editorial serves to point out to readers the similarities and differences, as well as advantages and limitations, when examining different approaches to peanut oral immunotherapy.

The correspondence takes issue with my statement about the lack of food challenges, which simply stated: “The authors acknowledge certain limitations...For example, baseline food challenges were not performed so the magnitude of efficacy remains uncertain.”² The authors themselves state in their original article that “clinicians modified patient treatment according to their judgment” and specifically say that “because all patients were not challenged before beginning POIT, we cannot be certain that they were all peanut allergic.”³ Therefore, it is merely a statement of fact on my part that baseline food challenges were not performed for the patients in their cohort, and not an implication of inferiority. However, I would not agree with Wasserman et al’s conclusion that “the only bias was the choice parents made in seeking care for their children” when we are discussing a retrospective review of an open treatment.

Wasserman et al¹ further question “would it have been ethical to challenge patients with known peanut allergy?” Although it is understandable why this “real-world” study decided not to routinely perform food challenges, I take issue with the comment that doing so is unethical. There are dozens of completed and ongoing clinical trials of peanut allergy that are sponsored by the National Institutes of Health, investigator-initiated or

pharmaceutical trials that include baseline food challenges for patients with known peanut allergy. These studies have all undergone review and received approval by different institutional review boards and Data Safety Monitoring Boards. The mandate of institutional review boards is to provide ethical and regulatory oversight of research that involves human subjects. Therefore, challenging patients with known peanut allergy has repeatedly been found to be an acceptable procedure to be included in peanut allergy studies.

Wasserman et al allege that the editorial is promoting a specific product. First, there is no mention of any specific product anywhere in the editorial.² Second, the word “product” is used as a generic term throughout the editorial, defined as “something that is marketed or sold as a commodity.”⁴ This term was chosen because there are different sources of peanut protein available (including peanut, peanut butter, peanut flour) that have been used for peanut oral immunotherapy (OIT). The authors also mistakenly interpret the editorial statement on allergic reactions due to OIT, erroneously assuming that it refers only to the use of nonstandardized peanut. The editorial notes that Wasserman et al’s report is in fact similar to other published reports in finding that allergic symptoms to OIT are common. The references I cite included 4 different studies that used different peanut sources/products, 3 of which used nonstandardized products (Blumchen et al⁵ used crushed roasted peanut and Anagnostou et al⁶ and Varshney et al⁷ used lightly roasted flour).

Another point related to safety brought up in the editorial to which Wasserman et al take offense is that switching between peanut protein sources during OIT could pose a potential safety concern. This concern was raised on the basis of data published by Filep et al⁸ and Hindley et al,⁹ which demonstrate variability in peanut protein content across different peanut foods. Following Wasserman et al’s suggestion to compare peanut OIT to subcutaneous immunotherapy for environmental allergies, I would point out that the practice parameter on allergen immunotherapy¹⁰ specifically states that:

“[A]n allergen immunotherapy extract must be considered different from a clinical standpoint if there is any change in the constituents of the allergen immunotherapy extract. These include changes in the lot, manufacturer, extract type (eg, aqueous, glycerinated, standardized, and nonstandardized), and component allergens and their respective concentrations in the allergen immunotherapy extract. There is potentially an increased risk of a systemic reaction if the allergen immunotherapy extract is changed and the patient’s dose is not modified.”

As such, an analogous approach should not be unexpected for peanut OIT in that caution would be warranted when switching between peanut protein sources from different manufacturers, both standardized and nonstandardized. Although Wasserman et al³ did not report any problems when their patients switched between peanut products, these data from a single cohort are insufficient to deem this concern to be irrelevant, such that no caution is warranted for any patient.

Wasserman et al also take offense to the points made in my editorial about reasons why practices may find implementing OIT to be challenging. The reasons listed for physician concern are taken directly from the study by Greenhawt and Vickery¹¹ who conducted a survey of American Academy of Allergy, Asthma