A practical focus on oral immunotherapy to tree nuts

Stephanie Erdle, M.D.[1] and Victoria E. Cook, M.Sc., M.D.[1,2]

ABSTRACT

Tree nut (TN) allergy is common, with a global prevalence of up to 4.9%. TN allergy is persistent in most patients, and accidental reactions are common. There is considerable clinical cross-reactivity between cashew and pistachio, and between walnut and pecan. A diagnosis of TN allergy is based on a history of clinical reaction on ingestion, along with confirmed sensitization through either skin-prick or serum immunoglobulin E (IgE) testing. Component testing and food challenges may be required in patients with birch pollinosis to distinguish between IgE-mediated allergy to a heat-stable protein and pollen food allergy syndrome. There is available evidence that TN oral immunotherapy (OIT) is reasonably safe and effective. There are numerous nonpharmaceutical food products to facilitate TN-OIT dosing. TN OIT should be offered as a treatment option for patients with TN allergy.

(J Food Allergy 4:120–126, 2022; doi: 10.2500/jfa.2022.4.220020)

ALLERGY TO TREE NUTS

Tree nuts (TN) are defined as any nut grown on trees, including cashew, pistachio, walnut, pecan, hazelnut, almond, Brazil nut, macadamia nut, and pine nut.[1] In North America, the prevalence of TN allergy is reported to be 1%–2%, with a global prevalence of up to 4.9%.[2–4] In a large Australian population–based cohort study, the prevalence of challenge-confirmed TN allergy was 3.3% at age 6 years, and 2.3% at ages 10–14 years.[5] TN allergy can be severe, with reported cases of fatal anaphylactic reactions.[2] Accidental exposures in TN allergy are common.[6,7] TN production worldwide has increased by 65% over the past decade,[8] and TNs are increasingly recognized as healthy snacks,[9] factors that may make avoidance more burdensome for patients with TN allergy. Without treatment, TN allergy is thought to be lifelong, with only 9% of patients experiencing spontaneous resolution of the allergy.[10,11] TN oral immunotherapy (OIT), therefore, is increasingly sought after by patients and parents.

From the [1]Division of Clinical Immunology and Allergy, Department of Pediatrics, University of British Columbia, Vancouver, British Columbia, Canada; and [2]Allergy Victoria, Victoria, British Columbia, Canada

V.E. Cook has been a member of advisory boards for Sanofi Genzyme, Bausch Health, and ALK, and has received honoraria from Aralez Pharmaceuticals and CSL Behring. S. Erdler has no conflicts of interest to disclose pertaining to this article

No external funding sources reported

Address correspondence to Victoria E. Cook, M.Sc., M.D., Division of Clinical Immunology and Allergy, Department of Pediatrics, University of British Columbia, Suite 130, 3200 Shelbourne St., Victoria, British Columbia, Canada V8P 5G8

E-mail address: victoria.cook@allergyvic.com

*This manuscript is part of the **Journal of Food Allergy** collection of published works referred to as the "Oral Immunotherapy Manual." The contents of this work reflects the opinion(s) of the author(s) and is not intended to replace published guidelines or the clinician's medical advice in the doctor-patient relationship*

TN ALLERGENS AND CROSS-REACTIVITY

The majority of allergens implicated in TN allergy are seed storage proteins, including vicilins (7S globulins), 2S albumins and legumins (11S globulins).[12] These proteins are heat stable and resistant to proteolytic digestion, which contributes to their allergenicity. There are additional allergens that have high cross-reactivity with pollens and are thought to contribute to pollen food allergy syndrome (PFAS). These allergens are termed pan-allergens and include profilins, heveins, and lipid transfer proteins.[12] These allergens are more heat labile and susceptible to proteolytic digestion and, therefore, do not typically lead to systemic symptoms.[12] Component immunoglobulin E (IgE) testing can be a valuable diagnostic tool to distinguish PFAS from IgE-mediated allergy to heat-stable proteins (Table 1).

The distinction between cross-sensitization (positive serum-specific IgE or skin-prick test without clinical reactivity) and cross-reactivity (the presence of clinical reactivity) is particularly relevant in TN allergy, in which cross-sensitization is common. True cross-reactivity is high between cashew and pistachio (both members of the Anacardiacea family), and between walnut and pecan (both members of the Juglandaceae family).[12] This is advantageous in OIT because for most patients, OIT to cashew will induce cross-desensitization to pistachio, and OIT to walnut will induce cross-desensitization to pecan.[13,14]

EXISTING EVIDENCE FOR TN OIT

The existing data for TN OIT is limited to a single-center retrospective study on hazelnut OIT[15] and a single-center prospective cohort study on walnut OIT,[13] in addition to data extrapolated from omalizumab-supported

Table 1 **Tree nut allergens***

	Seed Storage Proteins: IgE-Mediated Food Allergy to Heat-Stable Protein	Pan-Allergens: Pollen Food Allergy Syndrome#
Walnut	Jug r 1§; Jug r 2¶; Jug r 4‖; Jug r 6¶	Jug r 3; Jug r 5
Pecan	Car i 1§; Car i 2¶; Car i 4‖	N/A
Cashew	Ana o 1¶; Ana o 2‖	N/A
Pistachio	Pis v 2‖; Pis v 3¶; Pis v 5‖	N/A
Hazelnut	Cor a 11¶; Cor a 14§	Cor a 1; Cor a 8
Almond	Pru du 6‖	Pru du 3
Brazil nut	Ber e 1§; Ber e 2‖	N/A
Pine nut	Pin p 1§	N/A
Macadamia nut	Mac i 1¶; Mac i 2‖	

IgE = Immunoglobulin E; N/A = not applicable.
**From Refs. 12, 19, 30.*
#Pan-allergens: lipid transfer protein, ribosome-inactivating protein.
§2S albumin allergen.
¶Vicilin allergen.
‖Legumin allergen.

multifood OIT studies, which included cashew, walnut, hazelnut, and almond (Table 2).[16,17] Although outcomes varied, desensitization ranged from 34% to 100%.[13,15–17] Analysis of preliminary safety data is promising, with primarily mild reactions, comparable with peanut OIT data.[18,19] Quality of life seems to improve significantly in children with food allergy who were undergoing OIT, including TN OIT.[20]

PRACTICAL APPLICATION OF TN OIT

This article will address practical aspects of OIT specific to TNs. For an in-depth review of food allergy diagnosis, patient selection, dosing protocols, multifood OIT, and assessment of efficacy, including the role of challenges.[21–26]

Choosing a Candidate

An accurate diagnosis of IgE-mediated food allergy is essential before initiation of OIT, regardless of the food allergen.[27] This is particularly relevant in the case of TN allergy, in which cross-sensitization is common. A diagnosis requires a history of IgE-mediated symptoms on ingestion, either based on parent or patient report, or during oral food challenge (OFC), along with confirmation of sensitization with serum specific IgE $\geq$ 0.35 kU/L or skin-prick test results $\geq$ 3 mm. OFCs are indicated in the absence of a convincing history; determination of the eliciting dose can be helpful when selecting the starting dose, although not all clinicians will base the starting dose on OFC result.[27] OFC to potentially cross-reactive nuts before OIT for a more dominant TN (*e.g.,* OFC to pistachio before OIT to cashew) is not required.[28] For patients with concomitant birch pollinosis, component IgE testing and possibly OFC may be required to distinguish IgE-mediated allergy to heat-stable TN proteins from PFAS, for which OIT is not indicated.

Role of Cross-Reactivity

Consideration of the cross-reactivity of TNs can be used to minimize the number of nuts needed for OIT.[14,28] OIT to cashew will protect most patients against pistachio.[16,17] Similarly, OIT to walnut will offer protection to pecan.[13,16,17] Although there is some evidence of partial desensitization to hazelnut and, to a lesser extent, cashew, with walnut OIT,[13] we still recommend performing OIT to these nuts separately through multifood OIT given the limited data. For instance, if a patient has multiple TN allergies (cashew, pistachio, hazelnut, walnut, and pecan), it would be recommended to perform OIT to cashew, hazelnut, and walnut. Based on available evidence, OIT with cashew results in cross-desensitization to pistachio in 83%–94% of patients, and OIT with walnut results in cross-desensitization to pecan in 97%–100% of patients.[14,16] Because most patients experience cross-desensitization, it is reasonable to forgo additional challenges to pecan or pistachio to prove treatment coverage because reactions are uncommon and, when they occur, are typically at doses well above trace exposure levels.[14] However, some patients and providers may prefer to definitively demonstrate cross-desensitization. It is our current practice to offer challenges to equivalent amounts of these cross-reactive TNs once the patients reach maintenance dosing (*e.g.,* after reaching 300 mg of cashew protein, returning for a challenge to 300 mg of pistachio protein). In the event of a

Table 2 **Existing evidence for TN OIT**

Study, y	Country	Study Design	OIT Food	*N* (median age in years)	Starting Dose Range, mg	Maintenance Dose, mg	Duration at Maintenance, mo	OFC Results	Adverse Event
Andorf *et al.*,[16] 2018	U.S.	Blinded phase II clinical trial	Multifood with omalizumab, including almond, cashew, hazelnut, walnut	48 (8)	5–625*	2000	3–4.5 (median duration at maintenance)	Desensitization (2000 mg) rates: 100% to almond, cashew, hazelnut, walnut; co-desensitization rates: 83% to pistachio, 100% to pecan	No serious or severe (grade 3+) reactions
Elizur *et al.*,[4] 2020	Israel	Single-center prospective cohort	Walnut	73 (7.9)	50–465*	1200	6	89% desensitized (4000 mg) to walnut; all the patients with pecan co-allergy desensitized to pecan; desensitized to a lesser degree to hazelnut and cashew	Most mild (grade 1 or 2); 20% required I.M. epinephrine at hospital and 15% required I.M. epinephrine at home. 5% had OIT-induced gastrointestinal and eosinophilic responses
Moraly *et al.*,[15] 2020	France	Retrospective single center	Hazelnut	100 (5)	51–249#	One-half of the ED	6, if not desensitized	34% desensitized (1635mg); median ED at 6 mo was 523 mg	70% had no adverse effects, and 30% had mild adverse effects; no patients developed EoE

continued

TN = Tree nut; OIT - oral immunotherapy OFC = oral food challenge; I.M. = intramuscular; ED = eliciting dose; EoE = eosinophilic esophagitis.
**Highest tolerated dose during initial dose escalation.*
#One-tenth of the ED during OFC.

Table 3 **Sample TN-OIT dosing schedule**

Dose*	Food Protein Dose, mg	Cashew Flour (5 g protein/28 g cashew flour), mg#	Walnut Meal (5 g protein/30 g walnut flour), mg#	Hazelnut Flour (5 g protein/28 g hazelnut flour), mg#	Almond Flour (6 g protein/28 g almond flour), mg#
1§	1	5.6	6	5.6	4.8
	2.5	14	15	14	12
	5	28	30	28	23
	10	56	60	56	47
2	20	112	120	112	93
3	40	224	240	224	187
4	80	448	480	448	373
5	120	672	720	672	560
6	160	896	960	896	750
7	240	1344	1440	1344	1120
8	300	1680	1800	1680	1400

TN = Tree nut; OIT = oral immunotherapy.

**Dose increases are performed every 2–4 wk by us when using this protocol; the timing of the dose intervals may vary by center and protocol; intervals of 1–4 wk are common.*

#The exact allergen content may vary according to brand; confirm dose calculations of the protein content for a particular brand or form of food before use of these dosing suggestions for patients.

§Some centers may perform a day-1 escalation, with starting doses of 0.01–0.1 mg of protein and ending doses of 1–6 mg; we no longer perform this and, instead, select a starting dose that ranges from 1 to 10 mg of protein based on age, test values, and symptoms and/or eliciting dose based on history or oral food challenge.

reaction, the patient is offered the option of adding treatment to the specific TN (*e.g.*, pistachio or pecan).

Buildup Protocol Selection

The goals of OIT can be achieved through different protocols with varying initiation doses, maintenance doses and dosing schedules. Refer to Table 2 for a summary of initial doses, dosing intervals, and maintenance dose selection used in published TN-OIT studies. There is little evidence to support specific schedules compared with others.[23,28] It would be reasonable to select a maintenance dose of ≤300 mg of protein with Brazil nut OIT, particularly in younger patients, to avoid surpassing the upper daily limit of selenium.[29] Existing protocols are useful as a reference but may require adaptation to the specific patient and their goals.[28] A sample dosing schedule used by us and by multiple centres across Canada for preschool-age children, with promising preliminary safety data[17] extrapolated from preschool peanut OIT data are provided in Table 3.[19,30] Multifood OIT can be particularly beneficial in the case of multiple TN allergies.[27] The preferred approach in these patients is to treat the TNs simultaneously.[27] Many practitioners, including us, prefer to stagger the starting doses (either the same day or different days) and, once these are shown to be tolerated, to perform dose increases for all TNs concurrently.

Food Selection

There are no pharmaceutical products for TN OIT. Current practice uses nonpharmaceutical food products, including TN flours, meals, butters, whole or crushed TNs, TN milks, and preprepared snack foods (*e.g.*, hazelnut spreads, cashew cheese). In some centers, office- or pharmacy-prepared doses, often in the form of capsules, can be used.[28] Key considerations for the various food forms are summarized in Table 4. For small doses, we prefer office- or pharmacy-prepared doses, TN milks, diluted nut flours (often in a slurry), or butters measured by using "micro scoops" (measuring spoons that go down to 6–10 mg weight). Once at larger doses, whole nuts (in a nonchoking hazard form) and preprepared snack foods are alternative options.

Nonpharmaceutical food products should only be used if the protein content is clearly labeled or can be obtained from the manufacturer.[28] Precision dose preparation is critical. For this to be accurately done by patients at home, a precise scale that reads to three significant figures (e.g., 0.00 g), and clear written instructions on weighing and dosing are recommended.[28] TN milks can alternatively be used by either weighing out the milk or drawing up the milk into a marked syringe. We advise caution with the use of portions of a TN kernel (*e.g.*, "half a cashew") because there is considerable variability in weight, which leads to significant differences in protein doses (*e.g.*, among 30 cashews weighed

Table 4 **Special considerations for nonpharmaceutical food products used in TN OIT**

Nonpharmaceutical Food Product	Benefits	Special Considerations
Office or pharmacy prepared doses	Can be used for very low initial doses; minimal preparation for the patient and/or parent; improved accuracy and precision of dosing; can be swallowed to minimize oropharyngeal contact and/or symptoms	Pharmacy compounding cost; reliance on a pharmacy can lead to delays in initiation of treatment
Patient-prepared slurry	Can be used for very low initial doses; inexpensive	A need for frequent preparation (fresh batches every few days)
TN milks	Can be used for very low initial doses; commercially available; minimal preparation for the patient and/or parent; inexpensive	Watch for variable protein content per volume, even among the same brands; watch out for hidden ingredients (*e.g.*, some cashew milks also contain almond); may be less available in rural and remote locations; if dosing from frozen, must ensure that it is completely thawed before drawing up to avoid dosing errors; must shake well before drawing up to ensure more uniform protein distribution
TN butters	Use of micro-scoops can facilitate low initial doses; commercially available; minimal preparation for the patient and/or parent; inexpensive	Must be well mixed to ensure consistent dosing
Whole nuts	Commercially available; minimal preparation for the patient and/or parent; inexpensive	Challenging to use for low initial doses; variable protein content by weight for raw vs roasted; choking hazard in certain age groups; variability in weight of whole nuts, requires use of a scale for accurate dosing
Preprepared snack foods (*e.g.*, hazelnut spread, cashew "cheese" spread)	Commercially available; minimal preparation for the patient and/or parent	May contain additional ingredients, must confirm TN protein per total weight with the manufacturer to ensure accurate dosing

TN = Tree nut; OIT = oral immunotherapy.

by us, the weights ranged from 0.89 to 2.1 g per cashew nut).

In addition, use of raw versus roasted whole nuts can impact the protein content per total weight, which necessitates adjustments in dosing. Ideally, the same protein source should be used during the escalation phase to provide consistency in terms of the protein content.[27] The protein content may vary within the same product over time. It, therefore, is recommended that each new package be checked before use. It is recommended to either reduce or maintain the dose when switching food forms during buildup.[27] Practitioners may find it helpful to generate dose conversion tables for food forms commonly used by their clinics (Table 5 can be used as an example). Once at the maintenance phase, equivalent protein doses among the food sources can be used to provide variety, which, in our experience, can help with adherence.

CONCLUSION

Despite theoretical concern for variability of nonpharmaceutical food products, there is no evidence to suggest that pharmaceutical products are superior to nonpharmaceutical food products in terms of safety or efficacy.[31] In addition, pharmaceutical

Table 5 **Sample dosing conversion for different nonpharmaceutical food–based walnut products**

Dose	Food Protein, mg	Walnut Meal (5 g protein/30 g walnut flour), mg*	Walnut Milk (3 g protein/240 mL), mg*
1#	1	6	0.1
	2.5	15	0.2
	5	30	0.4
	10	60	0.8
2	20	120	1.6
3	40	240	3.2
4	80	480	6.4
5	120	720	9.6
6	160	960	12.8
7	240	1440	19.2
8	320	1800	24

**The exact allergen content may vary according to brand, confirm dose calculations of protein content for a particular brand or form of food before use of these dosing suggestions for patients.*

#Some centers may perform a day-1 escalation, with starting doses of 0.01–0.1 mg of protein and ending doses of 1–6 mg; we no longer perform this and, instead, select a starting dose that ranges from 1 to 10 mg of protein based on age, test values, and symptoms and/or eliciting dose based on history or oral food challenge.

products are more costly to patients.[27] The nonpharmaceutical approach further allows for de-medicalization through ingestion of "regular food."[18]

CLINICAL PEARLS

- TN allergy is common, and there is a significant burden to patients, given the poor natural history, frequent accidental exposures, severe reactions, and increasing consumption of TN worldwide
- Analysis of available evidence suggests that TN OIT is safe and effective, and results in improved quality of life and, therefore, should be offered as a treatment option to patients with TN allergy
- Consideration of the cross-reactivity of TNs can be used to minimize the number of nuts needed for OIT
- There are many options for nonpharmaceutical food products that can be used with common OIT dosing schedules

REFERENCES

1. Tree nuts-priority food allergens. 2008. Available online at https://www.canada.ca/en/health-canada/services/food-nutrition/reports-publications/food-safety/tree-nuts-priority-food-allergens.html. Accessed March 26, 2022.
2. Fleischer DM, Conover-Walker MK, Matsui EC, et al. The natural history of tree nut allergy. J Allergy Clin Immunol. 2005; 116:1087–1093.
3. Soller L, Ben-Shoshan M, Harrington DW, et al. Adjusting for nonresponse bias corrects overestimates of food allergy prevalence. J Allergy Clin Immunol Pract. 2015; 3:291–293.e2.
4. Elizur A, Appel MY, Nachshon L, et al. Clinical and molecular characterization of walnut and pecan allergy (NUT CRACKER Study). J Allergy Clin Immunol Pract. 2020; 8:157–165.e2.
5. McWilliam V, Peters R, Tang MLK, et al. Patterns of tree nut sensitization and allergy in the first 6 years of life in a population-based cohort. J Allergy Clin Immunol. 2019; 143:644–650.e5.
6. Sicherer SH, Muñoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. J Allergy Clin Immunol. 2003; 112:1203–1207.
7. Ewan PW, Clark AT. Long-term prospective observational study of patients with peanut and nut allergy after participation in a management plan. Lancet. 2001; 357:111–115.
8. INC. Nuts & dried fruits statistical yearbook 2020/2021. Int Nut Dried Fruit Counc Found. 2021; 1–78.
9. Coates AM, Hill AM, Tan SY. Nuts and cardiovascular disease prevention. Curr Atheroscler Rep. 2018; 20:48.
10. Fleischer DM. The natural history of peanut and tree nut allergy. Curr Allergy Asthma Rep. 2007; 7:175–181.
11. Abrams EM, Sicherer SH. Diagnosis and management of food allergy. CMAJ. 2016; 188:1087–1093.
12. Smeekens JM, Bagley K, Kulis M. Tree nut allergies: allergen homology, cross-reactivity, and implications for therapy. Clin Exp Allergy. 2018; 48:762–772.
13. Elizur A, Appel MY, Nachshon L, et al. Walnut oral immunotherapy for desensitisation of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study. Lancet Child Adolesc Health. 2019; 3:312–321.
14. Wasserman RL, Windom HH, Lie D, et al. Exploiting nut cross-reactivity to facilitate real-world treatment of tree nut allergy. Ann Allergy Asthma Immunol. 2021; 127:149–151.
15. Moraly T, Pelletier de Chambure D, Verdun S, et al. Oral immunotherapy for hazelnut allergy: a single-center retrospective study on 100 patients. J Allergy Clin Immunol Pract. 2020; 8:704–709.e4.
16. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2018; 3:85–94.
17. Andorf S, Purington N, Kumar D, et al. A phase 2 randomized controlled multisite study using omalizumab-facilitated rapid desensitization to test continued *vs* discontinued dosing in multifood allergic individuals. EClinicalMedicine. 2019; 7: 27–38.
18. Erdle SC, Soller L, Wong T, et al. First real-world safety analysis of preschool tree nut oral immunotherapy. Allergy. 2020; 75:120–274.
19. Soller L, Abrams EM, Carr S, et al. First real-world safety analysis of preschool peanut oral immunotherapy. J Allergy Clin Immunol Pract. 2019; 7:2759–2767.e5.
20. Epstein-Rigbi N, Goldberg MR, Levy MB, et al. Quality of life of food-allergic patients before, during, and after oral immunotherapy. J Allergy Clin Immunol Pract. 2019; 7:429–436.e2.
21. Abrams E. Overview of food allergy: Symptoms and diagnosis. J Food Allergy. 2022; 4:19–21.
22. Greiwe J. Optimal patient selection for oral immunotherapy. J Food Allergy. 2022; 4:49–52.

23. Graham F. Variations in protocol development during oral immunotherapy. J Food Allergy. 2022; 4:86–97.
24. Windom H. A practical focus on multi-food oral immunotherapy. J Food Allergy. 2022; 4:158–161.
25. Upton J. Efficacy, effectiveness and other patient-centered outcomes of oral immunotherapy. J Food Allergy. 2022; 4:28–33.
26. Wasserman RL. Long term management: assessment of OIT success including integration of oral sustained unresponsiveness challenges. J Food Allergy. 2022; 4:94–97.
27. Bégin P, Chan ES, Kim H, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol. 2020; 16:20.
28. Wasserman RL, Factor J, Windom HH, et al. An approach to the office-based practice of food oral immu-notherapy. J Allergy Clin Immunol Pract. 2021; 9:1826–1838.e8.
29. National Institutes of Health Office of Dietary Supplements. 2021. Selenium. Fact sheet for consumers. Available online at https://ods.od.nih.gov/factsheets/Selenium-Consumer. Accessed March 26, 2022.
30. Soller L, Abrams EM, Carr S, et al. First real-world effectiveness analysis of preschool peanut oral immunotherapy. J Allergy Clin Immunol Pract. 2021; 9:1349–1356.e1.
31. Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy (PACE): a systematic review and meta-analysis of efficacy and safety. Lancet. 2019; 393:2222–2232. □