

Peanut Oral Immunotherapy

State of the Art



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KEYWORDS

- Oral immunotherapy • Peanut • Desensitization • Sustained unresponsiveness
- Quality of life • Food challenge • Adjuvant

KEY POINTS

- Cumulative evidence shows that peanut oral immunotherapy (OIT) is effective at inducing desensitization through downregulation of effector pathways in the allergic reaction cascade; however, only a subset of patients achieve sustained unresponsiveness (remission), which requires redirection of the underlying allergic response toward tolerance.
- Desensitization refers to a temporary increase in reaction threshold and theoretically offers the patient protection from accidental exposure to small amounts of allergen; however, this incremental benefit is only maintained if the patient continues with regular (usually daily) treatment or allergen ingestion, and because the reaction threshold that is achieved can fluctuate over time, patients can and do react to their continuing treatment.
- A recent meta-analysis of peanut OIT randomized trials found that OIT is associated with a threefold greater risk of anaphylaxis and twofold greater risk of epinephrine use than allergen avoidance. Therefore, although peanut OIT can lead to the immunologic outcome of desensitization, this fails to reduce the number of allergic reactions or epinephrine use (for the treatment of allergic reactions) as intended, raising doubt as to whether OIT provides greater benefit over risk for patients.
- Improvement in patient quality of life may mitigate the risks associated with increased reactions; however, available low-level evidence indicates that OIT does not deliver an improved quality of life.
- Strategies to reduce adverse events associated with OIT and/or improve the ability for OIT to induce sustained unresponsiveness (which would remove the need for daily ongoing therapy) are required to improve the benefit-risk of peanut OIT.

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INTRODUCTION

Oral immunotherapy (OIT) for the treatment of food allergy has generated intense research interest. OIT involves ingesting a daily dose of allergen, starting at a very low dose. Typically several increasing doses are administered on the first day (rush phase), followed by a buildup phase during which the last tolerated dose on rush day is continued daily with dose increases performed every 1 to 2 weeks until the maintenance dose is reached. Daily dosing at the top maintenance dose is then continued in the maintenance phase.¹ The measurable outcomes of OIT as a food allergy treatment are desensitization (DS) and sustained unresponsiveness.² DS is defined as an increase in the reaction eliciting threshold dose to the allergen while receiving active treatment.² This is a temporary state of protection that is only maintained while regular OIT dosing is continued (usually daily) and protection is lost rapidly (within 1–2 weeks) on discontinuation of regular allergen exposure.³ Sustained unresponsiveness (SU) is a long-lasting state of nonreactivity to the food allergen that persists weeks or months after cessation of OIT.² It is currently considered that some level of intermittent allergen exposure is required to maintain SU although the amount or frequency of such exposure remains to be defined. DS is assessed by performing double-blind placebo-controlled food challenges (DBPCFC) before OIT and after maintenance dosing is achieved to demonstrate an increase in the reaction eliciting threshold for individual patients. SU is assessed by performing a DBPCFC at least 4 to 8 weeks after treatment has been discontinued (with continuing allergen elimination during this period). The optimal duration of allergen elimination before performing the SU challenge and the cumulative dose of allergen that should be tolerated in this SU challenge have not been standardized; however as the outcome of SU is intended to indicate an absence of the allergic response at the time of testing, the period of allergen elimination should be sufficient to exclude any residual DS effect and the cumulative dose of allergen tolerated should be at least equivalent to what would be used in a diagnostic food challenge where a negative challenge is considered to exclude presence of food allergy. Food OIT randomized trials have generally applied a period of 4 to 8 weeks allergen elimination before SU challenge as DS is expected to be lost in this time frame and the cumulative dose of peanut protein that is tolerated in the SU challenge should be at least 4 g peanut protein as in a diagnostic challenge.

Oral tolerance refers to the permanent resolution of allergy, a state of nonreactivity to allergen that does not require any ongoing allergen exposure. Tolerance is the ultimate aim of any food allergy treatment including OIT; however, such an outcome cannot currently be demonstrated within the context of food allergy clinical trials because permanence of an effect cannot be proven and accurate biomarkers with high sensitivity and specificity for detection of oral tolerance remain limited.² The absence of allergen-specific immunoglobulin E (sIgE) provides a reliable biomarker with high specificity for resolution of allergy yet has poor sensitivity as clinical allergy may resolve before allergen-specific IgE becomes negative. Improved biomarkers that can detect the resolution of allergy with high sensitivity in addition to being specific for absence of allergy are required. In the absence of additional biomarkers for tolerance acquisition, it has been suggested that demonstration of SU that persists years after discontinuation of treatment, so-called long-term SU, may offer a surrogate marker of oral tolerance.

PEANUT ORAL IMMUNOTHERAPY CLINICAL OUTCOMES

OIT has been evaluated in a broad range of food allergies, with peanut allergy drawing greatest interest. Most randomized controlled trials of peanut OIT have assessed for

DS with few evaluating SU. Cumulative evidence from meta-analyses indicates that OIT is effective at inducing DS in most treated subjects but is less effective at inducing SU with only a small subset of patients achieving SU even after 4 or 5 years of treatment. There is great heterogeneity in published peanut OIT randomized trials including differences in dose escalation schedules, maintenance doses, duration of treatment, cumulative allergen doses in study exit food challenge and duration of allergen elimination before assessment of SU.

Induction of Desensitization with Oral Immunotherapy

The first published trial of peanut OIT, an uncontrolled open-label study evaluating a variable maintenance dose of 300 to 1800 mg, reported a DS rate of 69% (27/39) by intention to treat (ITT) analysis, in which DS was defined as passing a 3.9 g peanut protein challenge.⁴ The first double-blind placebo-controlled randomized trial⁵ reported a DS rate of 84% (16/19) by ITT analysis in the OIT group (maintenance dose 4000 mg peanut protein) as compared with 0% (0/9) in the placebo group, where DS was defined as passing a 5-g peanut protein DBPCFC. Other published randomized controlled, open-label, and uncontrolled trials have reported DS rates ranging from 49% to 87%, with DS defined as tolerating 300 mg to 10 g peanut protein in the different studies (Table 1). A large phase 3 multicenter trial evaluating a proprietary peanut OIT (AR101; 300 mg peanut protein maintenance dose) was recently completed in 551 participants (age 4–55 years), with the primary analysis group limited to children aged 4 to 17 years (n = 496). Subjects were eligible to enroll in the trial if they had a reaction threshold at or below 100 mg peanut protein during DBPCFC at study entry; 67.2% in the active group (age 4–17 years) achieved DS to a dose of at least 600 mg (1043 mg cumulative) of peanut protein as compared with 4% in the placebo group at the exit DBPCFC.¹⁷ No beneficial effect was observed in participants aged 18 to 55 years.¹⁷ Peanut OIT has also been performed in the clinical setting (outside of clinical research) and a retrospective review of clinical cases reported that 81% of patients (211/262) were desensitized to a target maintenance dose of 3000 mg peanut protein and of those, nearly every patient passed a 6000 mg peanut protein DS challenge.¹⁸ There was no control group and patient treatment was modified according to the judgment of the clinician, which may introduce potential biases.¹⁸

Induction of Sustained Unresponsiveness with Oral Immunotherapy

Few peanut OIT studies have examined for SU.^{19–21} An uncontrolled study reported 2-week SU (SU assessed 2 weeks after treatment discontinuation/allergen elimination) in 13% (3/23) of children who received 500 mg peanut OIT for 2 months.⁶ A second uncontrolled study (maintenance dose 4 g peanut protein for 5 years) reported 4-week SU (SU assessed at 4 weeks after treatment discontinuation/allergen elimination) in 31% (12/39) of children by ITT analysis.⁹ However, as there was no entry peanut challenge and no control group, it is difficult to ascertain the benefit from OIT over and above natural resolution, which can occur in approximately 20% of children within 5 years.^{22,23} An open-label controlled study of 4 g peanut protein OIT for 2 years in 43 subjects (5–45 years of age) reported 12-week SU in 30.4% (7/23) of the OIT group compared with 0% (0/20) of control subjects.¹⁰ However only 3 (13%) of 23 passed a second food challenge after avoiding peanut for a further 3 months,¹⁰ suggesting that SU was lost in more than 50% of initial treatment responders, within a short time frame. A study in preschool children aged up to 3 years (9–36 months) that compared peanut OIT at maintenance doses of 300 mg versus 3000 mg peanut protein over a median treatment period of 29 months and assessed for 4-week SU reported an SU rate of 78% in the 300-mg arm and 71% in the 3000-mg arm by ITT

Table 1
Published randomized controlled, open label and uncontrolled trials of Peanut OIT

Study	Design	Sample Size and Duration of OIT Treatment	Maintenance Dose (mg Peanut Protein)	Desensitization (ITT Analysis)	Sustained Unresponsiveness (ITT Analysis)
Jones et al, ⁴ 2009	Open label	39 36 mo	300–1800	3.9 g peanut protein OFC: 69% (27/39)	—
Blumchen et al, ⁶ 2010	Open label	23 8 wk	125	61% (14/23)	4 g peanut protein DBPCFC after 2 wk elimination: 13% (3/23)
Varshney et al, ⁵ 2011	Randomized, placebo-controlled	OIT n = 19; Placebo n = 9 48 wk	4000	5 g peanut protein DBPCFC: OIT 84% (16/19) vs Placebo 0% (0/9)	—
Anagnostou et al, ⁷ 2011	Open label	22 32 wk	800	6.6 g peanut protein OFC: 64% (14/22)	—
Anagnostou et al, ⁸ 2014	Randomized controlled	OIT n = 49; Avoidance n = 50 26 wk	800	1.4 g peanut protein DBPCFC: OIT 49% (24/49) vs Avoidance 0% (0/50)	—
Vickery et al, ⁹ 2014	Open label	39 up to 5 y	1800–4000	—	5 g peanut protein DBPCFC after 4 wk elimination: 31% (12/39)
Syed et al, ¹⁰ 2014	Age-matched controlled	OIT n = 23; Avoidance n = 20 24 mo	4000	3.9 g peanut protein OFC: OIT 87% (20/23) vs Avoidance 0% (0/20)	3.9 g peanut protein OFC after 3 mo elimination: 30% (7/23); after 6 mo elimination: 13% (3/23)
Narisety et al, ¹¹ 2015	Randomized OIT vs SLIT	OIT n = 11; SLIT n = 10 16–22 mo	OIT 2 g, SLIT 3.7 mg	10 g peanut protein OFC: 16 mo OIT 9% (1/11), 22 mo OIT + 6 mo SLIT 45% (5/11) vs 16 mo SLIT 0% (0/10), 22 mo SLIT + 6 mo OIT 50% (5/10)	10 g peanut protein OFC after 4 wk elimination: • 16 mo OIT 9% (1/11), • 22 mo OIT + 6 mo SLIT 27% (3/11) • 16 mo SLIT 0% (0/10), • 22 mo SLIT + 6 mo OIT 10% (1/10)

Vickery et al, ¹² 2017	2 Doses of OIT	Low Dose n = 20; High Dose n = 17 up to 48 mo	300 (Low dose); 3000 (High dose)	5 g peanut protein DBPCFC: Low dose 85% (17/20) vs high dose 76% (13/17)	5 g peanut protein DBPCFC after 4 wk elimination: Low Dose 85% (17/20) vs High Dose 71% (12/17)
Kukkonen et al, ¹³ 2017	Randomized controlled	OIT n = 39; Avoidance n = 21 8 mo	800	1.255 g peanut protein DBPCFC: OIT 67% (26/39) vs Avoidance 0% (0/21)	—
Bird et al, ¹⁴ 2018	Randomized, placebo- controlled	OIT n = 29; Placebo n = 26 Up to 36 wk	300	≥443 mg peanut protein DBPCFC: OIT 79% (23/29) vs Placebo 19% (5/26) 1043 mg peanut protein DBPCFC: OIT 62% (18/29) vs Placebo 0% (0/26)	—
PALISADE/Vickery et al, ¹⁷ 2018	Randomized, placebo- controlled	4–17 y old: OIT n = 372; Placebo n = 124 12 mo	300	≥600 mg peanut protein DBPCFC: OIT 67.2% (250/372) vs Placebo 4% (5/124)	—
TAKE-AWAY/Reier- Nilsen, et al, ¹⁵ 2019	Randomized controlled	OIT n = 57; Avoidance n = 20 24 mo	250–5000	7.5 g peanut protein OFC: OIT 61% (35/57)	—
Blumchen et al, ¹⁶ 2019	Randomized, placebo- controlled	OIT n = 31; Placebo n = 31 16 mo	125–250	≥300 mg peanut protein OFC: OIT 74.2% (24/31) vs Placebo 16.1% (5/31)	—

Abbreviations: DBPCFC, double-blind placebo-controlled food challenge; ITT, intention to treat; OFC, oral food challenge; OIT, oral immunotherapy; SLIT, sublingual immunotherapy.

(Modified from Nurmatov U, Dhami S, Arasi S, et al. Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. *Allergy* 2017;72(8):1133-1147.)

analysis.¹² However, in the absence of a “no-treatment” control group, these results must be interpreted with caution given that resolution of peanut allergy is most likely to occur in the first 5 years of life²² and a recent study demonstrated that 22% of children outgrew their peanut allergy by age 4.²³

SAFETY OF PEANUT ORAL IMMUNOTHERAPY

OIT as a standalone therapy is associated with a high rate of allergic reactions and consequently a high study withdrawal rate. Using data pooled from 3 peanut OIT studies ($n = 104$), Virkud and colleagues²⁴ reported that 80% of subjects receiving peanut OIT experienced adverse events (AEs), with 72% of these AEs occurring during buildup and 47% during maintenance. Forty-nine percent experienced gastrointestinal symptoms and up to 42% of participants experienced systemic reactions.²⁴ Twenty percent of participants receiving peanut OIT withdrew from these studies, with half withdrawing due to persistent gastrointestinal symptoms. Interestingly, higher overall AE rates were seen in participants with allergic rhinitis (2.9-fold) and larger peanut skin prick test (SPT) wheal size (1.4-fold for every 5-mm increase) but not baseline-specific peanut IgE.²⁴ The presence of asthma was associated with an increased AE rate (2.3-fold) only during the maintenance phase.²⁴ In the phase 3 multicenter peanut OIT trial of AR101 (PALISADE), more than 95% of participants age 4 to 17 years experienced AEs in both the active and placebo group.¹⁷ Severe AEs were reported in 4.3% of the active group as compared with 0.8% of the placebo group and gastrointestinal AEs were reported in 85.8% of the active group compared with 69.4% of the placebo group.¹⁷ Of concern, epinephrine was required for treatment of severe allergic reactions in 14.0% of those receiving active therapy as compared with 6.5% in the placebo group.¹⁷ Furthermore, 21.5% of subjects receiving AR101 peanut OIT withdrew from the study compared with 8% from the placebo group; 11.6% of AR101 participants withdrew due to AEs and 6.5% due to gastrointestinal AEs, compared to 2.4% and 1.6% of the placebo group, respectively.¹⁷ In a follow-up study of PALISADE, eligible AR101-treated participants continued on daily maintenance for another 6 months, and the rates of reaction did not reduce over time - the rate of AEs reported by AR101 treated subjects was 81.2% in the follow-on period and 88% in PALISADE.²⁵ A recent 2019 systematic review and meta-analysis of peanut OIT trials reported that peanut OIT increased the risk of anaphylaxis 3-fold and the use of epinephrine 2-fold as compared to no OIT/allergen avoidance.²⁶ Moreover, patients continuing on OIT must adopt lifestyle restrictions such as avoiding exercise and showering/bathing for at least 2 to 4 hours post-OIT dose, and the withholding of doses during infections, asthma exacerbations, and menstrual periods²⁶ which may limit the benefit to patients. The investigators concluded that the benefit from peanut OIT may not outweigh the risks and lifestyle impact associated with treatment.

Eosinophilic esophagitis (EoE) has been reported with OIT; however, it remains unclear whether OIT plays a direct causal role in development of EoE or if OIT instead unmasks preexisting EoE in food-allergic individuals (as a result of allergen exposure with OIT). A 2014 meta-analysis of EoE with OIT reported a prevalence of 2.7% (95% confidence interval 1.7%–4.0%),²⁷ which is not higher than the rate of EoE reported among food-allergic individuals (4.7%).²⁸ A review of all patients participating in peanut OIT clinical studies (including case reports, open-label, and randomized controlled trials) reported a rate of biopsy-confirmed EoE of 5.2%.²⁹ In a more recent meta-analysis that limited the analysis to randomized controlled trials, 3 cases of EoE were reported across 5 peanut OIT randomized controlled trials ($n = 719$), all of which

occurred in patients receiving peanut OIT.²⁶ Furthermore, as baseline endoscopies are not routinely performed before starting OIT and endoscopy is also not performed routinely in patients with EoE-like symptoms during OIT, it is possible that allergen exposure during OIT reveals existing EoE that is asymptomatic while the patient is adhering to allergen avoidance. In a study in 21 adults, baseline endoscopies were performed before commencement of peanut OIT and 24% (5/21) were shown to have preexisting esophageal eosinophilia (>5 eosinophils per high-power field [eos/hpf]), whereas 14% (3/21) had greater than 15 eos/hpf associated with endoscopic changes.³⁰

A critical yet unaddressed issue is the long-term safety of continuing DS with OIT. There is a lack of long-term follow-up data for peanut OIT. As the level of protection from DS is unstable and can be lost both in association with known cofactors (such as exercise, viral illness, asthma exacerbation, menstruation) and in the absence of any cofactors, patients continuing on OIT can react to their OIT dose despite having tolerated this same dose for many months.²⁴ It is therefore important to understand the long-term safety of being desensitized with OIT. Long-term and follow-up studies of DS with cow's milk OIT suggest that allergic reactions do not decrease over time. In a follow-up study conducted 5 years after children had been desensitized with cow's milk OIT, 50% of children were still experiencing reactions with more than 20% reporting at least a single episode of anaphylaxis in the preceding 12 months.³¹ In another follow-up study conducted 7 years post-OIT, 64% of patients reported having 1 or more allergic reactions and 25% (33/132) required epinephrine for treatment of reactions.³² Another concern is whether desensitized patients will adhere to continuing regular (daily) allergen dosing, which is necessary to maintain the DS state. Follow-up of 21 patients who were desensitized with peanut OIT or sublingual immunotherapy at 3 to 8 years after study completion revealed that only 57% (12/21) continued to ingest peanut with taste being the main reason for discontinuing regular peanut intake.³³

Given the high rate of AEs associated with OIT that do not reduce substantially over time and the lifestyle restrictions placed on patients continuing on OIT/allergen ingestion, there is a need to develop alternate approaches that reduce the rate of AEs associated with OIT and/or increase the likelihood of achieving SUs.

IMPROVING TOLERABILITY AND EFFICACY OF PEANUT ORAL IMMUNOTHERAPY

There is a need for novel approaches that improve tolerability and efficacy of peanut OIT. The combined administration of OIT with adjuvant therapies has been investigated with the aim of improving safety or efficacy or both. The anti-IgE monoclonal antibody Omalizumab has been shown to reduce AEs and hence improve safety; however it has not been shown to improve the rate of SU.³⁴ Moreover, Omalizumab is expensive and must be used continually to avoid AEs associated with OIT.

Studies suggest that the use of immune response modifiers, such as probiotics or other Toll-like receptor (TLR) agonists alongside OIT may provide improved safety of OIT and effectiveness in inducing SU. A phase 2 proof of concept double-blind, placebo-controlled randomized trial evaluating *Lactobacillus rhamnosus* CGMCC 1.3724 in combination with peanut OIT (PPOIT) in 62 children with peanut allergy reported similar withdrawal rates in active and placebo-treated groups (9.7% in each group) with no study withdrawals due to AEs or gastrointestinal AEs and a high rate of 2-week to 6-week SU following 18 months of treatment.³⁵ ITT analysis showed that 74% of PPOIT-treated subjects achieved SU and 84% achieved DS to a cumulative dose of 4 g peanut protein.³⁵ Long-term follow-up of trial participants 4 years after

completing treatment showed that PPOIT-treated subjects were significantly more likely to have continuing peanut intake than placebo participants (67% vs 4%; absolute difference 63%, 95% confidence interval 42–83; $P = .001$).³⁶ Furthermore, persistent SU (assessed by DBPCFC after 8 weeks of peanut elimination at 4 years posttreatment) was shown in 58.3% (7/12) of PPOIT-treated participants compared with 6.7% (1/15) of placebo participants ($P = .012$).³⁶ At 4 years posttreatment, PPOIT participants had significantly smaller peanut SPT and significantly higher peanut sIgG4:sIgE ratio in than placebo participants. These findings suggest that the addition of a live bacterial immune modifying adjuvant (*L. rhamnosus* CGMCC 1.3724) alongside OIT can reduce AEs and increase effectiveness at inducing SU compared with OIT alone.³⁶ Further studies directly comparing PPOIT versus peanut OIT are required to confirm this.

TLR agonists such as TLR-9 CpG and TLR4 monophosphoryl lipid A and glucopyranosyl lipid A (MPL/GLA) have been shown in mouse models to reduce anaphylaxis³⁷ but efficacy at inducing SU has not been evaluated in clinical trials. Other adjuvants or adjunctive therapies such as the use of nanoparticles, peptide, and recombinant vaccine immunotherapy, interferon-gamma, leukotriene receptor antagonists, and ketotifen together either single or multifoed OIT are currently being investigated, with studies either in pilot/preclinical and phase I trials.³⁷

QUALITY OF LIFE FOR PEANUT ORAL IMMUNOTHERAPY

The benefit-risk profile of OIT may be enhanced if there is improvement in quality of life (QoL). Yet, few randomized controlled OIT trials have assessed patient QoL and there is currently no convincing evidence to suggest that OIT when compared with placebo improves QoL. A recent systematic review concluded that peanut OIT does not improve QoL (ie, no difference between groups) based on low-certainty evidence.²⁶ Open studies have suggested improved QoL while on OIT but do not report findings for a control group and QoL may improve as a result of participating in a study. On the other hand, QoL has been reported to deteriorate in some patients during OIT.³⁸ A summary of QoL outcome with peanut OIT is shown in [Table 2](#). Thus far, the only study that demonstrated improved QoL after cessation of treatment was the PPOIT study evaluating the combination of *L. rhamnosus* CGMCC 1.3724 with peanut OIT, and this improvement in QoL was shown to be related specifically to the acquisition of SU.⁴² Further studies comparing QoL in desensitized patients (who experience frequent allergic reactions to their daily dose of allergen/OIT) and patients with SU (who are able to adopt ad libitum peanut intake) should be pursued to clarify the benefits offered by these different treatment outcomes.

SUMMARY AND FUTURE DIRECTIONS

Current peanut OIT approaches (where OIT is administered as a standalone therapy) are associated with frequent and severe AEs, and of greater concern result in higher rates of anaphylaxis, gastrointestinal AEs and epinephrine use than allergen avoidance.¹⁷ Although OIT is effective at inducing desensitization, the ability to induce SU is limited. Desensitized patients must continue on regular (typically daily) dosing of allergen to maintain the desensitized state, yet they experience frequent allergic reactions to their daily allergen dose because the level of protection with desensitization is unstable and the underlying allergic response remains. In contrast, SU is considered to reflect redirection of the immune response away from allergy toward tolerance and is therefore expected to avoid allergic reactions following allergen ingestion. Novel approaches that improve the safety of OIT and increase the ability of OIT to induce SU

Table 2
A summary of QoL outcome with peanut OIT

Study	Design	Quality-of-Life Assessment	Findings
TAKE-AWAY/ Reier-Nilsen et al, ¹⁵ 2019	Open label, randomized: • 37/57 completed 2 y peanut OIT • 20 controls – observation/peanut avoidance	At enrollment, end of updosing, and after 2 y of OIT. • Children: PedsQL v4.0 • Parents: PedsQL v4.0 parental proxy and FAQL-PB MCID ≥ 5.3	Mean change in QoL from enrollment to year 2: • Child self-report: 4.4 (0.5,8.3) • Parental proxy: 9.3 (4.3,14.3) • Two years of OIT improved child-QoL compared with controls as reported by parents, but not by the children. • These findings suggest that parents may overestimate improvement in child-QoL by OIT.
Blumchen et al, ¹⁶ 2019	Double-blind, randomized, placebo- controlled. 62 participants enrolled: • 31 OIT group • 31 placebo group	At enrollment and 4 wk after end of treatment/ final OFC: • Children/Teenagers: FAQLQ-CF/FAQLQ-TF • Parents: FAQLQ-PF MCID ≥ 0.5	• After final OFC, parents on the OIT group, but not on the placebo group reported MCID > 0.5 within the domain "social and dietary limitation." • Comparing OIT and placebo groups, no significant difference was found in median change in HRQOL for all domains of the FA-QLQ-PF reported by parents after the treatment with OIT. • When compared HRQOL before and after OIT, children in the active group had the median improvement for the total score as well as for each domain of the FAQLQ-CF ≥ 0.5 of the MCID. • After final OFC, children on the OIT group, but not on the placebo group reported statistically significant improvement within the 2 domains: "risk of accidental exposure" and "emotional impact."

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Study	Design	Quality-of-Life Assessment	Findings
Zhong et al, ³⁹ 2018	Open trial No control group • 7/9 completed peanut OIT treatment	At enrollment, 2 wk after reaching maintenance dose and 4 wk after end of treatment: • Children/Teenagers: FAQLQ-CF/FAQLQ-TF • Parents: FAQLQ-PF	• The median baseline scores were 3.8, 4.1, and 7 out of a maximal possible 7 for PF, CF, and TF respectively. • 4 wk after end of treatment, FAQLQ-PF scores decreased by 0.5 (n = 5), FAQLQ-CF scores increased by 0.1 (n = 5) and FAQLQ-TF score decreased by 0.6 (n = 1). • There was no statistically significant improvement in QoL 4 wk after the end with peanut OIT.
STOP II Anagnostou et al, ⁸ 2014	Randomized, controlled, crossover trial. Phase I (26 wk) completed by: • 39/49 peanut OIT group • 46/50 controls –peanut avoidance Phase II (26 wk) controls allocated to receive active intervention	At enrollment and post –treatment. Performed only in the under 13-year-old participants: • Parents: FAQLQ-PF	• QoL scores were similar in active and control groups at baseline. • No comparative results between OIT and control group were reported at the end of the first phase of the study. • Both the active and control groups demonstrated a significant improvement (decrease) in Food Allergy QoL scores after OIT in the under-13-year-old participants: –1.61 and –1.41, respectively (both $P < .001$).
Factor et al, ⁴⁰ 2012	Open trial No control group • 90/100 participants reached maintenance dose	At enrollment, and when achieving maintenance dose: • Children/Teenagers: FAQLQ-CF/FAQLQ-TF • Parents: FAQLQ-PF MCID ≥ 0.5	• A significant improvement in QoL was found in all survey domains, with the exception of the emotional impact domain on the adolescents' survey. • QoL significantly improved ($P < .02$) on all 30 questions when parents assessed their children 5–12 y old. • When children (8–12 y old) and teens assessed themselves, QoL improved ($P < .05$) on 22 of 24 questions and 12 of 18 questions, respectively.

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Table 2
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Study	Design	Quality-of-Life Assessment	Findings
Kamilaris et al, ⁴¹ 2012	Open label No control group • OIT: 16 children 9–36 mo old	At enrollment, completion of the buildup phase and 1 year of study maintenance	• Compared with baseline after participation in peanut OIT, parents report an increase in the areas of emotional, physical, and social well-being. • Issues relating to finding time to take the daily dose and remembering to take the daily dose were areas of stress reported by the parents. • Parents reported being less anxious about their child participating in activities in which they are not present and less anxious about their child becoming more independent in food selection.

Abbreviations: CF, child form; FAQLQ, food allergy quality of life questionnaire; HRQOL, health-related quality of life; MCID, minimal clinically important difference; OFC, oral food challenge; OIT, oral immunotherapy; PF, parent form; QoL, quality of life; TF, teenager form.

are required. Although a commercial peanut OIT treatment AR101 is currently being evaluated in a Biologics License Application by the US Food and Drug Administration⁴³ and may soon be available for clinical use, more studies are required to clarify the long-term safety of remaining desensitized in the real world.

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