Peanut Oral Immunotherapy: Is It Ready for Clinical Practice?

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The prevalence of peanut allergy in the United States and other Westernized countries has tripled in the past 15 years, now affecting more than 1% of the population. Strict peanut avoidance is the current standard of care. In the past decade, a number of small, largely uncontrolled clinical trials have suggested that oral immunotherapy (OIT) can effectively desensitize most children with peanut allergy. Some in the allergy community now feel that OIT is ready for clinical practice. In this review, the evidence base in the medical literature is examined. Although peanut OIT shows promise, the evidence currently available on its effectiveness, risk benefit, and potential long-term consequences is insufficient to support its use in clinical practice. Appropriately designed, prospective clinical trials are urgently needed to determine whether OIT is a safe, effective form of therapy for food allergy. © **2013 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol: In Practice 2013;1:15-21)**

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In the past 15 years we have witnessed an alarming increase in peanut allergy among children in the United States and other Westernized countries[1-3]; 0.4% to 1.4% in the United States from 1997 to 2008, 0.5% to 1.2% in the United Kingdom from 1994 to 2002, and 0.73% to 1.15% in the capital territory of Australia. A recent birth cohort study in Australia found a food challenge-proven peanut allergy prevalence of 2.9% in young infants.[4] Perhaps even more disturbing is a 3.5-fold increase in hospitalizations between 2000 and 2006 in the United States because of food allergy noted by the Centers for Disease Control and Prevention[5] and a 3.5-fold increase in hospitalizations because of food-induced anaphylaxis in Australia between 1997 and 2005.[6] Although the cause of this rise is unknown, it appears to be caused by environmental factors associated with the modern lifestyle of Westernized countries.[7] Commonly cited factors include improved hygiene and less exposure to microbial organisms that result in altered gastrointestinal and cutaneous microbiomes, increased use of antibiotics, changes in dietary patterns, and less exposure to sunlight that could result in insufficient vitamin D levels.

Guidelines on the Diagnosis and Management of Food Allergy were recently developed by a National Institutes of Health–sponsored expert panel of specialists from 34 relevant professional organizations, federal agencies, and patient advocacy groups. After extensively examining available evidence that supported current diagnostic and therapeutic approaches in the management of food allergy,[8] the expert panel recommended "that patients with documented IgE-mediated food allergy should avoid ingesting their specific allergen or allergens"[9(S27)] and did "not recommend using allergen-specific immunotherapy to treat food allergy in clinical practice settings."[9(S29)] These guidelines are consistent with the current practice parameters of the American Academy and College of Allergy, Asthma and Immunology.[10] Both the guidelines and the practice parameters recommend appropriate diagnosis of food allergy, which includes a detailed clinical history, relevant laboratory studies and possibly oral food challenges (OFCs), and education of patients and their families on food allergen avoidance, recognition of early signs of an allergic reaction, and education and detailed instructions about initial self-management of allergic reactions. Although general awareness and educational materials for dealing with food allergies have improved dramatically over the past 15 years, many patients with food allergy continue to have allergic reactions due to accidental allergen ingestions,[11] and the quality of life (QoL) for patients and their families remains suboptimal.[12-16] In view of this, allergists are eager to identify new approaches to manage food allergy.

In the past decade, increased emphasis has been on developing active approaches to treat food allergies. Initial attempts at using traditional subcutaneous immunotherapy (SCIT) were short lived because injection therapy provoked unacceptably severe adverse reactions.[17,18] Subsequently, investigators have pursued a number of alternative approaches, as reviewed previously.[19] At the present time, oral immunotherapy (OIT) has become the most actively investigated and appears to be the most promising form of immunotherapy for food allergies. Although the first report of successful OIT in a child with egg-induced anaphylaxis was published in 1908,[20] there were only a few scattered case reports until 1998, when Patriarca et al[21] described a protocol for desensitizing a small cohort of children with food allergy. Since then, numerous reports have been published on the use of OIT in patients with food allergy.[22-38] Given the potential risk of anaphylactic reactions in patients with food allergy and the detrimental effect it has on their QoL and that of their families,

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Abbreviations used
DBPCFC- Double-blind, placebo-controlled food challenge
EoE- Eosinophilic esophagitis
FDA- Food and Drug Administration
OFC- Oral food challenge
OIT- Oral immunotherapy
QoL- Quality of life
RR- Relative risk
SCIT- Subcutaneous immunotherapy

and given that peanut allergy is not "outgrown" in most patients, it is understandable that clinicians want to do something to help their patients, and recently some allergists have begun calling for the use of OIT in clinical practice.[39]

The question of whether OIT has been adequately studied to enter the clinical arena has led to some disagreement between university-based allergists and allergists in practice.[40] Both groups are motivated by a desire to do something to help their patients and both respect the philosophy of *primum non mocere* (first do no harm), first put forth by Hippocrates more than 2300 years ago. As noted above, there are more than a dozen clinical studies in the published literature indicating that a significant proportion of patients with food allergy can be "desensitized" to food, at least in the short term. The basic question for peanut OIT is whether investigative studies have provided sufficient data to eliminate the state of *equipoise*, that is, the state of uncertainty between the relative benefits of 2 therapeutic approaches, for example, OIT and allergen avoidance. Are we reasonably certain that peanut OIT is safe and effective? If so, *equipoise* no longer exists, and OIT should be used in clinical practice. At this time, OIT for food allergy has not been approved by the Food and Drug Administration (FDA) in the United States or by the European Medical Agency in Europe and is not covered by insurance companies, but what is the evidence?

In addition to a number of review articles,[19,41] 4 meta-analyses on immunotherapy for food allergy have been published,[42-45] including a recent Cochrane report specifically on peanut OIT.[44,45] The meta-analyses all used a broad search strategy of electronic databases typically including the following: MEDLINE, EMBASE, and all Evidence-Based Medicine Reviews, for example, Cochrane Database of Systematic Reviews, ACP Journal Club, Database of Abstracts of Reviews of Effects, Cochrane Methodology Register, Health Technology Assessment, and NHS Economic Evaluation Database; online tables of contents of key specialty journals, for example, *Pediatric Allergy*, *Journal of Allergy and Clinical Immunology*, and *Allergy*; and reference lists of retrieved articles. The first meta-analysis by Fisher et al[42] focused on English language studies appearing in the literature from 1950 to July 2009 that met the following inclusion criteria: children between birth and 18 years of age with IgE-mediated food allergy proven by double-blind, placebo-controlled food challenge (DBPCFC) at the start of the study; outcome success of OIT with the use of outcome measures of desensitization/tolerance/allergy objectively assessed with OFC or DBPCFC to establish desensitization/tolerance and DBPCFC to establish allergy, and scored $\geq$1 with the use of the National Institute for Health and Clinical Excellence 25 criteria for quality assessment. In considering the outcome of these studies, the term *desensitization* refers to a reversible state after short-term exposure to incremental doses of an allergen that renders effector cells less reactive or nonreactive, but, once administration of the allergen is discontinued, the previous level of clinical reactivity returns. In contrast, *tolerance* refers to the relatively long-lasting effects of immunotherapy, presumably because of effects on B cells and T cells, which persist for prolonged periods even after the treatment is discontinued (although tolerance may not always be permanent). *Allergy* refers to symptomatic IgE-mediated reactions, typically established by OFCs. Although 232 articles were identified, only 3 studies (Staden et al,[26] Longo et al,[24] and Skripak et al[27]) fulfilled the inclusion criteria of this analysis, and only the study by Skripak et al[27] that involved 20 children used a double-blind, randomized control study design. In total, these 3 studies treated 68 children with egg or cow's milk OIT. The meta-analysis of the 3 studies found a lower relative risk of clinical reactivity after OIT, but this did not reach statistical significance. Fisher et al[42] concluded that "no difference could be established between the children receiving OIT and those practicing avoidance of the relevant food," that OIT "cannot yet be recommended in routine practice as a means to induce tolerance in children with IgE-mediated food allergy," and that further research is needed with the use of large, high-quality randomized controlled trials to assess the long-term efficacy, safety, and cost-effectiveness of OIT.

In a second meta-analysis, Brozek et al[43] used less-stringent criteria (evaluated randomized controlled trials and observational studies) to screen 1034 articles published before May 2011 to assess the evidence to support the use of OIT in children with milk allergy.[43] Five randomized trials[24,27,46-48] and 5 observational studies[21,49-52] were included in their analysis. The randomized controlled trials compared 116 children undergoing OIT with 114 untreated or placebo-treated children, and the observational studies added an additional 49 OIT and 34 control subjects. Overall, the investigators concluded that, compared with avoidance alone, OIT increased the likelihood of achieving desensitization/tolerance to cow's milk [relative risk (RR) = 10; 95% CI: 4.2-24.2]. However, adverse reactions to OIT in the randomized controlled trials were frequent with increased RR of laryngospasm (RR = 12.9; 95% CI, 1.7-98.6), wheezing symptoms (RR = 3.8; 95% CI, 2.9-5.0), need for corticosteroids (RR = 11.3; 95% CI, 2.7-46.5), and need for intramuscular epinephrine (RR = 5.8; 95% CI, 1.6-21.9). The investigators concluded that, although some randomized controlled trials are available in the published literature, the "overall low quality of evidence leaves important uncertainty about anticipated effects of immunotherapy due to very serious imprecision of the estimates of effect and the likelihood of publication bias for some of the critical outcomes."[43(p372)] They questioned whether the apparent benefit of OIT is outweighed by the frequent and sometimes serious adverse reactions and called for additional, larger randomized controlled trials to evaluate all patient-important outcomes.

Two meta-analyses specifically addressing peanut OIT were published recently.[44,45] Both used the search criteria and grading of the Cochrane Collaboration, and in both cases the investigators contacted experts in the field for further information on ongoing and unpublished studies. However, only the most recent analysis, which strictly adhered to all Cochrane criteria, was published by the Cochrane Collaboration.[45] That analysis included all randomized controlled, quasi-randomized controlled and case-controlled trials of peanut OIT published

TABLE I. Systematic review of 8 clinical trials of peanut OIT

Trial	No. of participants	Age (y), range [mean]	Inclusion criteria	Intervention	Outcome measures
Blumchen et al[32]	6	3-10 [5.7]	DBPCFC	Crushed PN (up to 0.5 g)	Change in threshold dose
Clark et al[31]	4	9-13 [12.5]	History + increased PN-IgE or PST	Peanut flour (800 mg)	Threshold dose
Jones et al[28]	39	1-9.3 [4.8]	History + increased PN-IgE or PST	Peanut flour	Threshold dose
Buchanan et al[54]*	7	[4.4]	History + increased PN-IgE	No details	Change in threshold
Nash et al[55]*	13	No details	History + increased PN-IgE or PST	Peanut flour	Tolerate 7.8 g of peanut
Wasserman et al[59]*	≥16 ?	No details	History + increased PN-IgE or PST	No details	Tolerate ≥1 peanut
Anagnostou et al[36]†	22	4-18 [11]	DBPCFC (up to 100 mg)	Peanut flour (800 mg)	6.6 g protein (0.83 mg × 8)
Varshney et al[34]†	28 (16 completed PN OIT)	2-11 [6.4]	History + increased PN-IgE or PST	Peanut flour (up to 4 g)	5 g flour (increasing doses)
Total subjects treated with OIT	116	1-18	2 of 8 studies confirmed peanut allergy by DBPCFC	Peanut flour or crushed peanut	Variable

PN, Peanut; *PST*, prick skin test.
*Published abstract.
†Additional studies not reviewed in the meta-analysis by Sheikh et al.[44]

from 1990 through January 2012. Overall the investigators identified 746 titles; 16 were selected for detailed analysis but only 1 study fulfilled the inclusion criteria and was considered to be at low risk of bias in all domains (Varshney et al[34]). In that study, 28 children with peanut allergy (ages of 1-16 years) were randomly assigned 19:9 (OIT to placebo) and treated for 48 weeks. Children were enrolled if they had a clinical history of reaction to peanut within 60 minutes of ingestion, a peanut-specific IgE >15 kU_A/L or >7 kU_A/L if a significant reaction occurred within 6 months of enrollment, and a positive skin prick test 3 mm or greater than the negative control. After 48 weeks of treatment, subjects underwent OFCs with up to 5 g of peanut protein (equivalent to ~20 peanuts). The build-up and home-dosing phases lasted approximately 44 weeks, and the maintenance phase about 4 weeks before the second OFC. During the initial day of treatment, 26 of 28 children (93%) reached the maximum cumulative dose of 12 mg of peanut protein or placebo. Two subjects in the intervention arm failed to reach the 1.5-mg minimal, initial first-day dose and were dropped from the study; 1 subject withdrew during subsequent dosing because of adverse reactions. Overall, 16 children received the full course of peanut OIT and 9 children completed the placebo arm. All 16 children who received the full course of active treatment were able to ingest the maximum cumulative dose of 5000 mg (although 1 subject experienced mild upper respiratory symptoms and moderate urticaria) compared with a median cumulative dose of 280 mg in the placebo-treated group (range, 0-1900 mg; $P < .001$).[34] Adverse reactions were seen in all subjects treated with OIT, but most reactions were mild. In the intervention arm, 47% (n = 9) of subjects experienced clinically relevant adverse reactions during the initial-day escalation (none in the placebo arm), and clinically relevant symptoms occurred during the build-up phase after 1.2% of 407 build-up doses. Nine children (47%) receiving peanut OIT were treated with antihistamines during the initial-day escalation and 2 children required epinephrine, but no medication use was reported during the build-up dosing. None of the placebo subjects required treatment during initial-day escalation or build-up dosing. The investigators of the Cochrane Report concluded that "Although promising, based on the findings of this one small trial, we cannot recommend that peanut OIT be used routinely for people with peanut allergy. There is a need for further larger studies investigating safer OIT regimens and establishing the long-term effectiveness of OIT after treatment is stopped."[45(p3)]

In the other of these 2 meta-analyses on peanut OIT, which was done earlier by several of the same investigators who published the Cochrane report described earlier, the search period included all potential studies from 1990 to February 2010.[44] Overall, 1059 potential studies and 48 potentially appropriate abstracts were identified. No studies fulfilled the standard Cochrane criteria, and only 3 full-text articles and 3 abstracts noted in Table I met the lesser inclusion criteria used in this analysis. With the addition of 2 other clinical trials published since this meta-analysis (including the study by Varshney et al[34] discussed earlier)[36] depicted in Table I, only 116 subjects with peanut allergy treated with a variety of different OIT regimens have evaluable data. Greater than 90% of the patients treated experienced adverse reactions, and, although most of these reactions were mild, they were seen after 2% to 25% of OIT doses in various studies. It is apparent from these few studies and others directed at other food allergens that "rush" protocols are associated with higher rates of adverse reactions. Consequently, most of the clinical trials of OIT now under way are using more prolonged escalation stages. In the trial by Jones et al,[28] which, like the study by Varshney et al,[34] provided adequate details for review, adverse reactions occurred in 92% of subjects: upper respiratory symptoms in 69%, nausea and abdominal pain in 44%, diarrhea and vomiting in 21%, mild-to-moderate skin symptoms in 62%, and lower respiratory symptoms in 15%. Adverse reactions occurred after 46% of the build-up doses and 3.7% of the home maintenance doses. Intramuscular epinephrine use was reported in 4 of the 8 trials.

In the only report of OIT being done in an office-based practice, 6 of 16 subject (38%, although the denominator is uncertain) required intramuscular epinephrine for treatment of adverse allergic reactions.[53] Four of the 6 studies reported dropout rates, which varied from 0% in the 2 smaller studies[31,32] to 25% in the study by Jones et al.[28] None of these studies reported on changes in patient satisfaction/QoL, need for utilization of health care facilities, or cost effectiveness.

When considering the study quality, the investigators of this second meta-analysis on peanut OIT concluded that the six studies[28,31,32,53-55] analyzed were all at high risk of bias for the following reasons: (1) all but one of the studies were case reports, (2) no study reported consecutive recruitment of subjects so the risk of selection bias was high, (3) subjects and investigators were not blinded to treatment, and (4) the high risk of publication bias was inherent with case series reports.[44] Nevertheless, the investigators concluded that OIT for peanut allergy may be effective in inducing desensitization, but there is no evidence that this form of therapy will induce long-term tolerance, and that the high rate of adverse events is of concern. "Overall, OIT appears to be a promising new therapeutic approach, but its effectiveness, cost-effectiveness, and risk profile now need to be better established. We therefore recommend that OIT administration should, for the present, only take place in clinical trial settings."[44(p49)] This conclusion was basically reiterated in the recently released Cochrane review that concluded with the following: "Peanut OIT represents a promising, potentially disease-modifying therapeutic approach for the management of IgE-mediated peanut allergy. However, currently there is insufficient evidence in terms of long-term effectiveness, safety and cost-effectiveness of peanut OIT to recommend its routine use in clinical practice."[45(p9)]

In the 8 studies on peanut OIT which met minimal requirements for study design (Table I), there is no consistency in subject selection criteria (virtually all studies were confined to subjects ≤18 years of age), dosing regimens or timing of the escalation phase, optimal maintenance dose, length of maintenance therapy, or primary outcome measures. Although most subjects treated appeared to have been "desensitized" and could tolerate significantly more peanut protein after 4 to 6 months of maintenance therapy, approximately 15% of subjects could not tolerate OIT and dropped out because of persistent adverse reactions. In those studies, investigators also noted that a number of adjuvant factors could provoke "breakthrough" adverse allergic reactions in patients who had previously been tolerating their maintenance OIT dose: development of a viral illness, suboptimal control of asthma, exercise within a few hours of dosing, dosing during the pollen season in allergic persons, dosing around the time of menses in females, and dosing on an empty stomach.[38] Gastrointestinal symptoms were common in all studies and one of the most frequent reasons for discontinuing therapy. Several studies also have noted the development or unmasking of eosinophilic esophagitis (EoE) secondary to OIT.[56-61] In one report, 39 of 75 patients (52%) developed new gastrointestinal symptoms (eg, vomiting, dysphagia, abdominal pain, diarrhea); 15 of 40 patients (38%) were being treated for peanut allergy. Of these 15 patients, 3 discontinued therapy, 4 (10%) were diagnosed with EoE by endoscopy and biopsy, and 8 continued on to maintenance therapy.[59] Because the diagnosis of EoE requires an invasive procedure, most subjects developing symptoms of EoE in clinical studies withdraw rather than undergo full evaluation of their symptoms, because of ethical reasons. Consequently, current reports may underestimate the true rate of EoE induced by OIT. None of the studies showed that OIT can induce long-term "tolerance," and none of the trials have followed subjects for more than 2 years, so the long-term effects of OIT remain unknown.

Although these studies have led to a great deal of excitement and optimism in the food allergy community and among patients with food allergy, the question of whether peanut OIT is better than allergen avoidance (current standard of care) and therefore ready for introduction into the clinic, remains in a state of *equipoise*. Four meta-analyses have all concluded that the current evidence base on OIT is of poor quality and does not support the introduction of OIT into clinical practice. An NIAID-supported expert panel that represented experts from 34 professional organizations, federal agencies, and patient advocacy groups concluded that OIT was not ready for clinical practice, and the FDA has not yet even approved an Investigational New Drug for a phase III OIT trial. Given that the first reports of OIT for food allergy appeared within 10 years of the first reports of SCIT for seasonal pollen allergy, one must wonder why allergists continued to practice and perfect SCIT for airborne allergens for more than a century, whereas OIT for food was largely abandoned until about 15 years ago. Medical history is replete with examples of well-meaning clinicians performing medical practices that were subsequently shown to be of no value and in some cases harmful. In our own specialty, clinical impression, good intentions, and numerous poorly designed studies supported the use of SCIT with whole-body extracts for hymenoptera sting-induced anaphylaxis for decades. Furthermore, this practice was supported by professional organizations[62] until a well-designed, placebo-controlled trial compared the outcome of SCIT with venom, whole-body extract, and placebo.[63] That landmark study unequivocally showed that whole-body extract was no different than placebo and that, despite all the supportive studies in the literature and the clinical impression of most allergists, it was apparent that thousands of patients with insect sting allergy had received years of injections with no benefit of protection from their allergy. Similarly, only prospective, well-controlled, blinded trials of peanut OIT in patients with documented peanut allergy and well-defined clinical end points can ensure that we do not repeat such a mistake. Given that there is a lack of definitive evidence of efficacy for OIT and that there are substantial concerns about safety, it becomes even more imperative that appropriate clinical trials be completed expeditiously before this becomes a widespread clinical practice. At this time there are approximately 8 ongoing studies listed in ClinicalTrials.gov, incorporating a total of more than 250 pediatric study subjects and 20 adults, and a large peanut OIT trial of children between the ages of 1 and 4 years sponsored by the Immune Tolerance Network is expected to launch soon. Unfortunately, OIT dosing strategies and clinical end points are not uniform, so answers about safety and efficacy will require further studies. In addition, the FDA will require a large-scale phase III trial before it approves OIT for general use.

The study by Staden et al[26] highlighted the need for appropriate controls in OIT trials.[6] In their trial of egg and milk OIT,

36% of their subjects treated with OIT no longer responded to egg or milk after a trial period off immunotherapy, that is, developed tolerance, but 35% of the children in the untreated control group also developed tolerance in the same period of time. One might argue that the natural history of peanut allergy is quite different than that of allergy to egg and milk, which is true. However, in a recent peanut sublingual immunotherapy trial in which 40 patients with peanut allergy documented by pretreatment DBPCFCs (median dose <200 mg), 2 of 19 subjects who were randomly assigned to the placebo group and treated for 44 weeks tolerated a DBPCFC to 10 g of peanut powder, whereas none of 18 subjects who were randomly assigned to the active drug group and treated with peanut sublingual immunotherapy for 44 weeks was able to tolerate the 10-g challenge.[64] Such studies reinforce the importance of adequately controlled trials.

In all immunotherapy trials, safety is of paramount importance. Institutional review boards in virtually all OIT trials under way in academic institutions require oversight by a Data Safety Monitoring Committee and acquisition of an Investigational New Drug approval from the FDA. Rigorous rules and safeguards are stipulated, and yet adverse reactions that require the need for epinephrine rescue are seen during up-dosing and home maintenance therapy in most studies, although relatively infrequently, that is <5% of subjects. In the one report of peanut OIT done in clinical practice settings, 6 of 16 patients (denominator unclear) treated with OIT required epinephrine and 9 patients dropped out, both higher rates than reported in research-based clinical trials.[53]

There is no question that having a peanut allergy affects the QoL of patients and their families.[12-16] The constant fear and uncertainty about the possibility of ingesting a food contaminated with peanut and the severity of the subsequent reaction clearly exacts an emotional toll on patients and their families. In a recent practice-based, open-label, uncontrolled trial of peanut OIT in a selected, highly motivated patient cohort, investigators found a significant improvement in QoL, based on validated questionnaires before and after treatment.[65] In this study, 90 of 100 patients enrolled achieved a maintenance dose of 450 mg of peanut protein (3 peanut M&Ms per day); no information on the degree of desensitization in these patients after therapy is provided. Although this study suggests that the QoL in patients undergoing OIT may improve, the subjects were not compared with an untreated or placebo-treated control group, so the difference between treatment and the "study effect" or "placebo effect" cannot be fully differentiated. Unfortunately, some of the anxiety associated with peanut allergy likely has been generated by the emphasis of the medical and health communities on the potential severity of reactions in their well-meaning attempt to make certain that patients get the message to keep their emergency medications readily available and do not become less vigilant in their efforts to avoid possible allergen exposure. However, in a recent retrospective study of 782 children and adolescents with persistent peanut allergy diagnosed and followed in a tertiary allergy practice for a median of 5.3 years,[66] the overall rate of reactions after accidental peanut ingestion was 7.3% per year with less than one-third of the patients experiencing any reaction over the 5 years of follow-up. The rate of reactions considered severe was 1.6% per year, and the rate of reactions treated with epinephrine was 1.1% per year. These rates are significantly lower than the rates of adverse reactions and epinephrine use reported in most of the oral immunotherapy trials cited earlier.

As summarized in an editorial by Sheikh et al,[67] which remains equally pertinent today, preliminary evidence for peanut OIT is encouraging, but the evidence to date is based on "small case series conducted in highly motivated, selected, carefully monitored patients," different protocols of administration have been used in various studies, and results are from "studies at potentially high risk of bias…. [OIT] should not be taken-up in routine clinical settings. Reports that a few clinicians in the United States have taken this leap is very worrisome."[67(p264)] The investigators concluded that "It is important that our excitement about (the early success of OIT), which has the potential to transform the lives of millions of people worldwide, does not get the better of us, and that we wait for the science to lead the way."[67(p264)] Practice parameters on immunotherapy were recently updated by the Joint Task Force on Practice Parameters, representing the American Academy of Allergy, Asthma & Immunology; the American College of Allergy, Asthma & Immunology; and the Joint Council of Allergy, Asthma & Immunology, and were approved by the 3 organizations.[68] These parameters are based on an extensive review of the published literature, and publications were rated by category of evidence and used to establish the strength of a clinical recommendation. The third and most recent update of Practice Parameter on Immunotherapy concluded that "The safety and efficacy of oral and sublingual immunotherapy for food hypersensitivity is currently investigational."[68] As a specialty, there is no question that we are encouraged and excited about the potential that OIT offers our patients with food allergy, but we must decide if we are in fact committed to science and evidence-based medicine. If the answer is "yes," we have to conclude that peanut OIT remains in a state of *equipoise* and is *not* yet ready for routine clinical use.

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