Original Article

Peanut Oral Immunotherapy With or Without H_1 and H_2 Antihistamine Premedication for Peanut Allergy (PISCES): A Placebo-Controlled Randomized Clinical Trial

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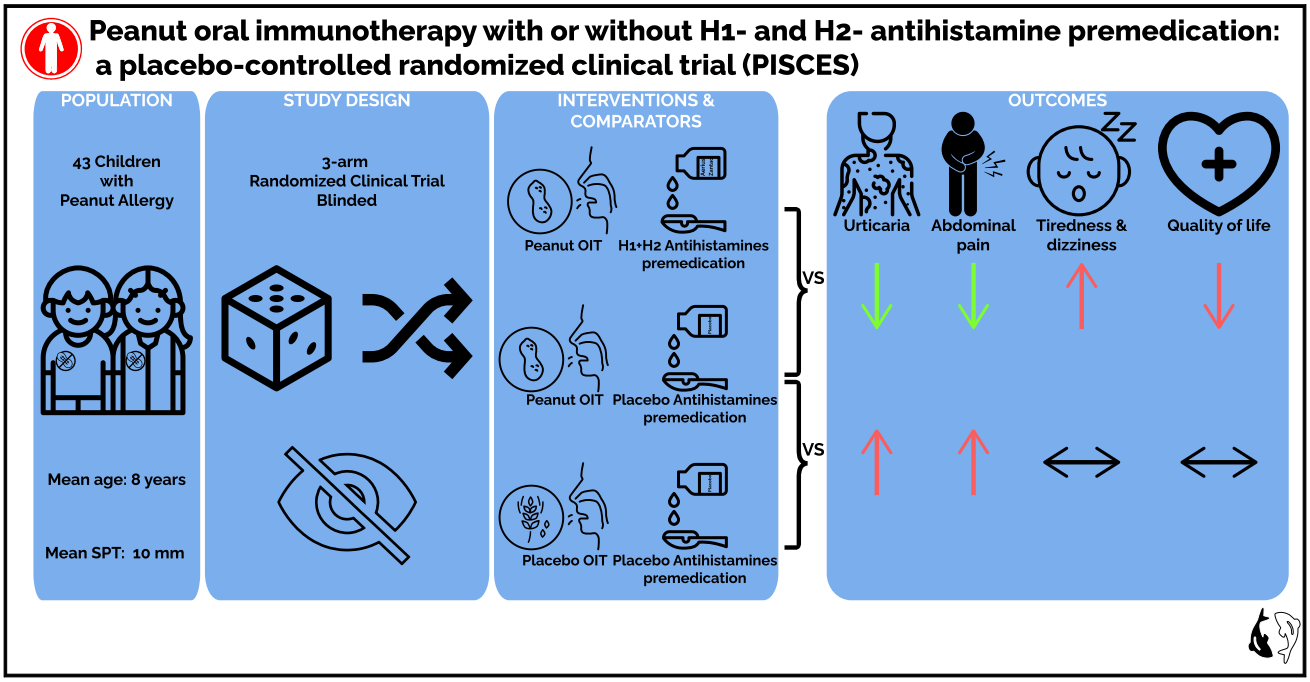
What is already known about this topic? Peanut allergy is a growing global problem, but current forms of treatment using oral immunotherapy (OIT) are associated with side effects and there is a lack of evidence addressing how to mitigate them.

What does this article add to our knowledge? H_1 and H_2 antihistamines added to peanut OIT modestly reduce the skin and gastrointestinal components of the high incidence of OIT-induced adverse reactions, and there is no clear difference in quality-of-life improvement whether treated with peanut OIT or with placebo OIT.

How does this study impact current management guidelines? Antihistamines are a low-cost option to add to OIT, but adding them to an already complex OIT regimen must be balanced against their modest benefits and added adverse effects. Safer food allergy treatments that importantly improve patient and family quality of life need to be proven in future randomized controlled trials.

VISUAL SUMMARY



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Abbreviations used
HR- hazard ratio
IRR- incidence rate ratio
OIT- oral immunotherapy
QoL- quality of life
RCT- randomized controlled trial

BACKGROUND: Current forms of peanut oral immunotherapy (OIT) are associated with side effects, and there is a lack of evidence addressing how to mitigate them.

OBJECTIVE: To determine whether premedication with desloratadine and ranitidine results in fewer side effects during peanut OIT/desensitization.

METHODS: A total of 43 patients with peanut allergy (mean age, 7.6 ± 2.1 years, 37% females, 63% males, baseline eliciting dose, 33 ± 26 mg) were randomized to OIT with or without concomitant H_1 and H_2 antihistamine blockade, or double-placebo. Patients, study staff/investigators, and statisticians were blinded. The primary outcomes were the frequency and severity of OIT-induced adverse events. The secondary outcomes were quality of life and eliciting doses to blinded food challenge.

RESULTS: Adverse reactions occurred more in the OIT groups compared with the double-placebo group (OIT with antihistamines vs double-placebo hazard ratio, 3.75 [95% CI, 2.79-4.72]; OIT with placebo antihistamines vs double-placebo, hazard ratio, 4.62 [95% CI, 3.61-5.62]). Patients given antihistamines cotreatment with OIT had a similar risk of adverse events compared with those who did not use antihistamines with OIT (hazard ratio, 1.23 [95% CI, 0.49-1.97]). OIT with and without antihistamines accelerated the incidence rate of adverse events compared with double-placebo (4.8 and 6.4 events per patient vs 3.5 per patient, incidence rate ratio, 2.49 [95% CI, 1.36-4.56] and 2.04 [95% CI, 1.01-4.15], respectively). Antihistamines pretreatment modestly reduced the frequency of moderate to severe adverse reactions among OIT-treated groups (1.9 per patient vs 4.2 per patient, incidence rate ratio, 0.46 [95% CI, 0.24-0.89]), primarily urticaria (0.6 vs 2.1 per patient) followed by abdominal pain (2.6 vs 4.2 per patient), but increased neuropsychiatric adverse events (primarily tiredness and sedation, 2.3 vs 0.7 per patient). Eliciting doses after treatment were similar in all groups. Quality of life improved similarly regardless of treatment with peanut OIT or placebo OIT.

CONCLUSIONS: Peanut OIT with antihistamines modestly reduce the skin and gastrointestinal components of the high incidence of adverse reactions during OIT, and there are no clear differences in improvement in quality of life whether treated with OIT, OIT with antihistamines, or placebo OIT despite OIT being effective in inducing desensitization. Safer food allergy treatment approaches that importantly improve quality of life need to be proved in future robust randomized trials. **(J Allergy Clin Immunol Pract 2022;■:■-■)**

Key words: *Peanut allergy; Oral immunotherapy (OIT); Food allergy; H_1 and H_2 antihistamine premedication; Desloratadine; Ranitidine; Randomized controlled trials (RCTs); Quality of life; Adverse events; Safety; Net benefit*

INTRODUCTION

Peanut allergy affects 3% to 5% of children, lasts for a lifetime in most patients, and is associated with allergic reactions and anaphylaxis.[1] The burdens of living with the condition can lead to a decrease in quality of life (QoL). Management centers around avoidance, with use of rescue medications, such as epinephrine, to treat severe allergic reactions.[1]

Desensitization to peanut, or immunotherapy, is one possible treatment for peanut allergy. Oral immunotherapy (OIT) has both potential benefits and harms. Randomized controlled trials (RCTs) have proven that, compared with placebo, current forms of OIT are associated with a high increase in adverse events, uncertain change in QoL, and clear ability to increase controlled food challenge thresholds.[2] How to improve the safety of food allergy immunotherapy is unclear.[1]

A common method of mitigating adverse events associated with allergen immunotherapy to inhaled allergens[3,4] or Hymenoptera venom[5-7] is to premedicate before immunotherapy doses using H_1 and/or H_2 antihistamines. RCTs comparing antihistamine ($H_1 \pm H_2$) premedication to placebo for both indications showed reduced local and systemic reactions.[4,6,7] Antihistamine premedication also was reported to enhance efficacy of venom-allergen immunotherapy.[8] Antihistamine premedication, however, has not been tested for food immunotherapy in RCTs. H_1 and H_2 antihistamines might mitigate the food allergen–induced adverse reactions during OIT and facilitate desensitization and improve QoL.[9-11] We therefore evaluated the potential benefit of adding H_1 and H_2 antihistamines to peanut OIT in an RCT of peanut OIT with or without premedication versus double-placebo.

METHODS

Peanut Immunotherapy Starting in Canada, Evaluation and DiScovery was a 3-arm, parallel-design, placebo-controlled RCT at Hamilton Health Sciences' McMaster Children's Hospital comparing peanut OIT with or without concomitant use of second-

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generation H_1 antihistamines (desloratadine) and H_2 blockers (ranitidine). We registered the trial (NCT01601522). We report this trial according to CONSORT[12] (see Online Repository Texts E1-E3 in this article's Online Repository at www.jaci-inpractice.org). The study was approved by the Hamilton Integrated Research Ethics Board. All enrolled participants provided written informed consent and as appropriate, assent.

Participants

Participants were enrolled if they were aged between 5 and 10 years and allergic to peanut based on a history of significant clinical symptoms within 60 minutes after the ingestion of peanut, the presence of specific IgE to peanut (a positive skin prick test result to peanut, defined as a wheal diameter 3 mm larger than that of the saline control); and a positive serum-specific IgE (ImmunoCAP) result (>15 kU/L). Patients were also accepted into the study if they had a clinical reaction to peanut ingestion within the 6 months before enrollment,[13] a positive skin prick test result to peanut, and a serum-specific peanut IgE result of 7 kU/L or greater. We excluded patients with significant or uncontrolled asthma (including, but not limited to, use of inhaled corticosteroids [fluticasone >500 μg daily, ciclesonide >400 μg daily, or budesonide >800 μg daily] or the corresponding inhaled corticosteroid/long-acting beta-agonist combination inhalers, oral prednisone in the preceding 1 month, and FEV_1 <80% predicted). Patients were also excluded if they received allergy injections (immunotherapy) to environmental allergens at any time in the past, had symptomatic atopic dermatitis or chronic urticaria, which may have interfered with ability to evaluate OIT and/or requiring daily medication including antihistamines, or were unable to tolerate the lowest dose of the study entry oral food challenge peanut flour (1 mg peanut protein), or if the highest dose of peanut flour was reached (4000 mg) and there was no evidence of an allergic reaction. Nasal steroids, bronchodilators, and leukotriene inhibitors were permitted.

Randomization, allocation concealment, and blinding

Using pharmacy-based centralized randomization, whose list was inaccessible by other study personnel, participants were allocated in blocks of 21 (8:8:5) to peanut OIT with H_1 and H_2 antihistamines, peanut OIT with placebo antihistamines, and placebo OIT with placebo antihistamines (double-placebo). There were no stratification variables. The pharmacy central randomization team communicated by phone to the study nurse/coordinator the blinded treatment assignment and provided identically packaged treatments. Patients, outcome assessors, study personnel, and the statistician were blinded to treatment assignment. Only the central pharmacy knew participant codes, and this was unblinded after statistical analyses by the independent statistician were completed.

Procedures

Peanut OIT. We adapted the protocol previously reported by Jones et al.[14] Participants underwent an initial dose escalation during the entry food challenge until they reacted (see Tables E1-E3 for schedules in this article's Online Repository at www.jaci-inpractice.org). Peanut flour (Light; Byrd Mill Company, Ashland, Va; 50% protein) was used for food challenges and for OIT. The typical food challenge vehicle was chocolate pudding, though we allowed families to bring their own vehicle if they preferred. The next day, participants started ingesting the highest single dose tolerated with their assigned premedication daily at home.

Updosing occurred in-person (in hospital) every 2 weeks by roughly doubling the amount of peanut protein, each time dispensed by pharmacy centrally in a blinded fashion, and observing at that visit in a monitored setting the first dose of the following 2-week schedule (see Table E1 for schedule). Participants who experienced adverse reactions decreased the amount of peanut protein 1 to 2 steps, based on the severity of such reactions, before attempting to increase after 1 to 2 weeks on that lower dose. Patients who reached a dose of 500 mg peanut protein once per day were maintained on that amount daily for 12 months. This was continued for a minimum of 4 weeks and then a blinded (patient and outcome assessor) food challenge done, with randomization centrally by pharmacy, to remeasure eliciting dose thresholds.[15,16] Patients completing this food challenge and who were initially randomized to placebo were eligible for cross-over, unblinded, into an OIT group and are not reported here.

Antihistamines pretreatment/cotreatment. The patients assigned antihistamines premedication were given desloratadine 2.5 mg in 5 mL by mouth once daily along with ranitidine 75 mg in 5 mL by mouth twice per day.

Precautions and monitoring. Patients received scheduling information for peanut dosing, for example, instructed to take the dose after school at home and with a meal. All participants were given an epinephrine autoinjector prescription, instructions on recognition of reactions, instructions on what to do in the event of a reaction to the OIT dose, including when and how to treat, and contact information for the physician with call coverage 24 hours per day. Patients who missed the dose(s) or developed an intercurrent illness were instructed to contact the physician for dose instructions regarding taking a lower dose transiently. They were also provided with an instruction sheet to provide to an emergency physician if they felt their reaction was severe enough to warrant going to the emergency room. All patients received a diary and were instructed to record daily peanut dose and time it was taken, and any symptoms that could develop, intercurrent illnesses, and medications. Participants classified the severity of any adverse events as mild if a symptom was present but easily tolerated; moderate if symptoms were present and bothersome, but tolerable; and severe if symptoms were hard to tolerate (eg, caused interference with daily activities or disturbed sleep). The diary was reviewed at every clinic visit (every 2 weeks during the updosing phase), and every 3 to 12 months during the maintenance phase.

Skin and blood tests. Skin prick tests done at baseline used commercial extracts from ALK (ALK-Abelló Pharmaceuticals Inc, Mississauga, ON, Canada) applied to volar forearm, pricked using Duo-Tip II, and mean wheal diameter read at 15 minutes. A positive test result was defined as a wheal diameter 3 mm or greater than that of the negative (saline) control. ImmunoCAP (Phadia, Uppsala, Sweden) quantified serum peanut-specific IgE and peanut component-specific IgE.

Outcomes/end points

The primary outcome was the risk and incidence rate of adverse reactions over time. The secondary end point was health-related QoL measured using Food Allergy Quality of Life Questionnaire Parental Form.[17] Additional outcomes were the rate of discontinuation and magnitude of change in thresholds from baseline to reaching maintenance at 4 (±2) weeks.

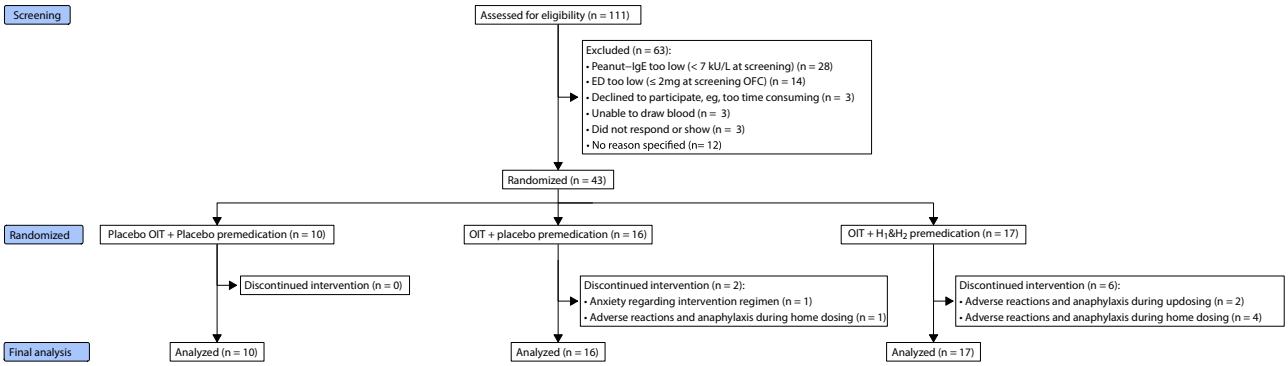

FIGURE 1. CONSORT participant flow. *ED*, eliciting dose; *OFC*, oral food challenge.

TABLE I. Demographic characteristics

Variable	Category	Peanut OIT $H_1 + H_2$ AH (n = 17)	Peanut OIT placebo AH (n = 16)	Placebo OIT placebo AH (n = 10)
Age (y), n, mean ± SD		17, 8.1 ± 1.88	16, 7.8 ± 2.00	10, 7.3 ± 2.42
Sex, n (%)	Female	5 (29)	8 (50)	2 (20)
	Male	12 (71)	8 (50)	8 (80)
SPT wheal diameter (mm), n, mean ± SD		16, 8.56 ± 2.66	15, 9.60 ± 3.89	10, 11.1 ± 3.57
PN-IgE (kU/L), n, mean ± SD		17, 79.81 ± 26.27	16, 76.17 ± 31.01	10, 76.33 ± 20.96
Anaphylaxis in the past 12 mo,n (%)	Yes	2 (12)	5 (31)	3 (30)
	No	11 (65)	10 (63)	7 (70)
	Missing	4 (23)	1 (6)	0 (0)
QoL—Baseline, n, mean ± SD		16, 4.33 ± 1.23	15, 3.83 ± 1.15	10, 4.02 ± 1.05
No. of additional food allergies, n (%)	0	11 (65)	6 (38)	6 (60)
	1	4 (23)	8 (50)	2 (20)
	≥2	2 (12)	2 (12)	2 (20)
Asthma, n (%)	Yes	9 (53)	5 (31)	2 (20)
	No	7 (41)	10 (63)	8 (80)
	Missing	1 (6)	1 (6)	(0)
Baseline oral food challenge cumulative eliciting dose (mg), n, mean protein ± SD		17, 45.53 ± 50.32	16, 26.13 ± 25.16	10, 14.90 ± 13.57

PN-IgE, Serum peanut-specific IgE; *SPT*, skin prick test.

Statistics

Baseline characteristics are summarized using descriptive statistics and reported by group as mean ± SD for continuous variables and count (%) for categorical variables. Analyses of the primary and all secondary outcomes follow the intention-to-treat principle. Continuous outcome variables were analyzed using linear regression and dichotomous outcome variables using binomial regression. The results of between-group comparisons are presented as mean differences (least-squares means adjusted for baseline values using analysis of covariance) for continuous variables, and relative risks for binary and count variables, with corresponding 95% CI and associated *P* values. Time-to-event outcomes were modeled using Cox proportional hazards regression after verifying proportional hazards (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org), with group comparisons being reported as hazard ratios (HRs), corresponding 95% CIs, and *P* values. Analyses were performed using SAS 9.4 (Cary, NC).

Role of the funding sources

The funders had no role in study design, collection, analysis, interpretation of data, writing of the report, or decision to submit the article for publication.

RESULTS

Flow

Of 111 assessed for eligibility from 2012 to 2015, 43 were randomized to placebo OIT + placebo premedication (double-placebo, n = 10), peanut OIT with placebo H_1 and H_2 premedication (n = 16), and peanut OIT with H_1 and H_2 premedication (n = 17) (Figure 1).

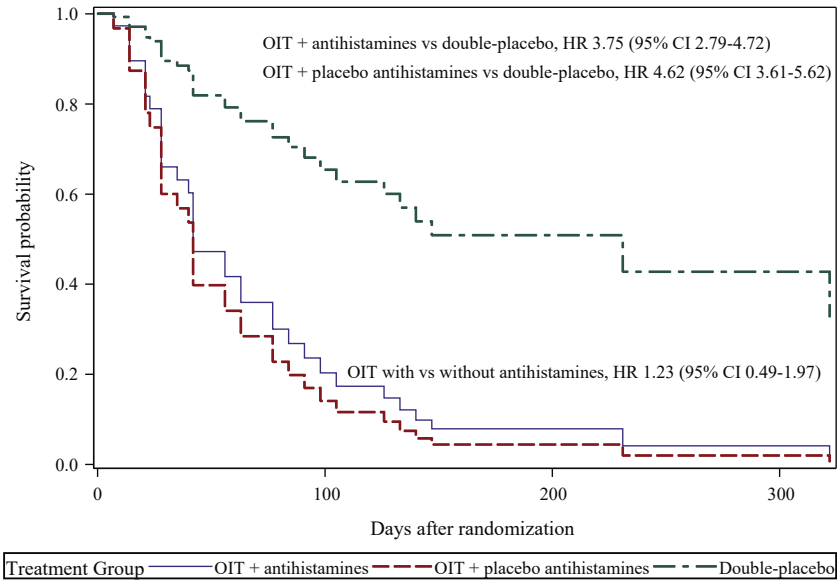

FIGURE 2. Adverse reactions survival curve.

TABLE II. Safety analysis—Overall Incidence of adverse events

Variable	Category	Peanut OIT $H_1 + H_2$ AH (group 1; n = 17)	Peanut OIT placebo AH (group 2; n = 16)	Placebo OIT placebo AH (group 3; n = 10)	Comparison of mean incidence	IRR (95% CI)	*P* value
No. of AEs	Mean incidence	4.82	6.38	3.50	Group 1 vs 2	0.82 (0.46-1.48)	.513
					Group 2 vs 3	2.49 (1.36-4.56)	.003
					Group 1 vs 3	2.05 (1.01-4.15)	.047
Severe or moderate	Mean incidence	1.94	4.19	0.90	Group 1 vs 2	0.46 (0.24-0.89)	.021
					Group 2 vs 3	4.65 (2.02-10.73)	<.001
					Group 1 vs 3	2.16 (1.01-4.60)	.047

AE, Adverse event; *AH*, antihistamine.

Participants

Table I summarizes baseline characteristics of the participants. Their mean age was 7.8 ± 2.1 years (range, 5-11 years) at enrollment, and 15 (35%) were female and 28 (65%) were male. The 3 assigned groups were similar regarding skin and blood parameters of allergic sensitization, burden of disease, and comorbidities. The distributions of baseline eliciting dose among groups were similar between groups. No patient reported gastrointestinal symptoms or a diagnosis of eosinophilic esophagitis/gastrointestinal disorder at baseline.

Clinical outcomes

Allergic/adverse reactions. The risk for 1 or more adverse reaction (Figure 2) was higher in both OIT groups compared with the placebo group (OIT with antihistamines vs double-placebo: HR, 3.75 [95% CI, 2.79-4.72]; OIT without antihistamines vs double-placebo: HR, 4.62 [95% CI, 3.61-5.62]). Time to first adverse event was not different between OIT groups receiving antihistamines versus placebo antihistamines (HR, 1.23 [95% CI, 0.49-1.97]).

Table II presents that the risk of having multiple adverse events (incidence rate) was elevated in the OIT groups compared with double-placebo (incidence rate ratio [IRR], 2.49 [95% CI, 1.36-4.56] cotreated with placebo antihistamines, and IRR, 2.05 [1.01-4.15] with $H_1 + H_2$ antihistamines), and not different between the premedication and no premedication OIT groups (IRR, 0.82 [95% CI, 0.46-1.48]).

Antihistamine premedication with OIT reduced moderate or severe adverse events compared with OIT without premedication (1.9 vs 4.2 events per patient, IRR, 0.46 [0.24-0.89]) (Table II). Compared with participants given double-placebo (0.9 events per patient), the rate of moderate or severe events was increased in patients on OIT without (IRR, 4.65 [95% CI, 2.02-10.73]) and with (IRR, 2.16 [95% CI, 1.01-4.60]) antihistamines. Table III presents that this reduction was primarily driven by a reduction in urticaria (OIT with antihistamines [0.6 events per patient] vs OIT with placebo antihistamines [2.1 events per patient], IRR, 0.28 [95% CI, 0.10-0.80]). Patients on OIT with placebo premedication had an increased rate of urticaria compared with those on double-placebo (2.1 events vs 0.7 events per patient, IRR, 3.04 [95% CI, 1.17-7.88]) and those assigned to OIT with premedication had a similar rate of urticaria compared with placebo (0.6 vs 0.7 events per patient, IRR, 0.84 [95% CI, 0.28-2.48]). Abdominal pain was slightly and non-statistically significantly reduced in the OIT groups with $H_1 + H_2$ antihistamines versus placebo antihistamines (2.6 vs 4.2

TABLE III. Safety analysis—Specific adverse events

Variable (counts)	Category	Peanut OIT $H_1 + H_2$ AH (group 1; n = 17)	Peanut OIT placebo AH (group 2; n = 16)	Placebo OIT placebo AH (group 3; n = 10)	Comparison of mean incidence	IRR (95% CI)	*P* value
Nausea/vomiting	Mean incidence	0.65	0.75	0.70	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.86 (0.31-2.42) 1.07 (0.24-4.87)93 0.92 (0.21-4.13).92	.78
Abdominal pain	Mean incidence	2.59	4.25	0.80	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.61 (0.27-1.37) 5.31 (2.53-11.16) 3.24 (1.55-6.74)	.23 <.001 .002
Require treatment	Mean incidence	2.53	3.44	1.20	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.74 (0.24-2.29) 2.87 (1.28-6.39) 2.11 (0.66-6.78)	.60 .010 .21
Urticaria*	Mean incidence	0.59	2.13	0.70	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.28 (0.10-0.80) 3.04 (1.17-7.88) 0.84 (0.28-2.48)	.018 .022 .75
Neuropsychiatric events†	Mean incidence	3.35	1.06	1.20	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	3.16 (1.84-5.42) 0.89 (0.42-1.85) 2.79 (1.50-5.21)	<.001 .75 .001
Tiredness or dizziness	Mean incidence	2.29	0.75	0.70	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	3.06 (1.60-5.84) 1.07 (0.42-2.72) 3.28 (1.47-7.33)	.001 .89 .004

AH, Antihistamine.
*Includes urticaria, angioedema, erythema, facial flushing, lip swelling, orbital edema.
†Includes tiredness, dizziness, headache, emotional lability.

TABLE IV. Safety analysis—Risk of 1 or more adverse events

Variable (ever/never), n (%)	Category	Peanut OIT $H_1 + H_2$ AH (group 1; n = 17)	Peanut OIT placebo AH (group 2; n = 16)	Placebo OIT placebo AH (group 3; n = 10)	Comparison of risks	Risk ratio (95% CI)	*P* value
Discontinued	Yes	5 (29.41)	2 (12.50)	0 (0)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	2.35 (0.53-10.45) 3.24 (0.17-61.21) 6.72 (0.41-110.13)	.26 .40* .09*
	No	12 (70.59)	14 (87.50)	10 (100)			
Anaphylaxis	Yes	1 (5.88)	2 (12.50)	1 (10)†	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.47 (0.05-4.70) 1.25 (0.13-12.06) 0.59 (0.04-8.41)	.52 .85 .70
	No	16 (94.12)	14 (87.50)	9 (90)			
Epinephrine use	Yes	1 (5.88)	0 (0)	1 (10)†	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	2.83 (0.12-64.89) 0.22 (0.01-4.83) 0.59 (0.04-8.41)	.492* .183* .70
	No	16 (94.12)	16 (100)	9 (90)			
Wheezing	Yes	2 (11.76)	2 (12.50)	0 (0)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.94 (0.15-5.91) 3.24 (0.17-61.21) 3.06 (0.16-57.93)	.95 .40* .42*
	No	15 (88.24)	14 (87.5)	10 (100)			

AH, Antihistamine.
*Based on χ^2 statistic with correction for 0.5 continuity correction.
†The 1 anaphylaxis and epinephrine use in the double-placebo group was due to accidental ingestion of peanut (a sibling's peanut dose).

events per patient, IRR, 0.61 [95% CI, 0.27-1.37]) and elevated in both OIT groups compared with double-placebo (0.8 events per patient; comparison of OIT with placebo antihistamines vs double-placebo, IRR, 5.31 [95% CI, 2.53-11.16]; OIT with antihistamines vs double-placebo, IRR, 3.24 [95% CI, 1.55-6.74]).

Table II presents that antihistamine premedication, compared with placebo premedication, increased the incidence of neuropsychiatric events (3.35 vs 1.06 events per patient, IRR, 3.16 [1.84-5.42]), primarily tiredness and dizziness.

The risks of discontinuation, anaphylaxis, epinephrine use, and wheezing were all uncommon and not statistically different between groups (Table IV). Other adverse reactions were similar between those assigned to peanut OIT with or without premedication and were generally higher than those on double-placebo (see Table E4 in this article's Online Repository at www.jaci-inpractice.org).

Food challenge eliciting doses. After 12 months of treatment, patients underwent blinded placebo-controlled oral

TABLE V. Desensitization

Variable	Category	Peanut OIT $H_1 + H_2$ AH (group 1; n = 17)	Peanut OIT placebo AH (group 2; n = 16)	Placebo OIT placebo AH (group 3; n = 10)	Comparison of means*	Mean difference (95% CI)	*P* value
Cumulative dose (mg), n, mean ± SD	Baseline	17, 45.53 ± 50.32	16, 26.13 ± 25.16	10, 14.9 ± 13.57	—	—	—
Cumulative dose (mg), n, mean ± SD	Post	11, 3697.7 ± 734.9	14, 3592.9 ± 1121.310	18.7 ± 28.72	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	−46.20 (−675.84 to 583.44) 3513.62 (2891.18 to 4136.06) 3467.42 (2764.84 to 4170.00)	.886 <.001 <.001

Variable	Category	Peanut OIT $H_1 + H_2$ AH (n = 17)	Peanut OIT placebo AH (n = 16)	Placebo OIT placebo AH (n = 10)	Comparison of proportions	Risk ratio (95% CI)	*P* value
Cumulative dose post 100 mg or more, n (%)	Yes	11 (64.7)	13 (81.3)	1 (10)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	1.08 (0.93 to 1.25) 9.29 (1.44 to 59.95) 10.00 (1.56 to 4.20)	>.999 <.001 <.001
	No	0 (0)	1 (6.25)	9 (90)			
	Missing	6 (35.3)	2 (12.5)	0 (0)	—	—	—
Cumulative dose post 1000 mg or more, n (%)	Yes	11 (64.7)	13 (81.3)	0 (0)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	1.08 (0.93 to 1.25) 19.80 (1.31 to 298.57) 21.08 (1.40 to 317.07)	>.999 <.001† <.001†
	No	0 (0)	1 (6.3)	10 (100)			
	Missing	6 (35.3)	2 (12.5)	0 (0)	—	—	—
Cumulative dose post 4000 mg or more, n (%)	Yes	9 (52.9)	12 (75.0)	0 (0)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.96 (0.67 to 1.36) 18.33 (1.21 to 277.62) 17.42 (1.14 to 265.34)	>.999 <.001† <.001†
	No	2 (11.8)	2 (12.5)	10 (100)			
	Missing	6 (35.3)	2 (12.5)	0 (0)	—	—	—

AH, Antihistamine.
*Estimates adjusted for cumulative dose (mg peanut protein) at baseline.
†Based on χ^2 statistic with correction for continuity ($^1/_2$ used).

TABLE VI. FAQLQ-PF health-related QoL summary score

Variable	Category	Peanut OIT $H_1 + H_2$ AH (group 1; n = 17)	Peanut OIT placebo AH (group 2; n = 16)	Placebo OIT placebo AH (group 3; n = 10)	Comparison of means*	Mean difference (95% CI)	*P* value
Baseline n, mean ± SD		16, 4.33 ± 1.23	15, 3.83 ± 1.15	10, 4.02 ± 1.05	—	—	
Post n, mean ± SD		12, 4.36 ± 1.10	14, 3.28 ± 0.99	10, 3.63 ± 0.62	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.79 (0.21 to 1.37) −0.18 (−0.78 to 0.43) 0.61 (−0.01 to 1.24)	.009 .56 .053
					Comparison of proportions	Risk ratio (95%CI)	*P* value
Worsened, n (%)	Yes	6 (35.29)	3 (18.75)	2 (20)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	1.71 (0.82-3.60) 1.03 (0.46-2.33) 1.61 (0.82-3.15)	.17 .93 .19
	No	7 (35.29)	11 (68.75)	8 (80)			
	Missing	4 (23.53)	2 (12.50)	0 (0)	—	—	—
Improved, n (%)	Yes	2 (11.76)	6 (37.5)	5 (50)	Group 1 vs 2 Group 2 vs 3 Group 1 vs 3	0.43 (0.12-1.52) 0.89 (0.44-1.77) 0.42 (0.12-1.40)	.12 .73 .07
	No	11 (64.71)	8 (50.00)	5 (50)			
	Missing	4 (23.53)	2 (12.50)	0 (0)	—	—	—

AH, Antihistamine; *FAQLQ-PF*, Food Allergy Quality of Life Questionnaire Parental Form.
*Estimates adjusted for score at baseline (no significant baseline by treatment interactions).

food challenge in hospital. The mean cumulative eliciting dose was 19 ± 29 mg peanut protein in the double-placebo group, 3643 ± 1053 mg in the OIT and placebo antihistamines group, and 3683 ± 724 in the OIT with antihistamines group (Table V).

Quality of life. Mean quality-of-life scores at the end of the study were 4.36 ± 1.10 in the combined peanut OIT and $H_1 + H_2$ antihistamines group, 3.28 ± 0.99 in the combined peanut OIT and placebo antihistamines group, and 3.63 ± 0.62 in the double-placebo group (Table VI). Although small differences

were found between the combined peanut OIT and $H_1 + H_2$ antihistamines group and the other 2 groups, there were no differences between the peanut OIT + placebo antihistamines and double-placebo groups, and responder analyses showed that all 3 groups similarly improved and worsened by the minimally important difference of 0.5 points in QoL. Comparisons of changes in the subdomains, emotional impact, food anxiety, and social and dietary limitations showed similar results (see Table E5 in this article's Online Repository at www.jaci-inpractice.org).

DISCUSSION

Among children with peanut allergy, antihistamines cotreatment with peanut OIT reduced the frequency of moderate to severe but not mild adverse events and both types were elevated compared with no peanut OIT (double-placebo). Peanut OIT with or without antihistamines induced similar degrees of desensitization. Despite this, changes in QoL, both improvements and worsening, were similar whether patients were treated with peanut OIT or placebo OIT and regardless of antihistamines cotreatment. Antihistamines premedication increased neuropsychiatric adverse events, primarily fatigue and dizziness.

The use of antihistamines during aeroallergen and Hymenoptra allergen immunotherapy in general is common.[3,5] This is the first RCT to inform the impact of antihistamines premedication for peanut OIT. That antihistamines reduced moderate to severe but not mild OIT-induced adverse events and yet did not lead to important improvements in QoL suggests that more than just OIT-induced adverse events determine changes in QoL. The combined peanut OIT with antihistamines group had statistically worse QoL compared with the combined OIT with placebo antihistamines or double-placebo groups, which might be explained due to additional adverse effects (eg, sedation and dizziness) from added use of antihistamines. Responder analyses, however, showed that neither the double-placebo nor peanut OIT groups differed importantly; all groups similarly improved and worsened. These findings may also be consistent with antihistamines contributing only partially to immediate and delayed hypersensitivity reactions,[10,11] and one explanation for our findings might be that the benefits of antihistamines do not yield enough of a reduction in adverse events to translate into important QoL improvements. This is particularly relevant because the discontinuation rate among placebo-treated participants was 0%, whereas it was similar in both groups of OIT-treated patients (16% overall), consistent with other RCTs.[2,13] Multiple participants also reported taste aversion, and some developed behaviors such as hiding peanut doses or being diagnosed with anxiety. Because no patients treated with double-placebo developed such behaviors, the extent by which OIT-induced adverse reactions might facilitate psychoneuroimmune alterations requires further study. Together, these findings suggest that safer and less burdensome ways of treating food allergy are needed for patients with peanut allergy.

Although antihistamines are widely accessible, their modest benefits suggest that research priorities might favor interventions that target more upstream molecules in the cascade of immune events driving immediate hypersensitivity.[10,11] In this regard, the OUtMATCH study (NCT03881696) will inform the comparison of anti-IgE using omalizumab with or without OIT. Should combined treatment with both omalizumab and OIT prove to be highly effective in mitigating the large increase in adverse reactions induced by OIT, questions of affordability, cost effectiveness, and equity will arise using the combination of a biologic and the high price of current forms of OIT. For now, patients and caregivers who wish to pursue OIT will have to weigh the existing burdens and cost of such a treatment with whether the added burdens of using antihistamines routinely is worth the modest decrease in primarily skin, and possibly abdominal pain, adverse events, and no definite improvement in QoL.

Strengths of this study include being the first study to address antihistamine premedication, blinding of patients and multiple study personnel, and focus on patient-important outcomes of allergic reactions over time and QoL.

There are several limitations to this study. First, this RCT is small, albeit consistent in size and studied population of most other peanut OIT studies (median, 43 participants among RCTs systematically reviewed[2,13,14]), precluding very precise effect estimates though it supports no large differences in adverse effects or QoL with antihistamine use during OIT. We maximized power and accounted for any chance minor imbalance in baseline characteristics using analysis of covariance. With larger studies, it might be possible to detect more important differences in adverse effects between OIT groups using or not using antihistamines. Adverse effects caused discontinuation in 16% of individuals assigned to OIT, meaning that assessments such as QoL could be biased toward being overly optimistic about OIT because the QoL of those who experienced poor outcomes were not fully captured. We excluded people who were too sensitive (reacted to $\leq$2 mg at baseline food challenge), so the incidence of adverse reactions might be an underestimate if applied to peanut-allergic patients with any sensitivity. Given the low rate of systemic reactions and epinephrine use, this study does not definitively answer whether or not antihistamine use with OIT masks early manifestations of systemic reactions, which might delay prompt epinephrine administration. We used standard dosing for H_1 and H_2 antihistamines, which have been shown to be effective in reducing local and systemic reactions during allergen immunotherapy to pollens and venom,[4,7] but it is possible that higher doses could be more efficacious because studies in urticaria have shown that up to 4 times the standard dose of antihistamines can be necessary to adequately control urticaria and angioedema.[18] Higher doses of antihistamines may also have more side effects, which patients may prefer to avoid. We report outcomes after 12 months, and it is possible that longer duration of therapy would improve desensitization outcomes further, though QoL remains highly uncertain.[19] There is, however, increased risk of bias over time due to drop out and the potential for overly optimistic estimates that favor OIT groups over control groups due to differential drop out (and their underlying reasons). The H_2 antihistamine used in this trial was ranitidine, and this drug is available in multiple countries but currently not the United States, which could limit study generalizability. Other H_2 blockers such as famotidine, however, are used interchangeably with ranitidine (eg, for gastric acid suppression and as an adjuvant for H_1 antihistamine action in chronic urticaria[18]) and therefore these findings might apply to other H_2 blockers.

PISCES shows that peanut OIT causes a high incidence of adverse reactions that is modestly mitigated with H_1 and H_2 antihistamines, and no clear improvement over placebo OIT in food allergy–related QoL despite OIT effectively inducing desensitization. Safer food allergy treatment approaches that

importantly improve patient and family QoL need to be proved in robust randomized trials.

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