

Using randomised, double-blind, N-of-1 trials of food challenge to diagnose food allergy and assess the effectiveness of food allergen avoidance

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Food allergy leading to acute distress can result in chronic feelings of apprehension about recurrences. As the outcomes of food allergy include death, caution must prevail. The impact on the life of each person suspected of having a food allergy and those close to them can be substantial; so progress in valid identification of food allergy is very important. Specialists in allergies have been aware of these issues since the middle of the 20th century and have gradually developed stepwise experimental approaches through which alleged food allergies can be identified objectively and safely.

In 1950, Loveless¹ pioneered an improved method of establishing the existence of food allergy rigorously using placebos to blind both patients and clinicians.

Every attempt was made to prevent the subject from learning on which occasion milk was involved. The placebo consisted of one of three commercial antacids, Amphojel, Basaljel, or Titralac (see footnotes, Table II), mixed with water on one occasion and with milk on another. The consumer was asked to close his eyes and his nostrils until after the meal had been brought into the room and swallowed. An independent technician decided which feeding was to include milk and prepared both meals in an adjacent room without informing the patient or the physician of their identity.¹

In a series of eight patients with alleged milk allergy, two failed to demonstrate any symptom during the test. This new diagnostic technique provided evidence to assess whether symptoms actually resulted from food allergy.

Twenty-one years passed before Maslansky and Wein² used Loveless's experimental design to compare chocolate with a placebo to investigate alleged

allergy to the former, chosen for its high prevalence and relative safety.

Two sets of opaque capsules were prepared for us, one containing pure de-fatted cocoa with all but 2% cocoa than is found in 2 average $\frac{3}{4}$ ounce bars of packaged milk chocolate. The second capsules, which appeared identical to the first, contained an inert placebo.

Using a double-blind procedure, $\frac{1}{2}$ the cases were started on Code 1 and the other $\frac{1}{2}$ on Code 2. They took 6 capsules every morning after breakfast for 6 consecutive days...

After 2 day period, patients were interviewed, and the alternate capsules were supplied for an additional 6-day trial, ...²

Of eight cases of alleged chocolate allergy, symptoms were provoked in only three, none with placebo. Furthermore, of the three who tested positive in these blinded challenges, only one tested positive to the skin scratch test. The disparity between clinical symptoms, skin test results and the results of the placebo-controlled food challenge raised questions about the validity of then current approaches to diagnosing allergies.

Five years later, May³ applied the same diagnostic technique in 38 children with a variety of food allergies, including allergy to peanuts and eggs. Symptoms were provoked in only 11 of the 38 children.

Despite a few false-negative results,⁴ the double-blind placebo-controlled food challenge became a gold standard for diagnosing food allergies in clinical research and occasionally in clinical practice.⁵

In 2015, the diagnostic technique contributed to a paradigm shift in food allergy prevention.⁶ For over a decade, alleged peanut allergy appeared to have been on the increase. Du Toit et al.⁶ selected infants judged

to be at risk of peanut allergy and allocated them at random either to avoidance of peanuts, as the then-current guidelines recommended, or to sustained exposure to peanuts. The study showed a clear advantage for the peanut consumption group: only 1.9% of them had developed allergy by 60 months of age compared to 19.7% of those allocated to the avoidance group ($p < 0.001$).

The double-blind placebo-controlled food challenge trial design shares many similarities with N-of-1 trials.⁷ Both address individual response. The former is typically used to diagnose or to document harms or the absence of harms, using escalating doses with typically one cycle of comparison. N-of-1 trials, by contrast, are typically used to assess possible benefits, often using many cycles, with or without washout periods. As an acknowledgement of the important contribution of N-of-1 trials to the development of evidence, they were placed at the top of the evidence hierarchy in 2000.⁸

At the time of writing, a three-year-old boy died during an oral food challenge, the unblinded version of the double-blind placebo-controlled food challenge, the preferred test when the presenting symptoms are deemed to be objective. In their initial response to this tragedy, the learned societies have urged revision of protocols and settings but have emphasised the need to retain these important diagnostic tools.⁹

The introduction of double-blind placebo-controlled food challenges has contributed importantly to understanding and managing food allergies. Viewed more widely, this trial design can be seen as a vehicle for delivering more personalised medicine.

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