

There's a Much Safer Food Allergy Immunotherapy. Why Don't More Doctors Offer It?

Esther Landhuis

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This is part 1 of a three-part series. Part 2 is [here](#). Part 3 is [here](#).

For the 32 million people in the United States with food allergies, those who seek relief beyond constant vigilance and EpiPens face a confusing treatment landscape. In January 2020, the US Food and Drug Administration (FDA) approved an oral immunotherapy product (Palforzia) for peanut-allergic children. Yet the product's ill-timed release during a pandemic and its black-box warning about the risk for [anaphylaxis](#) has [slowed uptake](#).

A small number of allergists offer [home-grown oral immunotherapy](#) (OIT), which builds protection by exposing patients to increasing daily doses of commercial food products over months. However, as with Palforzia, [allergic reactions are common during treatment](#), and the hard-earned protection can fade if not maintained with regular dosing.

An alternate approach, sublingual immunotherapy (SLIT), delivers food proteins through liquid drops held in the mouth — a site rich in tolerance-inducing immune cells. In a 2019 study of peanut-allergic children aged 1–11 years, SLIT [offered a level of protection on par with Palforzia](#) while causing considerably fewer adverse events. And at the 2021 annual meeting of the American Academy of Allergy, [Asthma](#) and Immunology (AAAAI), held virtually in February, researchers reported that SLIT produced [stronger, more durable benefits in toddlers aged 1–4](#).



Dr Edwin Kim

Sublingual immunotherapy is "a bunch of drops you put under your tongue, you hold it for a couple minutes, and then you're done for the day," said Edwin Kim, MD, director of the UNC Food Allergy Initiative, University of North Carolina School of Medicine, Chapel Hill, North Carolina, who led the two recent studies. For protecting against accidental ingestions, SLIT "is pushing pretty close to what OIT is able to provide but seemingly with a superior ease of administration and safety profile."

Many parents don't necessarily want their allergic kids to be able to eat a peanut butter sandwich — but do want them to be able to safely sit at the same lunch table and attend birthday parties with other kids. SLIT achieves this level of protection about as well as OIT, with fewer side effects.

Still, because of concerns about the treatment's cost, unclear dosing regimens, and lack of FDA approval, very few US allergists — likely less than 5% — offer sublingual immunotherapy to treat food allergies, making SLIT even less available than OIT.

Concerns About SLIT

One possible reason: Success is slower and less visible for SLIT. When patients undergo OIT, they build up to dosing with the actual food. "To a family who has a concern about their kid reacting, they can see them eating chunks of peanut in our office. That is really encouraging," said Douglas Mack, MD, FRCPC, an allergist with Halton Pediatric Allergy and assistant clinical professor of pediatrics at McMaster University, in Hamilton, Ontario, Canada.

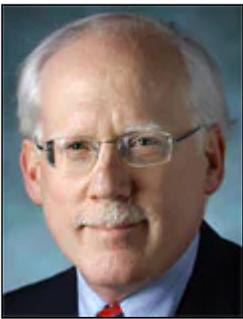


Dr Douglas Mack

On the other hand, ingestion isn't the focus for SLIT, so progress is harder to measure using metrics in published trials. After holding SLIT drops under the tongue, some patients spit them out. If they swallow the dose, it's a vanishingly small amount. Immune changes that reflect increasing tolerance, such as a decrease in IgE antibodies, tend to be more gradual with SLIT than with OIT. And because SLIT is only offered in private clinics, such tests are not conducted as regularly as they would be for published trials.

But there may be a bigger factor: Some think earlier trials comparing the two immunotherapy regimens gave SLIT a bad rap. For example, in studies of [milk-](#) and [peanut-allergic](#) children conducted in 2011 and 2014, investigators concluded that SLIT was safer and that OIT appeared to be more effective. However, those trials compared SLIT to OIT using a much higher dose (2000 mg) than is used in the licensed product (300 mg).

Over the years, endpoints for food allergy treatment trials have shifted from enabling patients to eat a full serving of their allergen to merely raising their threshold to guard against accidental exposures. So in those earlier articles, "we would probably write the discussion section differently now," said Corinne Keet, MD, PhD, first author on the 2011 milk study and an associate professor of pediatrics at Johns Hopkins University School of Medicine, in Baltimore, Maryland.



Dr Robert Wood

Indeed, "when you compare [SLIT] to Palforzia or other studies of low-dose OIT (300 mg/d), they look equal in terms of their efficacy," said senior author Robert Wood, MD, professor of pediatrics and director of pediatric allergy and immunology at Johns Hopkins. Yet, "I'm afraid we had a major [negative] impact on pharma's interest in pursuing SLIT."

Table. Types of Allergy Immunotherapies

Characteristics	Subcutaneous (SCIT), AKA allergy shots	Sublingual (SLIT)		Oral (OIT)	
		Tablets (Oralair, Grastek, Ragwitek, Odactra)	Drops	General	Palforzia
Delivery method	injection of liquid allergen(s)	tablet containing allergen held under tongue	liquid drop(s) containing allergen(s) held under tongue	ingestion (food product swallowed into stomach)	ingestion (peanut powder swallowed into stomach)
Type of allergens treated	environmental	environmental	environmental and food	food	peanut
Number of allergens	single or multiple	single	single or multiple; can treat	single or multiple	single (peanut only)

treated			environmental and food simultaneously		
FDA-approved products	none	standardized tablets for grass pollen, dust mite and ragweed allergies	none	none	standardized capsules for peanut allergy (ages 4–17)
Source material	commercial extracts sourced from raw allergen materials; FDA-approved for SCIT and skin testing	allergen extract formulated into a tablet; FDA-approved for grass pollen, dust mite and ragweed SLIT	commercial extracts sourced from raw allergen materials; FDA-approved for SCIT and skin testing, used off-label for SLIT	food or food powders (grocery store or commercial)	commercial peanut powder formulation; FDA-approved for peanut OIT
Age at which treatment can be used	varies; commonly 5 years and up	FDA-approved indications: 18–65 years for dust mite, 5–65 years for ragweed and grass	varies; infancy and up	varies; early childhood and up	FDA-approved indication: ages 4–17
Treatment duration	3–6+ months buildup plus 3–5 years maintenance; varies	no/minimal buildup; seasonal only or up to 3–5 years maintenance; varies	Highly variable buildup (2 months to 3 years) plus 1–2+ years maintenance; varies	5–12 months buildup plus maintenance (indefinite); varies	5–12 months buildup plus maintenance (indefinite); varies
Dosing frequency	1–3 office visits per week during buildup; 1–2 office visits per month during maintenance	daily at home (1st dose in office); follow-ups in office yearly during maintenance	1–3 times daily at home (1st dose in office); updose frequency varies (home or office) during buildup; follow-ups in office yearly during maintenance	daily at home (1st day in office); updoses in office every 1–2 weeks during buildup; follow-ups in office every 3–12 months during maintenance	daily at home (1st day in office); updoses in office every 2 weeks during buildup; follow-ups in office every 3–12 months during maintenance
Safety	notable risk for systemic reactions (treated by medical staff in office)	minimal systemic reaction risk	minimal systemic reaction risk	notable risk for systemic reactions (often treated by family at home)	notable risk for systemic reactions (often treated by family at home)
Common side effects	redness, hives, swelling at injection site	mild-moderate mouth itch, throat itch, ear itch	mild-moderate mouth itch, throat itch, ear itch	mild-moderate oral itch, hives, swelling, stomach/abdominal pain, vomiting	mild-moderate oral itch, hives, swelling, stomach/abdominal pain, vomiting
Payment	commonly covered by insurance, coverage varies widely with high-deductible plans	may be covered through insurance or pharmaceutical company savings programs	patient pay	patient pay	may be covered through insurance or pharmaceutical company savings programs
Availability and other considerations	most widely available form of immunotherapy; offered by many allergists and ENT doctors; methods somewhat standardized but protocols vary by clinic	offered by many allergists, ENT doctors and primary care doctors; standardized and obtained by prescription; not easily customized	(environmental) offered by growing number of allergists and ENT physicians, customized	rare; offered by < 5% of allergists with specialized skill set; customized, requires 2-hour rest period after each daily dose, desensitization generally faster/higher than SLIT	offered by growing number of allergists; standardized and obtained by prescription; not easily customized, requires 2-hour rest period after each daily dose
			(food) rarer than OIT, offered by very		

small subset of
allergists with
specialized skill set;
customized, can
serve as bridge to
OIT, success less
visible than OIT

NOTE: Treatment is not one-size-fits-all, according to the experts interviewed for this series. For each patient, the best treatment is unique to their circumstances and goals. Allergen avoidance may be the best option for some. Treatment protocols, cost, dosing, and other factors differ by clinic and provider.

Sources: interviews; AAAAI; American College of Allergy, Asthma and Immunology; drug websites.

Without corporate funding, it's nearly impossible to conduct the large, multisite trials required for FDA approval of a treatment. And without approved products, many allergists are reluctant to offer the therapy, Wood said. It "makes your life a lot more complicated to be dabbling in things that are not approved," he noted.

But at least one company is giving it a go. Applying the SLIT principle of delivering food allergens to tolerance-promoting immune cells in the mouth, New York-based Intromune Therapeutics recently started enrolling peanut-allergic adults for a [phase 1 trial of its experimental toothpaste](#).



Dr Jaclyn Bjelac

Interest in food-allergy SLIT seems to be growing. "I definitely think that it could be an option for the future," said Jaclyn Bjelac, MD, associate director of the Food Allergy Center of Excellence at the Cleveland Clinic, in Cleveland, Ohio. "Up until a few months ago, it really wasn't on our radar."

On conversations with Kim, philanthropists and drug developers said they found the recent data on SLIT promising, yet pointed out that food SLIT protocols and products are already in the public domain — they are described in published research using allergen extracts that are on the market. They "can't see a commercial path forward," Kim told *Medscape Medical News*. "And that's kind of where many of my conversations end."

Although there are no licensed SLIT products for food allergies, between 2014 and 2017, the FDA approved four sublingual immunotherapy tablets to treat environmental allergies — Stallergenes-Greer's Oralair and ALK's Grastek for grass pollens, ALK's Odactra for dust mites, and ALK's Ragwitek for short ragweed.

SLIT tablets work as well as allergy shots (subcutaneous immunotherapy) for controlling environmental allergy symptoms, they have a better safety profile, according to [AAAAI guidelines](#), and they can be self-administered at home, which has made them a popular option globally. "Our European colleagues have used sublingual immunotherapy much more frequently than, for example, in the US," said Kari Nadeau, MD, PhD, director of the Sean N. Parker Center for Allergy and Asthma Research at Stanford University, in Stanford, California.

Use of SLIT is also increasing in the United States, especially as FDA-approved products become available. In a 2019 survey, the percentage of US allergists who said they were offering sublingual treatment for environmental allergies [increased from 5.9% in 2007 to 73.5% in 2019](#). However, only 11.2% reported extensive SLIT use; the remainder reported some (50.5%) or little (38.3%) use.

As noted above, considerably fewer US allergists use SLIT to treat food allergies. Similarly, a [2021 survey of allergists in Canada](#) found that only 7% offered food sublingual immunotherapy; more than half reported offering OIT.



Jeff Kessler, MBA

One practice, Allergy Associates of La Crosse, in Wisconsin, has offered SLIT drops for food and environmental allergies for decades. Since the clinic opened in 1970, more than 200,000 people have been treated with its [protocol](#). Every patient receives customized sublingual drops — "exactly what they're allergic to, exactly how allergic they are, and then we build from there," said Jeff Kessler, MBA, FACHE, practice executive at Allergy Associates of La Crosse. "Quite frankly, it's the way immunotherapy should be done."

Jaclyn Bjelac has disclosed no relevant financial relationships.

Corinne Keet has disclosed no financial relationships with any companies. She is an associate editor at the Journal of Allergy and Clinical Immunology, is on an FDA scientific advisory board, is on the board of the American Board of Allergy and Immunology, and receives royalties from Up-to-Date.

Jeff Kessler is president and director of Allergychoices, a company that equips other doctors to provide sublingual immunotherapy.

Edwin Kim reports consultancy with Aimmune Therapeutics, Allako, AllerGenis, Belhaven Pharma, DBV Technologies, Duke Clinical Research Institute, and Nutricia; advisory board membership with ALK, DBV Technologies, Kenota Health, and Ukko; grant support from the NIH's National Institute of Allergy and Infectious Diseases, National Center for Complementary and Integrative Health and Immune Tolerance Network; Food Allergy Research and Education, and the Wallace Research Foundation.

Douglas Mack is a principal investigator for DBV and ALK and has consulted or spoken for ALK, Aimmune Therapeutics, Bausch Health, Kaleo, Medexus, and Pfizer.

Kari Nadeau reports receiving grants from the National Institute of Allergy and Infectious Diseases, the National Heart, Lung, and Blood Institute (NHLBI), and the National Institute of Environmental Health Sciences; Food Allergy Research and Education), director of the World Allergy Organization Center of Excellence at Stanford; advisor at Cour Pharma; co-founder of Before Brands, Alladapt, Latitude, and IgGenix; National Scientific Committee member at Immune Tolerance Network and National Institutes of Health (NIH) clinical research centers; DSMB member for NHLBI, US patents for basophil testing, multifoed immunotherapy and prevention, monoclonal antibody from plasmoblasts, and device for diagnostics.

Robert Wood receives research funding from NIH, Astellas, Aimmune, DBV, HAL-Allergy, Sanofi, Genentech, Regeneron, and Food Allergy Research and Education.

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