



Peanut Immunotherapy: Practical Applications

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Opinion statement

Purpose of review The recent approval of the first commercial peanut oral immunotherapy formulation ushered a new era of clinical food allergy treatment. With different options for peanut immunotherapy available, it is important review the evidence of efficacy, risks, and unique considerations for the individual modalities.

Recent findings Oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT) for peanut allergy have risen as possible treatments for peanut allergy. Numerous studies indicate that OIT effectively desensitizes by increasing the amount of peanut protein than can be consumed without symptoms. While this desensitization is to increased amounts of peanut protein when compared to SLIT or EPIT, OIT appears to have greater risk for anaphylaxis and other adverse events. EPIT has the unique benefit of a single-dose patch without the need for in-clinic visits for dose escalation, and it bypasses the oral route which may be advantageous in certain patients. The impact of peanut immunotherapy on health-related quality of life is not well studied and current data is conflicting, but suggests that improvement in certain domains of QOL, especially for caregivers of children with peanut allergy, may be an important target for immunotherapy.

Summary This review focuses on the data for efficacy, safety, and tolerability of OIT, SLIT, and EPIT with the aim of presenting information that will assist allergy practitioners in choosing an immunotherapy modality when indicated.

Introduction

Food allergy has become an increasingly common medical problem throughout the developed world and now poses a significant public health problem. There was an 18% increase in childhood food allergies from 1997 to 2007, with 8% of children and 10% of adults now suffering from one or more food allergies [1–3]. The diagnosis of food allergy creates necessary restrictions on eating and consequently has significant impact on social and cultural activities. Families with food allergy report that they avoid social gatherings because of fear of accidental ingestions and the effort required to avoid food allergens and provide alternatives [4]. These limitations and restrictions have also been shown to contribute to poor quality of life (QOL) and the development of anxious and depressed mood for both individual patients and their caregivers [5–7]. In addition to effects on individual patients and families, food allergy is a burden on the medical system and has a large economic impact. Most anaphylaxis treated in emergency departments is due to food allergy, with an estimated 200,000 emergency department visits and 9500 hospital admissions yearly for food-related reactions [2, 8]. Concordant with increasing incidence, direct medical costs for food allergy increased from \$225 million in 2007 to \$4.3 billion in 2011 [9]. What is more, each year about \$1.7 billion are spent arranging special diets and about \$857 million are spent for avoidance of unintentional exposures [10].

Currently, about 1–2% of children and adults in the USA are affected by peanut allergy [11]. Peanut remains one of the most common food allergens and is implicated in about half of cases of fatal food-induced anaphylaxis [12, 13]. Until very recently, the only widely available strategies for peanut allergy management were avoidance and epinephrine autoinjector carriage, which have done little to address the medical, psychosocial, and economic impact of food allergies. Peanut-free lunch tables, daycares, and schools were created in an effort to improve mealtime safety. However, these strategies may have inadvertently contributed some of the

psychosocial effects discussed above [4]. Despite these management strategies, about 10% of children with peanut allergy have an accidental ingestion each year [14]. Although epinephrine is a potentially life-saving medication, only around 44% of people prescribed with epinephrine autoinjectors report carrying it all of the time [15]. The challenges of avoidance and epinephrine carriage, as well as increasing psychosocial comorbidities of living with a diagnosis of peanut allergy, have led to the need for more proactive treatment-based strategies.

To meet this need, there has been extensive research on peanut immunotherapy. Immunotherapy is a process by which small amounts of allergen are administered at increasing doses to induce a state of clinical desensitization, such that a patient would not have an allergic reaction upon accidental exposure to peanut [16]. The state of desensitization is presumed to require continued exposure to the allergen. To investigate this, researchers have also sought to determine if a state of clinical nonreactivity could persist after immunotherapy is discontinued, termed sustained unresponsiveness (SU), but a precise duration of nonreactivity has yet to be defined [17]. Early attempts at subcutaneous immunotherapy (SCIT) for peanut allergy were deemed unsafe [18, 19], and research shifted to other modalities. Each of these modalities have been successful in desensitization to varying degrees and each has unique therapeutic considerations and limitations. As currently studied, the goal of food allergen immunotherapy is to provide protection in the case of accidental exposure to peanut and not necessarily to allow ad libitum consumption. Given the recent Food and Drug Administration (FDA) approval of the first commercial peanut oral immunotherapy formulation, the authors of this article present a review of the recent research on different peanut immunotherapy modalities with the specific aim of presenting practical considerations for adoption in the clinical setting.

Immunotherapy

Oral immunotherapy

Oral immunotherapy (OIT) for peanut allergy has been studied since the early 2000s and numerous studies have demonstrated success in desensitization; its

ability to induce SU is less well understood [20]. There is significant variability among the published studies, from the patient selection to the amount of peanut protein used as maintenance therapy and the duration of treatment [20]. However, the majority of the study protocols involve an initial dose escalation day (IDE), followed by a period of increasing build-up doses, then a maintenance phase [21, 22]. Double-blind, placebo-controlled food challenges (DBPCFC) are typically performed at baseline and then as a measure of clinical efficacy after treatment and sometimes again after a specified period of time after treatment has been stopped to assess SU [20, 21]. Almost all studies exclude patients with severe asthma, eosinophilic gastrointestinal disease, or a history of severe anaphylaxis. Currently, a peanut flour-derived product for OIT is the only formulation of food immunotherapy that has been approved by the US FDA. Prior to its approval in January 2020, there were frequent debates about the safety of OIT given the high rate of adverse reactions during treatment relative to patients receiving placebo or only practicing avoidance [23••]. Novel approaches for OIT continue to be developed, hoping to address concerns about the high rate of adverse reactions.

Systematic reviews and meta-analyses have supported that OIT is successful in desensitization, but with high rates of adverse reactions (Table 1) [20, 23]. In the PALISADE study, the largest study of OIT to date [29••], participants aged 4–55 years were included if they reacted during screening DBPCFC to 100 mg or less of peanut protein. Investigators chose to include patients reacting to the relatively low amount of peanut protein as a way to identify those at higher risk in the setting of accidental ingestions. Participants were randomized to receive 300 mg peanut protein or placebo for approximately 12 months. The majority of participants were ages 4–17 years (496 of 551). Of participants aged 4–17 years, 67.2% of those on treatment compared with 4% of those on placebo ($p < 0.001$) were able to ingest at least a cumulative 1043 mg without dose-limiting symptoms on exit challenge. In the group of participants 18–55 years, 41.5% on treatment and 14.3% on placebo were able to tolerate cumulative 1043 mg at exit challenge, but this did not reach statistical significance. Over 90% of participants in both the treatment and placebo groups experienced adverse events during the intervention period, but these declined over time. Gastrointestinal (GI) and respiratory adverse events were most common in both groups. Excluding DBPCFCs, the highest severity of symptoms was mild–moderate in 94.4% of participants in both groups. Severe adverse events were reported in 4.3% in the treatment group compared to 0.8% on placebo. Fourteen percent of participants in the active group required epinephrine throughout the course of the study, compared to 6.5% on placebo. Overall, 21.5% in the treatment group withdrew from the study, 11.6% due to adverse events, compared to 8% withdrawal rate among those receiving placebo, 2% due to adverse events. Of note, almost half of withdrawals due to adverse events were due to GI symptoms, and one participant (1/551, 0.18%) was diagnosed with eosinophilic esophagitis (EOE). Overall, this large study demonstrated that desensitization was successful in pediatric patients at higher risk for reactions to accidental ingestions, albeit with a high rate of mild–moderate adverse events.

Given high rates of adverse events observed across OIT studies, Blumchen et al. sought to determine if a slower build-up process and lower maintenance dose might decrease the rate of adverse events. Participants aged 3–17 years were randomized to receive placebo or build-up to a maintenance dose of

Table 1. Summary of OIT, EPIT, and SLIT studies

Study, year	# of participants	Age range (enrolled median)	Placebo group	Maintenance dose (mg peanut protein)	Treatment duration
OIT					
Varshney 2011 [24]	19 OIT 9 placebo	1–16 years (69 months)	Yes	4000 mg	12 months
Anagnostou 2014 [25] STOP II	49 OIT 50 control	7–15 years (12.3 years)	No	800 mg	6 months
Vickery 2014 [26]	39 OIT	1–16 years (4.8 years)	No	4000 mg	3–5 years
Bird 2018 [27]	29 OIT 26 placebo	4–26 years (7 years)	Yes	300 mg	22–36 weeks
Vickery 2017 [28•] DEVIL	37 OIT	9–36 months (28.5 months)	No	300 mg or 3000 mg	22–46 months
Vickery 2018 [29••] PALISADE	372 OIT 124 placebo	4–17 years 18–55 years ^b	Yes	300 mg	12 months
Blumchen 2019 [30•]	31 OIT 31 placebo	3–17 years (6.6 years)	Yes	125 mg or 250 mg	16 months
Chinthrajah 2019 [31••] POISED	60 Peanut-0 (OIT/avoidance) 35 Peanut-300 (OIT/300 mg) 25 placebo	7–55 years (11 years)	Yes	4000 mg	24 months
OIT + probiotic					
Tang 2015 [32]	31 OIT/probiotic (PPOIT) 31 placebo OIT/placebo probiotic	1–10 years (mean 6.1 years)	Yes	OIT: 2000 mg <i>L rhamnosus</i> CGMCC 1.3724: 2×10^{10} cfu	18 months
Hsiao 2017 [33•]	24 PPOIT 24 placebo	1–10 years (mean 6.1 years)	No	Ad libitum dietary peanut or avoidance	4 years
OIT + omalizumab					
Schneider 2013 [34]	13 omalizumab/OIT	7–25 years (10 years)	No	Omalizumab: per weight/IgE table OIT: 2000 mg	32 weeks
MacGinnitie 2017 [35•] EPIT	29 omalizumab/OIT 8 placebo/OIT	6–19 years (10 years)	Yes	Omalizumab: per weight/IgE table OIT: 2000 mg	38 weeks

Table 1. (Continued)

Study, year	# of participants	Age range (enrolled median)	Placebo group	Maintenance dose (mg peanut protein)	Treatment duration
Sampson 2017 [36] VIPES	165 EPIT 56 placebo	6–55 years (11 years)	Yes	50 µg or 100 µg or 250 µg	12 months
Jones 2017 [37] CoFAR6	49 EPIT 25 placebo	4–25 years (8.2 years)	Yes	100 µg or 250 µg	12 months
Fleischer 2019 [38••] PEPITES SLIT	238 EPIT 118 placebo	4–11 years (7 years)	Yes	250 µg	12 months
Kim 2011 [39]	11 SLIT 7 placebo	1–11 years (5.2 years)	Yes	2 mg	12 months
Fleischer 2013 [40] CoFAR4	20 SLIT 20 placebo	12–40 years (15 years)	Yes	1.4 mg	44 weeks
Burks 2015 [41] CoFAR4	37 SLIT	12–40 years (15 years)	No	1.4 mg or 3.7 mg	164 weeks
Kim 2019 [42] OIT vs SLIT	48 SLIT	1–11 years (6.5 years)	No	2 mg	3–5 years
Narisety 2015 [43•]	11 OIT/placebo SLIT 10 SLIT/placebo OIT	7–13 years (11.1 years)	Yes	OIT 2000 mg SLIT 3.7 mg	Blinded: 16 months Open combined: 6 months

Study, year	Efficacy results	% discontinued	Treatment emergent AEs (participants)	Epinephrine administration (participants)	Comments
OIT					
Varshney 2011 [24]	Desensitization (5000 mg) OIT: median 5000 mg Placebo: median 280 mg	OIT: 16% (3/19) Placebo: none	1.2% of OIT doses	OIT: 2/19 Placebo: none	1st double-blind peanut OIT study
Anagnostou 2014 [25] STOP II	Desensitization (1400 mg) OIT: 62% Control: 0 %	OIT: 12.2% (6/49) Control: 2% (1/47)	81% mouth itch 57% abd pain 33% nausea/vomiting	OIT: 1/49 Placebo: none	Improved QOL with OIT Control crossover 54% desensitized
Vickery 2014 [26]	4 weeks SU (5000 mg)	38% (15/39)	Not reported	Not reported	11/12 SU ingesting dietary peanut post-OIT

Table 1. (Continued)

Study, year	Efficacy results	% discontinued	Treatment emergent AEs (participants)	Epinephrine administration (participants)	Comments
Bird 2018 [27]	OIT: 31% Desensitization (443 mg) OIT: 79% Placebo: 19%	OIT: 21% (6/29) Placebo: none	OIT: 93% Placebo: 46% OIT: 66% GI AEs (1 EoE)	OIT: 1/29 Placebo: none	Aimmune phase 2 trial
Vickery 2017 [28•] DEVIL	4 weeks SU (5000 mg) 300 mg: 85% 3000 mg: 71%	300 mg: 5% (1/20) 3000 mg: 24% (4/17)	300 mg: 90% 3000 mg: 100% 1 EoE	300 mg: none 3000 mg: 1/17	1st study of OIT in preschool-aged children 1st dose finding OIT study
Vickery 2018 [29••] PALISADE	Desensitization (1043 mg) OIT: 67.2% Placebo: 4%	OIT: 21.5% (80/372) Placebo: 8.1% (10/124)	OIT: 98.7% Placebo: 95.2% OIT: 85.8% GI AEs (1 EoE)	OIT: 52/372 Placebo: 8/124	Aimmune phase 3 trial Largest prospective OIT study
Blumchen 2019 [30•]	Desensitization (400 mg) OIT: 74.2% Placebo: 16.1% Desensitization (4500 mg) OIT: 41.9% Placebo: 3.2%	OIT: 6.5% (2/31) Placebo: 19.4% (6/31)	OIT: 90% Placebo: 77% OIT: 66.7% GI AEs (0 EoE)	None	1st report of improved HRQOL with OIT Novel extended 14 months build-up
Chinthrajah 2019 [31••] POISED	3 months SU (4000 mg) Peanut-0: 35% Peanut-300: 54% Placebo: 4% 12 months SU (4000 mg) Peanut-0: 13% Peanut-300: 37% Placebo: 4%	Peanut-0: 15% (9/60) Peanut-300: 14% (5/35) Placebo: 8% (2/25)	Year 1: Peanut-0: 95% Peanut-300: 91% Placebo: 64% Year 2: Peanut-0: 73% Peanut-300: 65% Placebo: 26%	OIT: 18/95 Placebo: none	Longest study of SU (12 months) 1st study of decreasing maintenance dose
OIT + probiotic Tang 2015 [32]	2–6 weeks SU (4000 mg) PPOIT: 82.1% Placebo: 3.6%	PPOIT: 9.7% (3/31) Placebo: 9.7% (3/31)	Severe AEs: PPOIT: 45.2% Placebo: 32.3%	PPOIT: 3/31 Placebo: 2/31	No peanut OIT/placebo probiotic control

Table 1. (Continued)

Study, year	Efficacy results	% discontinued	Treatment emergent AEs (participants)	Epinephrine administration (participants)	Comments
Hsiao 2017 [33•]	Desensitization (4000 mg)				
	PP0IT: 89.7%				
	Placebo: 7.1%				
OIT + omalizumab	8 weeks SU (4000 mg)				
	PP0IT: 58%	PP0IT: 8.3% (2/24)	PP0IT: 17%	None	Real-world long-term follow-up of Tang 2015 [32]
	Placebo: 7%		Placebo: 25%		
Schneider 2013 [34]	IDE (250 mg)				
	Omalizumab/OIT: 100%	8% (1/13)	OIT: 76.9%	OIT: 2/13	12 weeks omalizumab, 8 weeks combined, 12 weeks OIT
	Desensitization (4000 mg)				
MacGinnitie 2017 [35•]	12 weeks post omalizumab				
	Omalizumab/OIT: 92%				
	Tolerate 2000 mg OIT				
	6 weeks post omalizumab				
	Omalizumab/OIT: 74%	Omalizumab/OIT: 6.9% (2/29)	Omalizumab/OIT: 25/29	Omalizumab/OIT: 3/29	Omalizumab/OIT: IDE (250 mg): 23/27
	Placebo/OIT: 12.5%	Placebo/OIT: 12.5% (1/8)	Placebo/OIT: 8/8	Placebo/OIT: 1/8	
	Desensitization (4000 mg)				
	12 weeks post omalizumab				
	Omalizumab/OIT: 75.9%				
EPIIT	Placebo/OIT: 12.5%				
	Responder rate: 50 µg: 45.3%	50 µg: 3.8% (2/53)	50 µg: 100%	None	Responder rate: eliciting dose ≥ 1000 mg and/or ≥ 10-fold increase
	100 µg: 41.1%	100 µg: 12.5% (7/56)	100 µg: 98.2%		
Sampson 2017 [36] VIPES	250 µg: 50%	250 µg: 5.4% (3/56)	250 µg: 100%		
	Placebo: 25%	Placebo: 3.6% (2/56)	Placebo: 92.9%		

Table 1. (Continued)

Study, year	Efficacy results	% discontinued	Treatment emergent AEs (participants)	Epinephrine administration (participants)	Comments
Jones 2017 [37] CoFAR6	Responder rate: 100 µg: 46% 250 µg: 48% Placebo: 12%	100 µg: 12.5% (3/24) 250 µg: none Placebo: 8% (2/25)	100 µg: 100% 250 µg: 100% Placebo: 88%	None	Responder rate: successfully consumed dose 5044 mg and/or ≥ 10-fold increase
Fleischer 2019 [38••] PEPITES	Responder rate: EPIT: 35.3% Placebo: 13.6%	EPIT: 10.5% (25/238) Placebo: 9.3% (11/118)	EPIT: 59.7% Placebo: 34.7%	EPIT: 7/238 Placebo: 1/118	Difference in responder rate did not meet lower bound of 95% CI
SLIT					
Kim 2011 [39]	Desensitization (2500 mg) SLIT: median 1710 mg Placebo: median 85 mg	None	SLIT: 11.5% of doses Placebo: 8.6% of doses	None	First double-blind peanut SLIT study
Fleischer 2013 [40] CoFAR4	Responder rate: SLIT: 70% Placebo: 15%	SLIT: 10% (2/20) Placebo: 5% (1/20)	SLIT: 40% of doses Placebo: 0.6% of doses	SLIT: 1/20 Placebo: none	Responder rate: successfully consumed dose 5000 mg and/or ≥ 10-fold increase
Burks 2015 [41] CoFAR4	Year 2 responder rate (2500 mg) 1.4 mg: 55% 3.7 mg: 23.5% Year 3 responder rate (5000 mg) 1.4 mg: 10% 3.7 mg: 11.8% Desensitization (5000 mg) SLIT: median 1750 mg	1.4 mg: 55% (11/20) 3.7 mg: 70.6% (12/17)	1.4 mg: 18.1% of doses 3.7 mg: 18.3% of doses	None	Follow-up of Fleischer study [40]. Year 3 responders also showed 8 weeks SU
Kim 2019 [42]		SLIT: 23% (11/48)	SLIT: 4.8% of doses	None	Extended maintenance of Kim 2011 study [39] 2–4 weeks SU: 21%
OIT vs SLIT					
Narisety 2015 [43•]	16 months responder rate (10,000 mg) OIT/placebo SLIT: 64% SLIT/placebo OIT: 70%	OIT/placebo SLIT: 36% (4/11) SLIT/placebo OIT: 10% (1/10) Open SLIT/OIT: 22% (2/9)	OIT/placebo SLIT: 100% SLIT/placebo OIT: 90%	OIT/placebo SLIT: 4/11 SLIT/placebo OIT: none Open SLIT/OIT: 1/9 Open OIT/SLIT: 1/7	Responder rate: ≥ 10-fold increase from baseline 14.1-fold OIT threshold increase vs 22-fold SLIT threshold increase

125 mg or 250 mg [30•]. The build-up period took place over a median of 13 months and maintenance continued for a total of 16 months. This contrasts with the PALISADE study in which build-up occurred for about 6 months until maintenance was reached, with a total study duration of 12 months [29••]. 74.2% of participants in the active group met the primary endpoint of being able to ingest at least 400 mg cumulative peanut protein at exit challenge compared with only 16.1% of those on placebo ($p < 0.001$). Interestingly, 41.9% in the treatment group were able to ingest 4500 mg of peanut protein at exit challenge, despite a maximum peanut OIT dose of 250 mg. The rate and severity of adverse events was similar between active and placebo groups (90 and 77% of participants respectively, $p = 0.3$), the majority being subjective symptoms and mild–moderate severity at worst. However, significant differences emerged in the number of participants experiencing abdominal pain (66.7 vs 19.4%, $p < 0.001$) and oral allergy syndrome (60 vs 25.8%, $p = 0.007$) with more in the active group for both, similar to prior OIT studies. Epinephrine was not required for any treatment-related adverse events in either group, nor did any patient develop EOE. Another notable aspect of this study was that investigators used validated food allergy related quality of life questionnaires (FAQLQ) [44–46] at baseline and after exit challenge and was the first placebo-controlled study to measure this. There was a significant improvement in health-related quality of life (HRQL) for children who received peanut OIT compared to those in placebo 11 weeks after exit challenge in the domains of risk of accidental exposure and emotional impact ($p = 0.02$ for both). The investigators also assessed burden of treatment through questionnaires, and the majority of children and their mothers reported that they would do OIT again. Compared to others, this study suggests that lower maintenance dose OIT protocols may still result in clinically important desensitization but with improved safety profile and positive impact on HRQL.

The majority of OIT studies have evaluated the ability to induce desensitization, but less have evaluated for SU. Following success of an earlier study in patients ages 1–16 years [26], Vickery evaluated participants ages 9–36 months for SU after completing OIT [28•]. Participants were randomized to either 300 or 3000 mg peanut protein. After a median of 29 months of treatment, participants underwent DBPCFC to 5000 mg to assess for desensitization. Then 4 weeks after treatment cessation, they underwent an identical DBPCFC to assess for SU. Of those in the 300 mg group, 85% were desensitized and achieved SU. Of those in the 3000 mg group, 76% were desensitized and 71% achieved SU. There was no significant difference in the rates of SU between high- and low-dose groups (difference in proportions 0.14, $p = 0.43$). While the majority of participants experienced adverse events, 85% of these were mild and 15% moderate. Only 1 participant required epinephrine for a dose given at home, not during a dose escalation. Two participants withdrew from the study due to GI symptoms, one of which was diagnosed with EOE. Overall, this study demonstrated safety and desensitization in a preschool age group, and efficacy in inducing SU, the strongest SU to date.

The recently completed POISED study sought to evaluate for SU up to 1 year after completion of OIT, while simultaneously investigating the effects of lower dose maintenance [31••]. Participants ages 7–55 years were randomized into 3 possible groups: 4000 mg peanut protein through week 104 followed by avoidance (Peanut-0); 4000 mg through week 104 then continue 300 mg daily

(Peanut-300); or placebo throughout the study. Starting at week 104, DBPCFC were every 3 months up to week 156. Eighty-five percent in Peanut-0 and 83% in Peanut-300 versus 4% placebo were successfully desensitized to 4000 mg peanut protein at week 104, but the desensitization waned quickly. As early as week 117, the proportion of participants able to ingest 4000 mg dropped to 35 and 54%, respectively, and remained at 4% (1 participant) for placebo. Response rates dropped further in subsequent challenges. There was a significant difference between Peanut-0 and Peanut-300 groups starting from the week 130 challenge to the final week 156 challenge, suggesting some benefit of continuing a lower maintenance dose versus complete peanut avoidance. However, the results suggested that even with continued lower dose OIT, desensitization to the amount previously tolerated on increased maintenance dose was rapidly lost.

Using a different approach, investigators in a double-blind, placebo-controlled study combined the probiotic *Lactobacillus rhamnosus* with peanut OIT (PPOIT) and assessed for SU 2–5 weeks after discontinuation [32]. This probiotic was chosen specifically given evidence that it may promote tolerogenic immune responses in the GI tract. Participants received probiotic and peanut OIT or placebo probiotic and placebo OIT. They found a significant difference in the number of patients who were desensitized to 4000 mg of peanut protein after the maintenance period (89.7 vs 7.1%, $p < 0.001$) and a significant difference in the ability to ingest 4000 mg of peanut protein after at least 2 weeks of discontinuation (82.1 vs 3.6%, $p < 0.001$). A follow-up study 4 years later determined that those in the PPOIT group were more likely to have continued consuming dietary peanut [33•]. However, these studies were greatly limited by lack of a control group that received OIT without probiotic, making it difficult to interpret the independent effect of probiotic on desensitization and SU.

Outside of clinical research, OIT has been available through community allergists utilizing commercially available peanut powder and peanut-containing foods, and some have published their experiences [47, 48]. A large retrospective chart review of 352 patients undergoing OIT across 5 community practices with widely varying protocols and target maintenance doses ranging from 415 to 8000 mg reported 10% of patients required epinephrine during dose escalation and 1% required epinephrine during maintenance, similar to what has been seen in clinical trials [47]. Peanut OIT for preschool-aged children performed in community and academic centers in Canada as part of a country-wide quality improvement project also appeared to safely induce desensitization [48•]. There were 270 patients, ages 15–33 months, of which 90% reached maintenance dosing. Reasons for withdrawal included symptoms suggestive of EOE (one of which was confirmed), repeated allergic reactions, child's refusal to eat the daily dose, and parental anxiety. One hundred eighty-three of 270 patients (67.8%) experienced at least 1 allergic reaction, about 60% of which were mild-moderate severity. Only 1 patient (0.4%) experienced a severe reaction related to OIT characterized by hypotension, sleepiness, and GI symptoms. About 4% of patients required epinephrine, 6 doses of which were given at clinic up-dosing visits and 6 were administered at home. Only 1 patient required epinephrine twice on separate days, for a rate of 2.93 epinephrine administrations per 10,000 doses (0.029%). This “real-world” analysis indicates that while adverse reactions occur commonly, epinephrine is used infrequently and adverse reactions rarely prevent reaching maintenance dose.

A 2019 systematic review and meta-analysis found that adverse events, anaphylaxis, and epinephrine use were significantly increased during peanut OIT versus no OIT and that QOL was not improved in those undergoing OIT as might have been expected [23••]. To address the high rate of adverse reactions, other strategies for OIT have been studied. In a study published in 2017, omalizumab, an anti-IgE antibody, was administered 6 weeks before starting OIT and continued until participants reached maintenance [35•]. The combination resulted in rapid desensitization: participants who received omalizumab were able to achieve much higher doses of peanut protein on the IDE (median 250 mg versus 22.5 mg, $p < 0.01$) and at subsequent challenges. Those who received omalizumab were more likely than placebo to tolerate 4,000 mg during open OFC 12 weeks after discontinuation of omalizumab (75.9% versus 12.5%), but of 16 participants who passed this challenge and then continued 4000 mg dose, 6 later reacted to daily dosing and converted back to 2000 mg. The study suggests that omalizumab-facilitated OIT might confer protection to larger amounts of peanut more quickly, but the effect may not be sustained when omalizumab is discontinued. Omalizumab continues to be studied both as an adjunct to OIT as well as monotherapy. Additional biologics such as the anti-IL-4/IL-13 monoclonal antibody dupilumab are similarly being studied for a potential role in food allergy.

Investigators have considered a novel delivery system for OIT that bypasses oral/gastric routes with a coated capsule for deposition in the lower GI tract to reduce the common GI/oropharyngeal effects seen in other studies [49]. The study of adolescents showed that while this route was effective for desensitization, participants still complained of mild GI and oropharyngeal symptoms compared to placebo. The overall number of adverse events was not different between the 2 groups, but there were more adverse events per participant, and with more severe symptoms in the active group compared to placebo.

In summary of the above observations, peanut OIT appears to be effective at inducing desensitization, especially at younger ages, and there is limited data that supports its ability to induce SU after 4–12 weeks of treatment discontinuation. While clinically relevant desensitization to peanut may provide benefit, risks of adverse events and anaphylaxis are significantly increased on OIT compared to standard management. While QOL has been expected to improve with successful desensitization, this remains to be shown. Novel strategies such as OIT with omalizumab, lower GI delivery of OIT, and OIT with probiotics might mitigate the common adverse effects and promote SU, but additional research is needed. In addition to known adverse effects of OIT, other challenges to implementation have been identified: these include refusal of allergenic foods due to oral aversion to peanut flavor and logistical challenges with the dosing schedule. Restrictions surrounding home dosing, including required observation time and restriction of exercise around dosing, and dose adjustments in the setting of menses or illness may be too restrictive for families [47, 48]. These challenges have led to research into different immunotherapy modalities.

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) for peanut allergy is a modality that entails application of a patch containing peanut protein to the skin. When the

wearer perspires, the protein solubilizes and disseminates into the skin. When compared to OIT, EPIT has the benefit of no build-up period, no restrictions on exercise, and no dose adjustments during illness. Additionally, bypassing the oral route means patients with peanut oral aversion could also consider this therapy. The largest trial to date, called PEPITES, built upon success of two earlier phase 2 studies which demonstrated safety and the ability to induce desensitization, with best responses in children under 11 years [36, 37]. In this phase 3 randomized, double-blind, and placebo-controlled trial, 356 participants aged 4–11 years were randomized to receive a patch with 250 µg peanut protein (Viaskin® peanut) or placebo daily for 12 months [38••]. After 12 months, participants underwent DBPCFC; for participants who reacted to 10 mg peanut protein or less at entry challenge, an eliciting dose of 300 mg or more was considered a responder. For those that reacted to 10–300 mg at entry challenge, an eliciting dose of 1000 mg or more was considered a responder. Overall, 35.3% of those in the active group were considered responders, compared to 13.6% using placebo patch ($p < 0.001$). Due to the higher than expected response rate on placebo, the difference in response rates between the 2 groups was lower than the minimum required to meet the primary endpoint; the clinical implications of this are not understood. 59.7% on peanut patch and 34.7% on the placebo had at least 1 adverse event related to the patch, with the majority of these being application site reactions that decreased after the first month. This was the first study of EPIT in which participants experienced anaphylaxis. Twenty-six episodes of anaphylaxis occurred, as defined by Sampson criteria [53], 10 of which were attributed to the patch in the active group and 1 in the placebo group, for an exposure adjusted rate of 0.04% in the active group. Epinephrine was required for 0.12% of doses during the study, with only 0.03% of administrations considered related to the patch in the active group. Ultimately, four episodes of anaphylaxis in four participants in the active group led to study discontinuation. The overall withdrawal rate of 10.5% in the peanut patch group was similar to 9.3% in the placebo group. None of these withdrawals were due to GI symptoms. Although the study did not meet its primary endpoint, it is notable that the very small dose of 250 µg induced desensitization to at least 300 mg peanut protein in about one third of active treatment participants with infrequent moderate to severe adverse events.

Sublingual immunotherapy

Sublingual immunotherapy (SLIT) for peanut allergy has also shown promise. Different from OIT and EPIT, SLIT utilizes glycerinated peanut extract which is administered sublingually where it is absorbed in the mucosa, bypassing first-pass metabolism. Patients are instructed to hold the solution in the sublingual space for 2 min prior to swallowing. Similar to OIT, there are escalation, up-dosing, and maintenance phases. The first double-blind, placebo-controlled study of SLIT for peanut allergy found that participants randomized to active treatment with 2 mg peanut protein for 12 months were able to ingest 20 times more peanut protein than those randomized to placebo and with favorable safety profile [39]. This first study provided the basis for additional investigation into SLIT. The first multicenter study also yielded promising results. Forty subjects ages 12–40 years were randomized to receive active SLIT at a target

maintenance dose of 1386 µg, or placebo for 44 weeks [40]. At 44 weeks, all subjects underwent DBPCFC, in which they were considered responders if they tolerated a 10-fold increased amount of peanut protein compared to entry challenge or if they tolerated 2500 mg peanut protein. Seventy percent of those on peanut SLIT compared to 15% on placebo were responders ($p < 0.001$). Participants on peanut SLIT continued maintenance dosing until week 68, then underwent a second DBPCFC. None of the non-responders converted to responders, 2 tolerated less at this challenge compared to week 44, and 13 tolerated the same or an increased amount of peanut protein. The median tolerated dose was significantly increased to 996 mg compared to baseline and week 44 OFCs ($p = 0.009$ and $p = 0.05$ respectfully), indicating that while there was variable response, longer duration of treatment could result in desensitization to increased amounts of protein. As far as safety, 59.9% of doses of peanut SLIT were symptom-free, and when isolated oropharyngeal symptoms were excluded, 94.7% of doses were symptom-free. Epinephrine was administered only once, in the home of a participant in the peanut SLIT group during build-up.

Kim evaluated SU in participants ages 1–11 years after 3–5 years of treatment with peanut SLIT [42]. Among 48 initial participants, 37 completed the 3–5 years of 2 mg daily maintenance SLIT. Overall, the median cumulative amount of peanut protein tolerated after treatment was 1750 mg and about 67% successfully tolerated at least 750 mg at exit DBPCFC. Twelve participants (25%) tolerated 5000 mg and were further evaluated for SU with 10 of these participants demonstrating SU at 4 weeks. There were relatively few adverse events in this study with only 4.8% of doses having associated symptoms, most of which were oropharyngeal pruritus. Epinephrine was not required for any dosing reactions and there were no reports of EOE. Additional larger studies are needed to identify barriers to ongoing treatment and to evaluate for long-term efficacy in larger numbers of patients.

Direct comparison between modalities

There is only one prospective study that directly compared peanut OIT to SLIT, and there are no such studies of EPIT comparing to other modalities [43•]. Nariesty et al. randomized 21 participants aged 7–13 years to receive active SLIT/placebo OIT or active OIT/placebo SLIT with goal maintenance doses of 3.7 mg for SLIT and 2000 mg for OIT. They underwent DBPCFC to 10,000 mg at 6 and 12 months of maintenance. Participants in either group who failed to tolerate a 10,000 mg peanut protein DBPCFC at 12 months were offered unblinded treatment or add-on active SLIT or OIT for an additional 6 months. At 12 months, there was a 22-fold increase in median tolerated dose in the original active SLIT group and a 141-fold increase for the original active OIT group ($p = 0.01$). During the blinded phase, 42.9% of doses in the original active OIT group compared to 9% in the original active SLIT group ($p < 0.001$) were associated with symptoms. However, most participants in both groups, 9/10 SLIT participants and 10/10 OIT participants, experienced symptoms with dosing at some point. Antihistamines were used to treat symptoms in 40.9% of OIT doses versus 23.1% of SLIT doses ($p < 0.001$) and β_2

agonists were also used for a significantly higher percentage of doses in the OIT group (1.9% versus 0.3%, $p < 0.001$). What is more, five doses of epinephrine were required to treat systemic reactions in 4 subjects in the active OIT group. During the blinded phase, there were 4 drop-outs (36.3%) in the active OIT group, one for EOE during build-up, one for GI symptoms, one for anaphylaxis, and one for non-compliance. In the active SLIT group, there was only one drop-out (10%) and this was due to GI symptoms. The results of this study found both modalities to be effective at inducing desensitization in the majority of participants, but OIT resulted in greater increases in the median tolerated amount of peanut protein. Similar to what has been seen in other trials, OIT was associated with greater adverse events, more epinephrine use, and higher drop-out rate.

Discussion

As discussed above, peanut OIT has been the most studied food immunotherapy: it more reliably induces desensitization to larger amounts of peanut protein, especially at younger ages, but is associated with high frequency of adverse events including anaphylaxis and dose-limiting GI symptoms. EPIT has a favorable safety profile and may have the greatest ease of use, but at the expense of decreased levels of desensitization compared to OIT and SLIT. SLIT studies are limited but suggest levels of desensitization that are likely to be clinically important with improved safety compared to OIT.

There is an estimated 300 mg peanut protein in 1 peanut kernel, and the eliciting dose for allergic reaction to peanut has been estimated around a median of 75 mg peanut protein (range 0.1–500 mg) [50]. A study by Baumert used a model to assess allergy risk reduction with immunotherapy, which suggested a 95% risk reduction at 300 mg desensitization [51]. It is important to keep these figures in mind when discussing the different modalities and ultimate choice for a patient. Factors to be considered when determining appropriate threshold of desensitization include index reaction, experience with previous accidental exposures, risk-taking behaviors, cognitive abilities that affect ability to reliably avoid peanut, and environmental factors such as school policies. OIT may be preferable for a patient/family that desires higher levels of protection (studies demonstrate successful desensitization in the thousands of milligrams), while EPIT or SLIT may be preferable for those with chronic GI symptoms or low tolerance for adverse effects who are comfortable with lower levels of protection. EPIT could be preferable for active families, those unable to commit to build-up dosing in clinic, and patients with extreme peanut aversion or oral allergy syndrome; it may not be a good choice in patients with poorly controlled eczema or participation in sports that make it difficult for the patch to remain adherent to skin. Additionally, considering the estimated median eliciting dose in a treatment naïve patient and the Baumert study above, EPIT may fail to provide a significant risk reduction in many people, though the level of desirable risk reduction also varies among peanut allergic patients and families. SLIT could provide a balance

between increased levels of desensitization with decreased risk of adverse effects including dose-limiting GI symptoms.

The decision to pursue any modality of immunotherapy requires candid and individualized discussion with patients/families about the risks inherent to all forms in relation to possible benefit. With regard to the Palforzia peanut OIT product, a formal Risk Evaluation and Mitigation Strategy (REMS) has been required by the FDA to describe the associated risks of therapy. In order to order, dispense, administer, and take the medication, this program requires healthcare providers, provider offices, and patients to demonstrate an understanding of the anaphylaxis risk and precautions that must be taken including dose monitoring periods and epinephrine carriage, as well as an understanding of the signs/symptoms of anaphylaxis and ability to appropriately respond in the healthcare setting [52]. Understanding the wide range of risk tolerance and perception of benefit that is likely across patients, researchers proposed a shared decision-making model for patients and healthcare providers to aid in patient selection for immunotherapy, specifically for choice of avoidance, OIT, or EPIT [53••]. The model takes into consideration patient/family goals, risk tolerance, and logistics. It presents comparative data on key benefits and risks in lay terms with visual aids and includes a self-assessment for informational adequacy and how to take next steps. While an early tool and not meant to substitute for discussion with a physician, this could be useful for clinical decision-making and improve communication between patients and providers.

Even with the approval of the first product for OIT, there remain significant gaps in our understanding of food immunotherapy. The long-term efficacy of food immunotherapy and the ability to induce SU past 4–12 weeks is not well understood, and data from OIT suggests that desensitization wanes after stopping immunotherapy. This is not only important for the health of the patient but also for understanding the cost-effectiveness of therapy. Economic modeling has suggested that peanut OIT might be a cost-effective treatment in the long term; however, this analysis was strongly dependent on the long-term outcomes of therapy [54]. An additional long-standing knowledge gap is the association between any form of immunotherapy and the development of EOE remains unclear but warrants additional study. A limitation of all immunotherapy studies is the exclusion of patients with severe anaphylaxis and poorly controlled asthma, those who might stand to benefit the most from immunotherapy. Few studies have used validated measures to determine the effect of immunotherapy on quality of life for individuals and their families. While some studies suggest that immunotherapy may decrease parental worry about accidental exposures in peanut allergic children and make a positive emotional impact, other studies contradict this, and the psychosocial impact of immunotherapy remains unclear. Head-to-head trials of the different modalities are needed and should incorporate validated measures of FAQL. With the recent approval of a product for peanut OIT, more patients are likely to request immunotherapy and allergy practitioners will gain real-world experience that will lend itself to improved understanding of patient and family goals of therapy, patient selection, and challenges to treatment in a more diverse population of patients.

Conclusion

As research has continued to demonstrate desensitization to peanut with oral, epicutaneous, and sublingual immunotherapy and patient and family awareness has simultaneously increased, attention has shifted to practical aspects of the various treatment approaches. Factors such as degree of desensitization, treatment side effects, ease of administration, and cost have become key considerations as food allergy care moves towards a shared decision-making model.

Data and material availability

Not applicable

Code availability

Not applicable

Declarations

Ethics approval

Not applicable

Human and animal rights and informed consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

Consent to participate

Not applicable

Consent for publication

Not applicable

Conflict of interest

Olivia Francis declares no conflict of interest.

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