Changing patient mindsets about non–life-threatening symptoms during oral immunotherapy: a randomized clinical trial

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Abstract: Background: Oral immunotherapy (OIT) can lead to desensitization to food allergens, but patients can experience treatment-related symptoms of allergic reactions that cause anxiety and treatment dropout. Interventions to improve OIT for patients are needed. Objective: To determine whether fostering the mindset that non–life-threatening symptoms during OIT can signal desensitization improves treatment experience and outcomes. Methods: In a randomized, blinded, controlled phase II study, 50 children/adolescents (28% girls, aged 7-17 years, M = 10.82, standard deviation = 3.01) completed 6-month OIT for peanut allergies. Patients and their parent(s) had monthly clinic visits at the Sean N. Parker Center for Allergy and Asthma Research between January 5, 2017, and August 3, 2017. All families received identical symptom management training. In a 1:1 approach, 24 patients and their families were informed that non–life-threatening symptoms during OIT were unfortunate side effects of treatment, and 26 patients and their families were informed that non–life-threatening symptoms could signal desensitization. Families participated in activities to reinforce these symptom mindsets. Results: Compared with families informed that symptoms are side effects, families informed that symptoms can signal desensitization were less anxious (B = −0.46, 95% confidence interval [CI]: −0.76 to −0.16; P = .003), less likely to contact staff about symptoms (5/24 [9.4%] vs 27/154 [17.5%] instances; P = .036), experienced fewer non–life-threatening symptoms as doses increased (BInteraction = −0.54, 95% CI: −0.83 to −0.27; P < .001), less likely to skip/reduce doses (1/26 [4%] vs 5/24 [21%] patients; P = .065), and showed a greater increase in patient peanut-specific blood IgG4 levels (BInteraction = 0.76, 95% CI: 0.36 to 1.17; P < .001). Conclusions: Fostering the mindset that symptoms can signal desensitization improves OIT experience and outcomes. Changing how providers inform patients about non–life-threatening symptoms is a promising avenue for improving treatment.

DOI: https://doi.org/10.1016/j.jaip.2019.01.022

Howe, Lauren C; Leibowitz, Kari A; Perry, Margaret A; Bitler, Julie M; Block, Whitney; Kaptchuk, Ted J; Nadeau, Kari C; Crum, Alia J (2019). Changing patient mindsets about non–life-threatening symptoms during oral immunotherapy: a randomized clinical trial. The Journal of Allergy and Clinical Immunology: In Practice, 7(5):1550-1559.
DOI: https://doi.org/10.1016/j.jaip.2019.01.022

Title: Changing Patient Mindsets About Non-Life-Threatening Symptoms During Oral Immunotherapy: A Randomized Clinical Trial

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Declarations of interest: none

Funders/sponsors: AJC supported by NIH/NCCIH Grant #DP2AT009511 and Foundation for the Science of the Therapeutic Encounter. KCN supported by Naddisy Foundation, FARE Center of Excellence, NIAID, and Sean N. Parker Foundation for Allergy & Asthma Research. LCH supported by the Shaper Family Stanford Interdisciplinary Graduate Fellowship. KAL supported by a Stanford Interdisciplinary Graduate Fellowship.

Role of the funding source: Funders/sponsors were not involved in the design and conduct of the study or collection, management, analysis, and interpretation of the data or the decision to submit the manuscript for publication.

Word count main text: 3,491 words

Word count abstract: 250 words

Abstract:

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Objective: To determine whether fostering the mindset that non-life-threatening symptoms during OIT can signal desensitization improves treatment experience and outcomes.

Methods: In a randomized, blinded, controlled phase II study, 50 children/adolescents (28% girls, aged 7-17, *M*=10.82, *SD*=3.01) completed six-month OIT for peanut allergies. Patients and their parent(s) had monthly clinic visits at the Sean N. Parker Center for Allergy & Asthma Research between 1/5/2017-8/3/2017. All families received identical symptom management training. In a 1:1 approach, 24 patients and their families were informed that non-life-threatening symptoms during OIT were unfortunate side effects of treatment, and 26 patients and their families were informed that non-life-threatening symptoms could signal desensitization. Families participated in activities to reinforce these symptom mindsets.

Results: Compared to families informed that symptoms are side effects, families informed that symptoms can signal desensitization were less anxious (B=-0.46, 95% CI (-0.76 to -0.16), p=0.003), less likely to contact staff about symptoms (5/24[9.4%] vs. 27/154[17.5%] instances, p=0.036), experienced fewer non-life-threatening symptoms as doses increased ($B_{\text{Interaction}}$=-0.54(-0.83 to -0.27), p<0.001), less likely to skip/reduce doses (1/26[4%] vs. 5/24[21%] patients, p=0.065), and showed greater increase in patient peanut-specific blood IgG4 levels ($B_{\text{Interaction}}$=0.76(0.36 to 1.17), p<0.001).

Conclusion: Fostering the mindset that symptoms can signal desensitization improves OIT experience and outcomes. Changing how providers inform patients about non-life-threatening symptoms is a promising avenue for improving treatment.

Trial Registration: clinicaltrials.gov NCT03513965

Word count abstract: 250 words

Highlights:

What is already known about this topic? Past studies have explored different ways of framing the prevalence of side effects to reduce their occurrence. No previously published studies have investigated the consequences of changing patients' mindsets about symptoms.

What does this article add to our knowledge? This is the first study to show that informing oral immunotherapy (OIT) patients that non-life-threatening symptoms of OIT can signal increasing desensitization can reduce patient and family anxiety and improve treatment experience and outcomes.

How does this study impact current management guidelines? This study provides initial evidence for a novel, promising strategy to improve OIT treatment experience and outcomes. It suggests that changing how providers inform patients about non-life-threatening symptoms of OIT will benefit patients and their families.

Keywords: allergy, food allergy, oral immunotherapy, peanut allergy, mindsets, patient experience, allergic symptoms, pediatric allergy

Abbreviations:

IgE=immunoglobulin E antibodies.

IgG4=immunoglobulin G antibodies.

IRB=Institutional Review Board.

92 *OIT*=oral immunotherapy.

93 *SAPS* = "Symptoms as Positive Signals" condition, in which patients and their parent(s)

94 were informed that non-life-threatening symptoms during OIT could be associated with

95 desensitization.

96 *SASE* = "Symptoms as Side Effects" condition, in which patients and their parent(s) were

97 informed that non-life-threatening symptoms during OIT are unfortunate side effects of

98 treatment.

99 *SNPC* = Sean N. Parker Center for Allergy & Asthma Research at Stanford University.

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Introduction

Approximately 5.9 million American children/adolescents have a food allergy.[1] Oral immunotherapy (OIT) is a promising treatment[2] in which patients consume gradually increasing doses of their allergen to build desensitization, which protects from accidental exposure and improves quality of life.[3] Some patients experience allergic symptoms after consuming doses.[4,5] Non-life-threatening symptoms patients may experience (e.g., itchy mouth, congestion) are generally mild, but may nonetheless provoke anxiety because of their association with allergic reactions. Symptoms can even prevent treatment completion.[5-7] Evidence-based strategies for improving OIT experience are needed.

Providers have an ethical responsibility to inform patients about possible treatment-related symptoms. However, the relationship of symptoms to treatment is often multifaceted and symptoms are sometimes associated with healing. For example, fevers, while uncomfortable, signal that the body is fighting infection and aid healing (e.g., bolstering immune function).[8] Wound inflammation (e.g., swelling) indicates that mast cells are releasing enzymes, histamines, and other amines as part of healing.[9] Delayed onset muscle soreness (DOMS) occurs when muscles are used vigorously, perhaps because of muscle micro-damage and inflammation,[10] but can signal that the body is strengthening. Symptoms during OIT could be interpreted similarly. Desensitization is believed to begin with the uptake of allergens in the mucosa of the oral cavity,[2] which might be associated with mild, transient symptoms like itchy mouth and/or congestion. Non-life-threatening symptoms could thus be understood as evidence that the treatment is active in the body and possibly increasing desensitization. Although the effects of symptoms are complex, patients may focus solely on negative aspects (e.g.,

discomfort) and fail to recognize that symptoms can be associated with treatment progress. For example, people are often unaware that fevers are part of healing and over-treat them.[11]

A person's mindset, or the particular lens through which information is perceived and interpreted, simplifies many possible interpretations of complex realities such as the relationship between symptoms and treatment. For example, past research has shown that people adopt different mindsets about stress: that it tends to have detrimental health effects (e.g., increasing disease risk) or that it can have beneficial health effects (e.g., enhancing cognitive function).[12] The true nature of stress is paradoxical; it can be both enhancing and debilitating. But informing people that stress can be enhancing shifts their mindsets about stress (i.e., what they focus on and therefore expect) to selectively interpret stress as enhancing, which consequently shapes responses to stressors.[12-14] By orienting a person toward one aspect of a complex reality, mindsets influence how people interpret and experience health-relevant situations and their health outcomes.[12-20]

When providers inform patients about possible symptoms, distinguish between life-threatening and non-life-threatening symptoms, and teach patients strategies for managing symptoms, they may unintentionally convey the message that symptoms are a negative aspect of treatment that should be avoided. This "symptoms as side effects" mindset may lead to anxiety and discouragement, a tendency to interpret symptoms as a sign that treatment is going poorly, and skipping doses to avoid symptoms. Alternatively, if providers additionally inform patients that non-life-threatening symptoms can sometimes signal that treatment is progressing positively into desensitization, it may prompt patients who experience these symptoms to adopt a mindset of symptoms as positive signals that the treatment is active in the body, and that it is potentially improving outcomes (i.e., desensitization). Although patients with a "symptoms as positive

signals" mindset may still be uncomfortable while experiencing mild symptoms, these symptoms may be interpreted as a positive signal that treatment is progressing as expected, towards desensitization. These patients may then feel less anxious about symptoms and be less likely to skip doses to avoid symptoms or drop out of OIT. The most effective and safe treatment would teach patients to treat non-life-threatening and life-threatening symptoms in an evidence-based, standardized fashion while at the same time helping them to adopt useful mindsets about non-life-threatening symptoms.

The current study sought to experimentally examine whether changing mindsets about non-life-threatening symptoms during OIT improves treatment experience and outcomes. Compared to the more typical approach of informing patients and parents that "symptoms are unfortunate side effects of treatment," fostering the mindset of "symptoms as positive signals" that can be associated with desensitization may improve subsequent OIT outcomes.

Methods

Study Design

This was a parallel, randomized phase II controlled trial conducted from 1/5/2017 to 8/3/2017. All procedures were approved by Stanford University's Institutional Review Board (IRB, Protocol #36282). Adults provided written informed consent and children/adolescents provided written assent. Study registered on clinicaltrials.gov (NCT03513965).

Participants

The Sean N. Parker Center for Allergy & Asthma Research at Stanford University (SNPC) recruited fifty patients aged 7-17 (power analysis in Methods, Online Repository). Eligible patients either had peanut-specific blood IgE (immunoglobulin E antibodies) level ≥60 Ku/L, or peanut-specific IgE levels <60 with peanut-specific skin prick test greater than 3mm and

peanut-specific IgE >5 Ku/L. Patients with anxiety and/or mood disorders (e.g., generalized anxiety disorder, bipolar disorder) diagnosed by a mental healthcare professional were excluded, following standard SNPC protocols. One potential participant was excluded on this basis. Additional detail and exclusion criteria in Methods, Online Repository.

Procedures and Intervention

Patients consumed doses at home over 24 weeks (dosing schedule in Table E1, Online Repository). Families were randomly assigned to either the "Symptoms as Positive Signals" (SAPS) condition or the "Symptoms as Side Effects" (SASE) condition. SAPS and SASE groups never interacted.

Families attended monthly group clinic visits by condition (six to seven patients per group) at SNPC throughout the 7-month study to participate in treatment-relevant activities. Each parent had a monthly call with the head of the patient support team, during which parents could express concerns about treatment or symptoms. Parents were encouraged to contact the head of the patient support team and/or the physician administering treatment with questions/concerns anytime.

Both groups received identical OIT instructions, including practical dosing strategies and symptom management (Appendix EA, Online Repository). To promote safety, all families were given identical training medication use (e.g., antihistamines) for non-life-threatening symptoms and comprehensive instructions for recognizing potentially life-threatening symptoms and administering injectable epinephrine when appropriate. Families were provided with materials to remind them of these steps (Figure E1, Online Repository). All families had the same access to resources (e.g., staff support) and patients' symptoms were carefully monitored.

SAPS families were additionally encouraged to think of symptoms as a positive signal associated with increasing desensitization. This mindset was reinforced using written information (Figure E2, Online Repository) and activities (Table 2) at monthly clinic visits throughout OIT (details in Methods, Online Repository). For example, children wrote letters to their "future selves" including either a reminder of a way to manage symptoms or a reminder that symptoms can signal that treatment is working. Mindsets were reinforced through direct communication with the patient support team when appropriate.

Randomization and Masking

SNPC staff and study personnel enrolled patients in the study. In a 1:1 approach, at enrollment, eligible study patients were randomly assigned to either the SAPS or SASE groups by the specific time block of the study they attended (see Methods, Online Repository). Patients/parents were masked to group assignment. Because of the intervention's nature, masking study personnel who delivered the intervention was not possible.

Measures

Patients and/or their parents completed daily online questionnaires through REDCap;[21] respondents indicated whether the child alone, parent alone, or parent/child together had completed the survey. Patients and parents each completed their own surveys at each monthly clinic visit.

Endpoints - Treatment Experience

Symptom mindsets: Patients/parents answered clinic survey questions about whether symptoms signal increasing desensitization (see measures in Methods, Online Repository).

Symptom anxiety: In clinic surveys, patients/parents who indicated that they/their child had experienced symptoms during the past month were asked how anxious they were about these symptoms (1=*not worried at all,* 4=*extremely worried*).

Dosing experience: In REDCap, respondents indicated how well dosing went on a given day (1=*very badly,* 4=*very well*).

Staff contact about symptoms: Researchers recorded how often parents contacted the patient support team with questions. An independent coder evaluated whether contact concerned symptoms.

Symptom occurrence: In REDCap, respondents indicated if they had experienced symptoms after each dose (yes/no) and selected specific symptoms experienced. *Non-life-threatening symptoms* included: swelling of lips/face, itchy mouth/throat, itchy skin, stomach pain, nausea, nasal congestion, diarrhea, hives, rash/redness/blotchiness, light-headedness, other. *Potentially serious symptoms* included: trouble breathing, tightness in throat, repetitive cough, vomiting, voice change/hoarseness.

Endpoints - Treatment Outcomes

Adherence: In REDCap, respondents indicated whether they had taken a partial/no dose and why: 1=advised by patient support team, 2=due to illness not related to dosing, 3=forgot, 4=due to travel, 5=no doses (e.g., ran out of supplies), 6=due to symptoms from dosing, 7=apprehensive about a possible reaction, 8=other. Patients were coded as skipping/reducing a dose because of symptoms if they/their parents indicated they did not take their full dose because of symptoms or apprehension about reactions.

Time to treatment completion: Researchers recorded whether patients completed treatment within the scheduled 24 weeks, or whether it took them an additional two or more weeks (the time period between each scheduled updose) to reach the final updose.

Biomarkers associated with desensitization: Blood samples were taken pre-OIT at the first clinic visit and again at 24 weeks for those patients who consented (14 SAPS patients, 16 SASE patients) and assayed for peanut-specific blood IgE/IgG4 levels. Prior research suggests that IgG4 levels may indicate OIT-related desensitization[,22-27] but offers mixed evidence as to whether IgE levels change during OIT, sometimes showing post-treatment decline.[5,23]

Statistical Analysis

Clinic survey and REDCap data were analyzed using multilevel longitudinal models; blood sample data were analyzed using multiple linear regression (additional details in Methods, Online Repository).

Results - Participants

Fifty children/adolescents (36 boys[72%], 14 girls[28%], 20 White[40%], 17 Asian[34%], one African-American[2%], 12 multiple race/ethnicity[24%]) with severe peanut allergies participated in the study. Patients were aged 7-17 (M_{Age}=10.82, *SD*=3.01). Patients were recruited into the study from 11/14/2016 to 1/4/2017. For baseline characteristics, see Table 1. No patients withdrew from the study or were excluded from analyses (see Figure 1). Families reported high levels of anxiety about treatment ("How nervous are you about the dosing process?", 1=*not nervous at all,* 4=*extremely nervous*) and symptoms ("How nervous are you about the possible symptoms or side effects of the dosing process?", 1=*not nervous at all,* 4=*extremely nervous*) (see Table 3). There were no baseline differences in groups in treatment-

related anxiety (M_{SAPS}=2.63, *SD*=0.99; M_{SASE}=2.67, *SD*=1.02), *t*(90)=0.20, *p*=0.843, or symptom-related anxiety (M_{SAPS}=2.84, *SD*=0.92; M_{SASE}=2.72, *SD*=0.88), *t*(90)=-0.61, *p*=0.541.

Results – Treatment Experience

Effect on Symptom Mindsets

SAPS families endorsed the mindset of symptoms as positive signals to a greater extent than SASE families, *B*=0.32, 95% CI (0.12 to 0.53), *SE*=0.10, *t*(67.05)=3.17, *p*=0.002. This difference persisted at three and six months post-treatment in an IRB-approved follow-up (Supplemental Analyses in Online Repository). Adoption of the mindset was also evident in participants' open-ended responses from clinic visit activities (Appendix EB, Online Repository). Notably, families of SAPS patients who experienced no symptoms in a given month did not evince greater concern that the treatment might not be working than families of SASE patients who in a given month experienced no symptoms, *B*=-0.03(-0.24 to 0.18), *SE*=0.11, *t*(59.69)=-0.30, *p*=0.766; a lack of symptoms did not appear to become a negative signal in the SAPS condition. In both conditions, clinic sessions were evaluated equally positively (e.g., utility, enjoyableness), and families did not differ in perceptions of treatment efficac7 (Supplemental Analyses, Online Repository). Families thus had similar experiences except for the different symptom mindsets.

Effect on Symptom Anxiety

SAPS families whose child experienced symptoms during a given month reported being less anxious about these symptoms, *B*=-0.46(-0.76 to -0.16), *SE*=0.15, *t*(69.28)=-3.03, *p*=0.003 (see Figure 2).

This pattern did not change over the course of treatment; an interaction with month was non-significant, *B*=-0.05(-0.14 to 0.04], *SE*=0.05, *t*(54.55)=-1.10, *p*=0.277. This pattern did not

differ between patients and parents; when an interaction with respondent was included in the model, it was non-significant, B=-0.14(-0.74 to 0.47), SE=0.31, t(68.81)=-0.45, p=0.657.

Effect on Dosing Experience

SAPS families were less likely to report through REDCap that dosing had *not* gone well on days when symptoms occurred. Respondents reported that the dosing went "very well" for 7,440/8,164[91.1%] doses, so we dichotomized the variable such that 0 indicated that a respondent reported that the dosing had gone very well, and 1 indicated otherwise. There was a significant interaction between intervention group and symptom occurrence, B=-1.81(-2.66 to -0.99), SE=0.43, z=-4.25, p<0.001 (Figure E3, Online Repository). When no symptoms occurred, there was no difference between the two groups in how well respondents reported the dosing went, $B_{\text{SimpleEffect}}$=0.38(-1.05 to 1.79), SE=0.71, z=0.54, p=0.592. But when patients did experience symptoms, respondents in the SAPS group were somewhat less likely to report that the dosing had not gone well, $B_{\text{SimpleEffect}}$ = -1.43(-2.92 to 0.00), SE=0.73, z=-1.96, p=0.050. In other words, SAPS families were less likely to associate symptoms with concerns that the treatment was going poorly. (Models including an interaction with assigned dose size did not converge, so it is unclear whether this varied over time.)

Effect on Staff Contact About Symptoms

SAPS parents were also less likely to contact staff with concerns about non-life-threatening symptoms (15/159[9.4%] instances) than SASE parents (27/154[17.5%] instances), $\chi^2(1)$=4.42, p=0.036, though the overall number of instances of contact (including calls regarding administrative issues, scheduling conflicts) did not differ by condition (Table E2, Online Repository).

Effect on Symptom Occurrence

Most patients did not experience non-life-threatening symptoms from dosing (only 538/8498[6.3%] doses resulted in symptoms), so we dichotomized the variable such that 1 indicated a patient experienced at least one symptom, and 0 indicated a patient reported no symptoms (specific symptom rates in Table E3, Online Repository).

When examining the occurrence of symptoms throughout the study period, there was a significant quadratic interaction such that SAPS patients were less likely to experience non-life-threatening symptoms as dose sizes increased toward one peanut, B=-0.54(-0.83 to -0.27), SE=0.14, z=-3.88, p<0.001 (see Figure 4); the model including the quadratic interaction explained significantly more variance than a model with a linear interaction, $\chi^2(2)=18.68$, p<0.001. Floodlight testing[28] revealed that, at the lowest dose size, conditions did not differ in the occurrence of non-life-threatening symptoms, B=0.09(-0.85 to 1.04), SE=0.46, z=0.19, p=0.849, nor did they halfway through treatment, B=0.45(-0.56 to 1.46), SE=0.50, z=0.91, p=0.365. However, at the largest dose size, SAPS patients were less likely to experience non-life-threatening symptoms than SASE patients, B=-1.63(-2.85 to -0.42), SE=0.60, z=-2.69, p=0.007. Effects were similar for an analysis testing condition differences on all symptoms experienced (e.g., including potentially serious symptoms such as trouble breathing and vomiting, see Supplemental Analyses, Online Repository). No patient in the course of the study needed to use an injectable epinephrine device in response to symptoms.

Results – Treatment Outcomes

Effect on Adherence

Few patients skipped/reduced doses because of symptom-related anxiety (6/50[12%] patients did at least once during treatment). One of 26 SAPS patients (4%) skipped or reduced a dose because of symptom-related anxiety, compared to five of 24 SASE patients (21%), $\chi^2(1)=3.41$,

p=0.065, offering preliminary evidence that the mindset intervention increased adherence.

Effect on Time to Treatment Completion

48 of 50 patients completed treatment in 24 weeks. Two SASE patients had a prolonged updose phase due to symptoms and completed treatment by 35 weeks. This rate of timely completion (100% for SAPS patients, and 92% for SASE patients) is greater than those observed in other studies (between 76% to 93% with various dosing schedules[5-7]).

Effect on Biomarkers Associated with Desensitization

Compared to baseline levels, SAPS patients' IgG4 levels increased to a greater extent over treatment (M_{Diff}=1.85, t(13)=6.91, p<0.001) than SASE patients (M_{Diff}=1.31, t(15)=5.55, p<0.001), $B_{Interaction}$=0.76(0.36 to 1.17), SE=0.20, t(26)=3.88, p<0.001 (see Figure 4). A nonparametric Mann-Whitney U-test assessing between-group differences in change in IgG4 levels from pre-OIT to post-OIT ($Median_{SASE}$=1.47; $Median_{SAPS}$=4.16) showed similar results, W=75, p=0.065 (see Table E4 and Figure E6). SAPS and SASE patients did not differ in their changes in IgE levels, $B_{Interaction}$=-0.03(-0.23 to 0.17), SE=0.10, t(26)=-0.35, p=0.732 (Figure E4, Online Repository), and also did not differ in their changes in IgG4/IgE ratios (Figure E5 and Supplemental Analyses, Online Repository).

Discussion

Although all study patients had good outcomes (e.g., achieving desensitization by 35 weeks of treatment), the "symptoms as positive signals" mindset (SAPS condition) improved treatment experience (e.g., anxiety, symptom rates) and outcomes (e.g., adherence, change in peanut-specific blood IgG4 levels) over-and-above the "symptoms are side effects" mindset (SASE condition). SAPS families reported less symptom-related anxiety and were less likely to contact staff with concerns about symptoms (notable because advising patients over phone/e-

mail is demanding for providers, particularly when patients are anxious[29]). SAPS patients' physical health also benefitted. SAPS patients were less likely to experience symptoms at the end of treatment when doses were highest and used real peanuts as opposed to peanut flour, which is notable because symptom occurrence can prevent or delay OIT completion.[5-7] Additionally, SAPS patients showed a greater increase in biomarkers associated with desensitization, indicating that changing mindsets bolstered a physiological marker related to OIT success. Importantly, these effects were achieved while distinguishing between life-threatening and non-life-threatening symptoms, ensuring the safety of all patients. This aligns with a larger body of work suggesting that mindsets shape physiological health outcomes[12-20] and can influence the course of medical treatment.

The difference in IgG4 increase between SAPS/SASE patients is important and intriguing. It is possible that SAPS patients experienced less overall stress, leading to fewer proinflammatory markers and more immunomodulatory markers and ultimately IgG4 synthesis. Or, SASE patients' higher anxiety levels may have muted immunologic changes that otherwise would have occurred. The link between anxiety, stress, and the immune system is robust but further studies are needed to test the association between mindset changes and immune modulation.[30]

The group format in which OIT was administered was not the central focus of the current study, but this format for delivering treatment differed from treatment-as-usual. Both SAPS and SASE conditions included ample social support for patients and parents, both from their fellow group members and from the patient support team, which may in part explain the high rates of treatment completion observed (>90% in each group vs. 76%-93% in existing studies[5-7]). Indeed, patient and parent feedback in both groups indicated that this group format was extremely useful (Appendix EC, Online Repository). A qualitative review of these reports

suggests that the group format was equally beneficial for both groups with respect to learning about practical strategies and the treatment process as well as gaining emotional support and a sense of shared experience. At the same time, the group format may have also fostered further integration of the mindsets due to the social and normative influence embedded in group discussions.[31,32] In light of these potential benefits of delivering OIT, future research should more directly evaluate how the social components intertwined in the group format might add to or interact with the mindset intervention to optimize patient outcomes as compared to treatment as it is typically delivered.[15,16,33]

Limitations

This initial research was conducted at a single site under the supervision of one healthcare provider; larger, multisite studies with diverse patient populations are needed. Findings regarding biomarkers are limited in that a subset of participants provided blood samples; larger studies are needed. This intervention involved several hour-long educational meetings; shorter interventions may be just as effective at changing mindsets.[12,18] Future research should explore the effects of simpler interventions to alter mindset as well as directly evaluate the efficiency and added efficacy of the group format. Though steps were taken to prevent treatment diffusion (e.g., SAPS and SASE groups never interacted), over time, SASE families began to agree more that symptoms can be a positive signal, though at the conclusion of treatment SAPS families still endorsed this mindset marginally significantly more than SASE families (see Supplemental Analyses). This may be a result of repeatedly answering questions about this mindset during clinic surveys. The results of the current study may thus underestimate the effect of changing symptom mindsets.

Though patients and their parent(s) in the current study reported high levels of anxiety at baseline, patients with a diagnosed anxiety disorder were excluded. Future research should assess whether this intervention can benefit sensitive populations, such as those with clinical levels of anxiety. This initial research was conducted with peanut allergies (one of the most prevalent food allergies), and future research should test these strategies in the context of other allergies and conditions. These findings may apply to other treatments in which common symptoms can signal that a treatment is working (e.g., fevers resulting from vaccines are deemed normal, harmless, and possibly helpful[34]).

Conclusions

This research adds to a growing body of work suggesting the need to systematically understand and leverage the psychosocial factors influencing treatment outcomes.[15,16,33] It demonstrates that treatment experience and outcomes (i.e., desensitization) can be improved by considering patient mindsets. Distinguishing between serious, debilitating side effects and mild symptoms that can signal treatment efficacy is a novel solution to the ethical and important need to disclose symptoms without causing unnecessary harm. These findings suggest that intervening to change patient mindsets about treatments broadly, and symptoms in particular, is a potential route for medical clinics and providers to help patients cope with challenging medical treatments and may benefit both patient experience and physiological treatment outcomes.

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Acknowledgments: We thank Marté Matthews, Frances Meneses, Natasha Purington, Alicia Rodriguez, Dana Tupa, and Sharon Chinthrajah for their invaluable assistance.

Author contributions: Dr. Howe had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of data analysis.

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Table 1. Baseline patient characteristics for all patients in the study, and patients who volunteered blood samples pre- and post-OIT, across study conditions and within the two treatment groups.

	SASE Patients (All)	SASE Patients (Blood Samples)	SAPS Patients (All)	SAPS Patients (Blood Samples)	Patients (All)	Patients (Blood Samples)
Number of Patients	24	16	26	14	50	30
Demographic characteristics						
Boys	17 (71%)	10 (63%)	19 (53%)	9 (64%)	36 (72%)	19 (63%)
Girls	7 (29%)	6 (38%)	7 (50%)	5 (36%)	14 (28%)	11 (37%)
Age	10.42 (2.75)	10.19 (2.99)	11.19 (3.24)	11.14 (3.16)	10.82 (3.01)	10.63 (3.06)
White	10 (42%)	7 (44%)	10 (39%)	7 (50%)	20 (40%)	14 (47%)
Asian	6 (25%)	5 (31%	11 (42%)	5 (36%)	17 (34%)	10 (33%)
Latino	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
African American	1 (4%)	0 (0%)	0 (0%)	0 (0%)	1 (2%)	0 (0%)
Mixed Race	7 (29%)	4 (25%)	5 (19%)	2 (14%)	12 (24%)	6 (20%)
Clinical characteristics						
Single Food Allergy	6 (25%)	5 (31%)	10 (39%)	6 (43%)	16 (32%)	11 (37%)
Multiple Food Allergies	18 (75%)	11 (69%)	16 (62%)	8 (57%)	34 (68%)	19 (63%)
Peanut-specific blood IgE		94.54 (138.54) Median=59.6 [0.66, 571.00]		61.26 (66.27) Median=45.25 [3.90, 232.00]		79.01 (110.37) Median=53.65 [0.66, 571.00]
Peanut-specific blood IgG4		2.08 (3.40) Median=0.67 [0.06, 13.60]		1.83 (2.24) Median=0.72 [0.01, 6.93]		1.96 (2.87) Median=0.72 [0.01, 13.60]

Note. Data are mean (SD) or n (%). For peanut-specific blood IgE and IgG4, ranges are presented in square brackets below medians. There were no statistically significant differences between SAPS and SASE groups (or SAPS and SASE patients who provided blood samples) in patient gender, age, race, or having a single or multiple food allergies. There were also no statistically significant

differences in patient peanut IgE baseline levels or peanut IgG4 baseline levels, either when comparing means in a *t*-test using log transformed data or when comparing medians in a Wilcoxon rank-sum test. *OIT*=oral immunotherapy. *SASE* = "Symptoms as Side Effects" condition, in which patients and their parent(s) were informed that non-life-threatening symptoms during OIT are unfortunate side effects of treatment. *SAPS* = "Symptoms as Positive Signals" condition, in which patients and their parent(s) were informed that non-life-threatening symptoms during OIT could be associated with desensitization. *IgE*=immunoglobulin E antibodies. *IgG4*=immunoglobulin G antibodies.

Table 2. Description of Clinic Visits

Visit 1	• Consent • Treatment Instructions • Blood Draws • **Introduction of Mindset about Symptoms** • Group Introduction/Discussion
Visit 2	• Group Check-in • Distribution of Magnets with Mindset Message (see Figure E7) • Updose Instructions • Review of Symptom Management Strategies • **Letter Writing Activity**
Visit 3	• Group Check-in • Updose Instructions • **Scenario Responses** • Bingo Ice Breaker
Visit 4	• Group Check-in • Updose Instructions • **Immune System Illustration**
Visit 5	• Group Check-in • Updose Instructions • **Letter Reading** • **Video Interviews**
Visit 6	• Updose Instructions • Life After Treatment • **Reflection on Treatment**
Visit 7	• Maintenance Dose Instructions • Certificates of Study Completion • Blood Draws
Visit 8	• Q&A with Nurse Practitioner

Note: Activities that helped to reinforce the mindsets are in bold.

Table 3. Baseline patient and parent anxiety, across study conditions and within the two treatment groups.

	SASE Patients	SAPS Patients	SASE Parents	SAPS Parents	Patients (All)	Parents (All)
Number of Patients	21	25	22	24	46	46
Anxiety about Treatment						
Not nervous at all	5 (23.8%)	6 (24%)	2 (9.1%)	2 (8.3%)	11 (23.9%)	4 (8.7%)
Not that nervous	3 (14.3%)	9 (36%)	7 (31.8%)	3 (12.5%)	12 (26.1%)	10 (21.7%)
Kind of nervous	9 (42.9%)	7 (28%)	7 (31.8%)	12 (50%)	16 (34.8%)	19 (41.3%)
Extremely nervous	4 (19%)	3 (12%)	6 (27.3%)	7 (29.2%)	7 (15.2%)	13 (28.3%)
Anxiety about Symptoms						
Not nervous at all	4 (19%)	4 (16%)	0 (0%)	1 (4.2%)	8 (17.4%)	1 (37%)
Not that nervous	7 (33.3%)	8 (32%)	5 (22.7%)	2 (8.3%)	15 (32.6%)	7 (63%)
Kind of nervous	9 (42.9%)	9 (36%)	10 (45.5%)	13 (54.2%)	18 (39.1%)	23 (110.37)
Extremely nervous	1 (4.8%)	4 (16%)	7 (31.8%)	8 (33.3%)	5 (10.9%)	15 (2.87)

Note. Data are n (%). Baseline data are missing for four patients and two parents; patients and/or parents were able to skip any survey questions and thus do not have responses to these questions. *SASE* = "Symptoms as Side Effects" condition, in which patients and their parent(s) were informed that non-life-threatening symptoms during OIT are unfortunate side effects of treatment. *SAPS* = "Symptoms as Positive Signals" condition, in which patients and their parent(s) were informed that non-life-threatening symptoms during OIT could be associated with desensitization.