Translational Medicine @ UniSa

September 2023

What Evidence-Based Medicine (EBM) doesn't say about allergen-specific immunotherapy (AIT)

Gabriele Di Lorenzo
Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy

Marcello Melluso
Medico di Medicina generale ASP 206 of Palermo, Palermo, Italy

Alessandro Rodolico
Psychiatry Unit, Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy

Follow this and additional works at: https://tmj.unisa.it/journal

Part of the Health Communication Commons, Life Sciences Commons, and the Medicine and Health Sciences Commons

Recommended Citation

REVIEW

What Evidence-based Medicine (EBM) Doesn't Say About Allergen-specific Immunotherapy (AIT)

Gabriele Di Lorenzo [a,*], Marcello Melluso [b], Alessandro Rodolico [c]

[a] Department of Health Promotion Sciences, Maternal and Infant Care, Internal Medicine and Medical Specialties (PROMISE), University of Palermo, Palermo, Italy
[b] Medico di Medicina Generale ASP 206 of Palermo, Palermo, Italy
[c] Psychiatry Unit, Department of Clinical and Experimental Medicine, University of Catania, 95123 Catania, Italy

Abstract

Evidence-based allergology for the treatment of allergic rhinitis with allergen-specific immunotherapy (AIT) has been used in publications by the companies manufacturing AIT. The purpose of randomized controlled trials (RCTs) is to provide physicians, health authorities, patients, and their families with the best evidence upon which to base treatment decisions. However, some RCT results may do more harm than good because they serve the commercial interests of the companies producing and marketing AIT more than the interests of patients. Allergic rhinitis is a trivial disease that is not life-threatening and is easily controlled by drugs. In this paper, we analyze some of the more controversial points underlying the EBM supporting the use of AIT.

The paradox behind RCT-based practice is that AIT is based on the results of incorrectly interpreted RCTs. International scientific societies and drug regulatory bodies should analyze trials more carefully, considering potential conflicts of interest.

Keywords: Conflict of interest, Evidence-based medicine, Allergen-specific immunotherapy, Randomized controlled trials, Meta-analysis, Systematic review

---

Key points

Question: How much is the evidence-based medicine (EBM) in allergology influenced by authors' conflicts of interest?

Findings: In this review, we have analyzed the controversial field of allergen-specific immunotherapy (AIT), showing how the indications given by drug regulators and international scientific societies are influenced not only by economic conflicts of interest (COIs) but, above all, by academic ones, with repercussions for both patients and national health systems.

Meaning: Randomized controlled trials, when affected by obvious COIs, can cause EBM indications to be misleading. Greater clarity and transparency are needed in the interest of patients, avoiding the practice of discrediting authors who present different points of view, and trying instead to establish constructive scientific relationships.

---

1. Introduction

The evidence-based medicine (EBM) approach has influenced physician decision-making profoundly over the past 30 years [1]. As is well known, the founders of EBM, Cochrane, Feinstein and Sachett, shifted decision-making from subjective judgments (based on the experience and opinion of the senior physician) to a formal analysis of the evidence which, with Shekelle, Alan and Guyatt, led to the drafting of guidelines, written with different methodol ogies up to GRADE [2—4]. In other words, there was a shift from opinion-based medicine, i.e. position papers in which a treatment was recommended if physicians believed that patients could benefit from it, to EBM, i.e., guidelines in which a treatment was recommended based on the results of the evidence (Fig. 1) [5].

But what is the evidence? Everybody knows the EBM pyramid, at the top of which is the systematic review (RS), with or without meta-analysis, of randomized controlled trials (RCTs) (Fig. 2).

The RS is a systematic analysis of RCTs which, in turn, are referred to as the gold standard for the "unbiased" evaluation of a treatment [6]. The concept of the impartiality of RCTs is due to the inclusion of at least one control group, which is compared with at least one intervention group which undergoes an experimental treatment. The control group may receive either a placebo (placebo-controlled study) or

Abbreviations

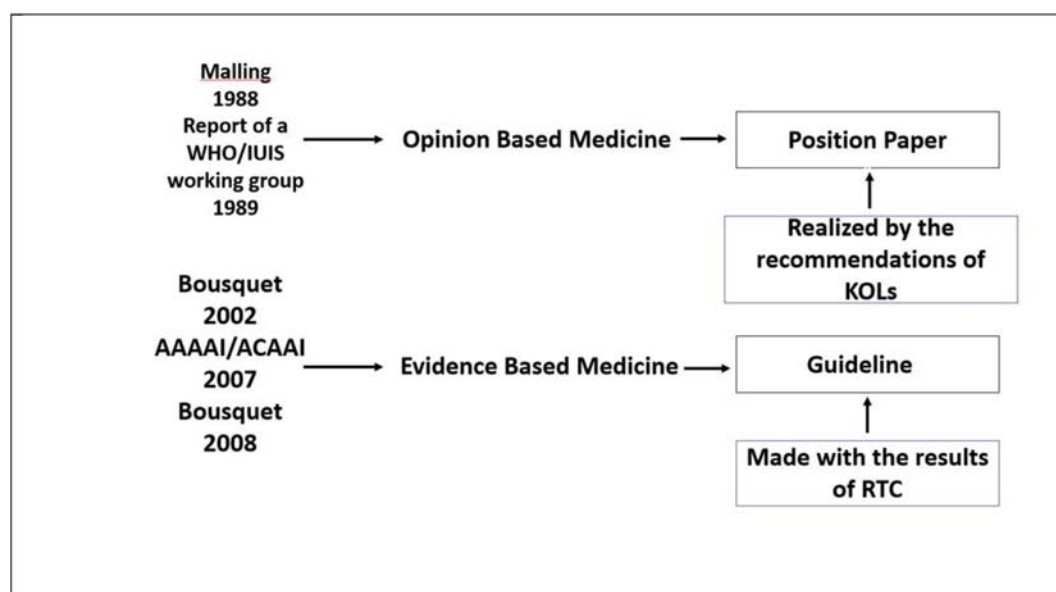|	
AAAAI	American Academy of Allergy, Asthma & Immunology
ACAAI	American College of Allergy, Asthma and Immunology
AdSS	Adjusted Symptom Score
ARC	Allergic rhinoconjunctivitis
AIT	Allergen-specific immunotherapy
COI	Conflict of interest
CAGR	Average compound annual growth rate
CS	Combined score
EBM	Evidence-based Medicine
EMA	European Medicines Agency
FAS	Full Analysis Set
FDA	Food and Drug Administration
FEV1	Forced Expiratory Volume in the 1st second
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
KOL	Key Opinion Leaders
KU_A/L	Kilo allergy unit per liter
IR	Index of reactivity
LS	Least squares
MA	Meta analysis
MS	Medication score
RCT	Randomized controlled trials
RMS	Rescue Medication Score
RTSS	Rhinoconjunctivitis Total Symptom Score
SCIT	Subcutaneous immunotherapy
SLIT-D	Sublingual immunotherapy Drop
SLIT-T	Sublingual immunotherapy Tablet
SPT	Skin Prick Test
SS	Symptom score
SR	Systematic review
WAO	World Allergy Organization
WHO	World Health Organization

Fig. 1. The shift from opinion-based medicine to evidence-based medicine. AAAAI: American Academy of Allergy, Asthma & Immunology; ACAAI: American College of Allergy, Asthma and Immunology; KOLs: Key Opinion Leaders; IUIS: International Union of Immunological Societies; RCT: randomized controlled trials; WHO: World Health Organization.
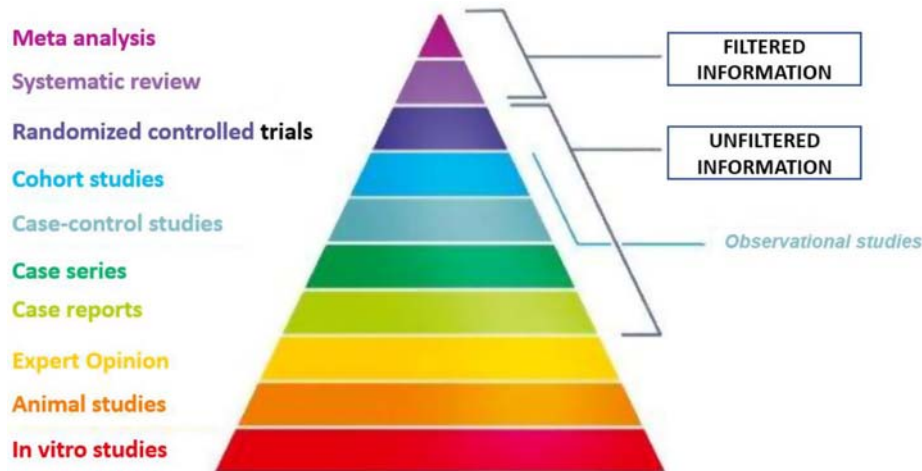
Fig. 2. The pyramid of evidence.

an already used "effective treatment" (positive control study). Another important feature of these studies is "randomization": subjects are assigned to the treatment or control groups randomly. The randomization sequence can be obtained through several methodologies, but recently the use of software has consistently replaced other ones [7]. If both the physician/experimenter and the patient do not know which treatment is assigned, it is a double-blind placebo-controlled study; whereas, if it is only the patient who does not know the treatment, it is a single-blind placebo-controlled study. However, as pointed out by Ioannidis in one of his landmark publications [8], many of the results of RCTs evaluating a new treatment may not be entirely reliable because, as is well known, RCTs are often sponsored by the very companies that manufacture and market the drug being examined. This problem has been well highlighted with antidepressant drugs [9]. Ioannidis's considerations point-out that, while the physician's primary goal is to improve the patient's health status, the pharmaceutical company's is to increase financial profit for its shareholders [8]. in example of this is Vioox® with the ADVANCE study [10].

Thus, in an RCT, there can be an important conflict of interest (COI) in favor of the use of a therapy, which manifests itself with key opinion leaders (KOLs). The COI of KOLs, who are independent consultants to a pharmaceutical company, can be economic, which is easily identified because it is almost always declared, but also academic, which is rarely declared and is more difficult to identify. In many fields of medicine, the two COIs are often interconnected [11].

In allergology, the therapy for respiratory allergic diseases includes environmental preventive measures, medications, and allergen-specific immunotherapy (AIT) [12]. In this paper, we will deal with AIT, considering it with the EBM methodology.

The global AIT market in 2018 was estimated by GlobalData to be $901 million, with a projected increase to $1.1 billion in 2028 and with an average compound annual growth rate (CAGR) of 2.3%; thus, it is predicted be a very slow-growing market [13].

1.1. When, why, and how can a COI materialize?

Psychiatrist Christiaan Vinkers and his collaborators selected and analyzed publications that contained positive or negative words about therapies. The number of articles with positive words, in the title or abstract of the publication, increased from an average of 2.0% in 1974–80 to 17.5% in 2014, while articles with negative words increased from 1.3% to 2.4% over the same period [14].

Let us analyze when, why, and how a COI can arise for physicians who are the KOLs of a pharmaceutical company:

- When: if negative judgments are used in a publication for a treatment which, instead, the KOLs have validated with the company's RCTs and RSs;
- Why: a negative judgment, if documented, calls into question what was previously published;
- How: first by attacking the author of the negative publication, and then by excluding him or her from the debate. To do this, KOLs minimize the importance of the study by highlighting points that KOLs consider weak, or by publishing the critique as correspondence, or by publishing an

article in a journal that gives no opportunity to respond to criticism.

It is also important, when evaluating a study, to know the history of its peer reviews. Reviewers, in fact, are 'Peer Reviewers' chosen by the Editor, and they themselves may have not only an economic but also an academic COI for the work under evaluation, thus influencing the Editor's decision for the outcome of a paper with their judgments [14]. The academic COI, in our opinion, is the most insidious, because it can block publication of a study that interferes with a strand of the peer reviewer's research or because it highlights the topic's lack of scientific importance, jeopardizing his/her position as Chief Researcher or his/her career progression [15,16].

In this way, a paper that criticizes diagnosis and therapy in a specialty branch, with data highlighting the scientific inconsistency of the claims of the KOLs of scientific societies, will be unlikely to be published by a journal of branch reference even if the observations are correct, noting rather the corporatist defense of specialized methods, such as *in vivo* diagnostics and AIT in allergology. In these cases, authors will have to seek space in a non-specialty journal. Thus, even if the non-specialty journal is extremely authoritative, this may result in a lack of the appropriate visibility of the paper for specialists in the field compared to the contrasting positions published in specialty-specific journals. Indeed, the specialist in the field practices according to the rules of the relevant scientific society; but, if these are questioned, the specialist's own professional activity is questioned. This was the case with Holt's article in 1967, published in the *New England Journal of Medicine* precisely because, in those years, its negative comments on allergy diagnostics and allergen-specific therapy were extremely provocative [17]. Francis Lowell, the President *pro tempore* of the American Academy of Allergy, Asthma & Immunology (AAAAI), hastened to write a very negative commentary on Holt's article, which was, of course, published in the *Journal of Allergy and Clinical Immunology*, AAAAI's flagship journal [18]. Holt had questioned *in vivo* allergy diagnostics, which at the time was the only diagnostic method practiced [17], along with the results of subcutaneous immunotherapy (SCIT), the only route of AIT administration practiced by allergists worldwide. In our opinion, it is important to remark that, while Holt's article was published in *New England Journal of Medicine*, the critique was published in a journal with a specialty focus, the reference point of a major scientific society of allergology, and, therefore, widely read by specialists in the field.

2. Analysis of the EBM on AIT

In recent years, the importance of *in vivo* testing alone for diagnosing and prescribing AIT has been greatly downgraded [19], as has that of SCIT, the use of which has greatly diminished due to the use of sublingual immunotherapy (SLIT) [20]. SLIT can be administered in drops (SLIT-D) or tablets (SLIT-T); the former is a product designated as a Named Patient Product (NPP), as is SCIT.

2.1. Historical background

SLIT was approved by the FDA in 2014 but is not a new therapy, having been widely used in the United States for many years. The early literature includes many articles by a variety of authors [21–26]. As reported by Hansel [21], in 1928 Black was the first to identify the successful management of a pollen allergy by SLIT. Moreover, the American Academy of Otolaryngic Allergy offered a course called "Sublingual Therapy in Allergy" from 1963 to 1980. In that period, SLIT was available in two different forms: drops and rapidly dissolving tablets. These latter have only recently been introduced in Europe [27].

The use of SLIT in the United States decreased markedly and almost "vanished" (an exception is the American Academy of Environmental Medicine, where Max Samter offered courses on sublingual treatments for years) [28]. With the exception of a few publications by David Morris [29], no further articles about SLIT were published in the United States between 1970 and 1993, when Nelson et al. [30] performed an RCT concluding that SLIT with high-dose standardized cat extracts was no more effective than placebo in reducing symptoms or affecting immunological measures of cat sensitivity.

The prescription of SCIT and SLIT-D is specific and nominal for an individual patient, and is shipped directly to their home, with an exclusive company-patient relationship borrowed from the prescribing physician. Only a few extracts have been registered as "drugs" by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA): Grazax®/Grastek®, sold in the EU by ALK and in the US by Merck, Sharp & Dohme, and Oralair® (Stallergenes/Greer) for respiratory allergy to grasses, and Accarizax®/Odactra® for respiratory allergy to house dust mites, sold in the EU by ALK and in the US by Merck, Sharp & Dohme. In Italy, Grazax® and Oralair® are dispensed by the national health system as SLIT-T, with a therapeutic plan and a spending cap [31,32].

SLIT has become the most prescribed route of administration in many EU countries which, however, still prefer SLIT-D over SLIT-T [33].

But, the question remains, whether what the regulatory agencies have approved has really been done right.

Many researchers are calling for more attention from regulatory agencies when evaluating the efficacy of a drug [34], and they may be right. Our misgivings are supported by the results of the RCT by Cox et al. [35], which is the only RCT performed in the US used by the FDA to authorize the marketing of SLIT-T (Oralair®) for grass rhinoconjunctivitis [36].

2.2. Criticalities present in Cox et al.'s RCT

2.2.1. Authors

We will evaluate the study by Cox et al. [35] to highlight some critical issues that emerge from the careful reading of this research, but which were omitted by the SLIT KOLs [37,38].

Curiously, the authors of Cox's RCT include three employees (Laurence Ambroisine, MSc, Michel Melac, MD, and Robert K. Zeldint, MD) of the company (Stallergenes SA, Antony, France) that sponsored the study. Only L. S. Cox, T. B. Casale, D. I. Bernstein, and P. S. Creticos report potential COIs, while the three Stallergenes employees declare no potential COIs. The role of each author in the publication is unknown because it is not stated.

2.2.2. Methods

2.2.2.1. Participants. The study enrolled men and women aged 18–65 years with documented grass pollen-related allergic rhinoconjunctivitis (ARC) for at least the 2 previous grass pollen seasons, a positive skin prick test (SPT) response to timothy grass (mean wheal diameter of 5 mm or greater than that elicited by the negative control; longest flare dimension, ≥10 mm), a retrospective Rhinoconjunctivitis Total Symptom Score (RTSS; scale, 0–18) of 12 or greater during the previous grass pollen season, and a Forced Expiratory Volume in the 1st second (FEV1) of 80% or greater of predicted value.

2.2.2.2. Outcome. Participants were provided with a daily record card for recording the 6 individual Rhinoconjunctivitis Symptom Scores (RSSs: sneezing, runny nose, itchy nose, nasal congestion, itchy eyes, and watery eyes) and rescue medication use during the previous 24 hours. The diary cards were to be completed at the same time every evening, from approximately 3 weeks before the pollen

season until its end, by using a 4-point descriptor scale for each symptom: 0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms. The daily RTSS was the sum of the 6 individual RSSs. The daily Rescue Medication Score (RMS) was derived as follows: 0, no rescue medication taken; 1, use of antihistamine (oral drops, eye drops, or both); 2, use of nasal corticosteroid; and 3, use of oral corticosteroid. If a study subject took 2 or more rescue medications on the same day, the highest score was used for the RMS.

Such a value, assuming an average Adjusted Symptom Score (AdSS) of 6 for the placebo group (as observed in previous grass pollen allergen studies), corresponds to a 20% relative mean difference, the threshold recommended by the World Allergy Organization (WAO) taskforce as clinically relevant for efficacy [37]. Assuming a screening failure rate of 20% and a dropout rate of 10%, the authors planned to screen approximately 550 subjects and randomize 424 subjects.

2.2.2.3. Statistical analysis. The primary efficacy end point [daily combined score (CS) during the pollen period while receiving treatment] was analyzed for the full analysis set by using a repeated measures analysis of covariance model, including treatment group and valid days as main effects, and patient as a random effect. The daily RTSS, RMS, AdSS, and RSSs were analyzed as per the primary efficacy criterion. We will only consider the RTSS because it is a parameter that was also used to recruit the participants (retrospective RTSS) of the study, in order to ensure the equivalence of rhinitis severity in the two treatment groups.

2.2.2.4. Results. Four hundred seventy-three participants were randomized for active treatment (n = 233) or placebo (n = 240). Because 35 study subjects did not have at least one CS during the pollen period while receiving treatment, the full analysis set (FAS) consisted of 438 participants: 210 in the 300IR group and 228 in the placebo group. The mean duration of ARC was 22.9 years (SD, 12.8 years).

Fig. 3 shows an extract of the original retrospective RTSS and RTSS data from the original article by Cox et al. [35] Specifically, we report only the data of the retrospective RTSS (Table I) and the RTSS (Table III).

More specifically, we will focus our analysis on the most critical methodological problem of the RCTs on SLIT-T: the metric used by the authors to evaluate the clinical benefit. This metric is mathematically incorrect because it calculates the percentage difference between SLIT and placebo, not considering the range

of the symptom score (SS) scale and enormously magnifying the difference between the groups. Using this metric, a 1-point difference between the two treatments would have the same percentage difference on an 18-point scale (the most used SS scale) as it would on a 100-point scale or any other scale, and this is mathematically unacceptable (Fig. 4A and B).

In Fig. 4 A and B, we show the calculation used in RCTs (horizontal arrow), which considers only the mean SS at the end of treatment, ignoring the scaling interval. The use of the latter is, in fact, critical in assessing the efficacy of SLIT-T vs. Placebo. Including the scale in the calculation significatively reduces the percentage of improvement, although the difference between the 2 groups remains the same. Alternatively, the difference between the groups can be calculated as follows: SSt SLIT (t = during treatment) - SSt Placebo (t = during treatment)/SSu (u = SS without treatment), thus the baseline value of the SLIT group and the placebo group, which are equal at the time of randomization (Baseline characteristics [35]). This calculation allows us to use the range of the symptom scale to assess clinical improvement, unlike the method used (SLIT SSt - Placebo SSt/Placebo SSt [t = during treatment]), which is incorrect in not considering the range of the symptom scale used and, thus, overestimating the treatment effect. The correct metric, which must consider the range of the scale, has been given by the WAO [37] and is based on the comparison of pre-treatment and post-treatment SS from the intervention and placebo groups. Using this metric, only a small difference between SLIT and placebo is demonstrated, far below the FDA (15%) and WAO (20%) efficacy thresholds [37,38]. The baseline value in the case of SLIT RCTs is the RTSS score (previous year), which is used by the investigators as an inclusion criterion. In other

words, the RTSS score is taken in RCTs as the SS that patients would have in the absence of treatment, and it corresponds to the clinical criterion (severity of rhinitis) for inclusion. Certainly, the RTSS could be inaccurate, but it should be similar to the SS of the treatment season, especially if the pollen counts of the two consecutive seasons are similar, and this possible inaccuracy should not affect the results.

In a meta-analysis, our group [39] also reported the difference between SLIT and placebo not only in terms of standardized mean difference (SMD), but also in terms of mean difference (MD), that is, the difference in SS points between SLIT and placebo. We showed that this difference is −0.83 SS points (95% CI, −1.03 to −0.63). In 2014, Devillier et al. [40] published that the minimally clinically important difference, defined as the smallest improvement considered beneficial by a patient, is between 1.1 and 1.3 SS points in patients with ARC from grass pollen. Therefore, the difference of −0.83 SS points reported in the previously published meta-analysis [39] is less than the minimal clinically important difference estimated by Devillier [40].

In conclusion, analyses based on Devillier's minimum important difference, which sets the efficacy threshold at 1.1 SS points, confirm the conclusions of our meta-analysis [39] which estimated a small benefit from SLIT-T, lower than the FDA's 15% or WAO's 20% difference thresholds, and that the flawed metric used in the RCT of Cox and the other RCTs with grass SLIT-T (*see RCTs reported in reference* [39]) significantly overestimated the modest, and perhaps clinically unimportant, treatment benefit.

Another observation on the fatuity of allergy guidelines can be made again by analyzing Cox's study which, unlike all other RCTs with SLIT-T, did

EXTRACT of TABLE I. Basic Characteristics (FAS) [35]			
	300IR group (n = 210)	Placebo group (n = 228)	*P*
RRTSS	14.9 (1.95)	14.9 (1.91)	NS
FAS: Full Analysis Set; RRTSS: Retrospective Rhinoconjunctivitis Total Symptom Score; NS: Not significant			

EXTRACT FROM TABLE III. SECONDARY EFFICACY ANALYSES (POLLEN PERIOD, FAS) [35]						
	300IR, LS mean (SE)	Placebo, LS mean (SE)	300IR vs placebo, LS mean difference			
			Point estimate	95% CI	P value	Relative difference (%)
Daily RTSS	3.21 (0.315)	4.16 (0.299)	-0.95	-1.59 to -0.31	0.004	- 22.9
FAS: Full Analysis Set; LS: Least squares; RTSS: Rhinoconjunctivitis Total Symptom Score						

Fig. 3. *Extracts of table I and table III of the original data of Cox et al.* [35].

A				
18-point scale.				
Example study	SLIT	Placebo	Difference	Percentage Improvement
RTSS	15	15		
Mean during treatment	3	4	-1	(3-4) / 4 = **-25% (not including the scale)**
Difference	-12	-11	-1	
Percentage Improvement	80%	74%		80%-74% = **-6%** (11-12) / 15 =-6% **(including the scale)**

B				
Hypothetical 100-point scale, with hypothetical RTSS (baseline score) =95, congruent with a 100-point scale.				
Example study	SLIT	Placebo	Difference	Percentage Improvement
RTSS	95	95		
Mean during treatment	3	4	-1	(3-4) / 4 = -25% **(not including the scale)**
Difference	-92	-91	-1	
Percentage Improvement	96.85%	95.80%		95.80%-96.85% = -1.05% (11-12) / 15 =-6% **(including the scale)**
RTSS: rhinoconjunctivitis Total Symptom Score				

Fig. 4. A and B mathematical demonstration of the fallacy of the calculation performed by Cox and proposed by World Allergy Organization [39].

not consider the presence of serum IgE concentration ≥0.7 kilo allergy unit per liter (KUA/L) among the inclusion criteria [37,41]. Cox et al. [35], in discussion, stated that they were consistent with the behavior of US allergists, and perhaps many non-US allergists as well, who in their daily practice base allergological diagnoses and prescriptions of AIT on SPT alone [35]. The authors report, however, that in 11% of the subjects enrolled in their study, the serum IgE specific for grasses was <1 KUA/L, that is, they were not allergic to grasses. One wonders, again, how these patients could be considered in the study and whether (and how much) their inclusion and then exclusion vitiated the reported results, even though they were not considered in the statistical analysis [35].

3. Discussion

3.1. Who controls the controllers?

In the meta-analysis of our group [39], the results obtained demonstrated only a small benefit of SLIT-T for seasonal ARC to grass pollen for symptoms and symptomatic drug use (antihistamines and nasal corticosteroids), and the conclusions were congruent with these findings: considering the low magnitude of benefit, convenience and ease of administration do not seem to be sufficient reasons for choosing SLIT-T.

These conclusions have sparked reactions by some Stallergenes KOLs (*see below*). Devellier [42], in the 'Translating Best Evidence into Best Care' section of the *Journal of Pediatrics*, after several criticisms of the meta-analysis [39], concluded, "Although the methodology of their meta-analysis was rigorous, their interpretation of the results is questionable." As soon as we read this comment, we wrote to the Editor *pro tempore* of the journal, Professor WF Balistrieri, who did not want to publish our response to Devillier nor our request to clarify the sentence "their interpretation of the results is questionable," with which he had concluded his letter. Professor Balistrieri sent me an e-mail in which he wrote that "our reply was not a priority for the Journal." A personal e-mail was, in addition, sent to Devillier (p.devillier@hopital-foch.org), but we never received a reply.

Finally, we feel it is important to point out that the Stallergenes KOLs themselves published their critique as a correspondence, not in *JAMA Internal Medicine* where the original article had been published, but in another journal, and they concluded with the following sentence: "In conclusion, Di Bona

et al. performed a rigorous meta-analysis but over-interpreted the results while losing sight of other important parameters." [43] Again, they were asked to contextualize what the above sentence referred to, but the clarifying reply never came.

In 2017, Passalacqua, Incorvaia and Ridolo, referring to our meta-analysis [39], wrote: "These conclusions claim to wipe out all the long process leading to the acknowledgement of the quality and to registration of grass pollen tablets, but are substantially unfounded because the meta-analysis is significantly flawed, as highlighted by Cox et al." [43,44]. From a simple PubMed search as of October 20 2022, we found that: Passalacqua, using the search [(Passalacqua G [Author]) AND (allergen immunotherapy)], has as many as 209 publications on AIT, placing him as the first researcher in the world in terms of number of publications on this topic; Incorvaia, a scientific advisor for Stallergenes Italy, using for research [(Incorvaia C [Author]) AND (allergen immunotherapy)], has 151 publications on AIT; Ridolo, using the search [(Ridolo E [Author]) AND (allergen immunotherapy)], has 54 publications on AIT. We also find it interesting to note that Passalacqua and Ridolo have never claimed to have any COIs. The article and this bibliometric check suggest a COI which is not economic, but academic because, in our opinion, it is difficult to explain such a high number of publications for a low-efficacy therapy.

4. Conclusions

Many KOLs have created academic space for themselves by exploiting EBM for diseases with high epidemiological impact but low clinical relevance, while proper drug therapy optimally controls the symptoms of seasonal ARC [45].

As internists, we would like to conclude by paraphrasing a 1904 aphorism by William Osler, which is still very relevant despite the 118 years that have passed: "There are two kinds of researchers, those who do research using their brains, and those who do research using only their mouths."

Author contributions

Gabriele Di Lorenzo had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Conceptualization: Gabriele Di Lorenzo; Methodology: Gabriele Di Lorenzo, Alessandro Rodolico; Investigation: Gabriele Di Lorenzo, Marcello Melluso Alessandro Rodolico; Formal Analysis: Gabriele Di Lorenzo, Alessandro Rodolico; Data Curation: Gabriele Di Lorenzo; Writing - Original Draft

Preparation: Gabriele Di Lorenzo; Writing - Review & Editing: Gabriele Di Lorenzo, Marcello Melluso, Alessandro Rodolico.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

References

[1] Fava GA. Evidence-based medicine was bound to fail: a report to Alvan Feinstein. J Clin Epidemiol 2017 Apr;84:3−7. https://doi.org/10.1016/j.jclinepi.2017.01.012. PMID: 28532614.

[2] Shekelle PG, Schriger DL. Evaluating the use of the appropriateness method in the Agency for Health Care Policy and Research Clinical Practice Guideline Development process. Health Serv Res 1996 Oct;31(4):453−68. PMID: 8885858; PMCID: PMC1070131.

[3] Eddy D. David Eddy. Interview by Bethan Hughes. Nat Rev Drug Discov 2010 Mar;9(3):186. https://doi.org/10.1038/nrd3134. PMID: 20190783.

[4] Jaeschke R, Guyatt GH, Dellinger P, Schünemann H, Levy MM, Kunz R, Norris S, Bion J, GRADE Working Group. Use of GRADE grid to reach decisions on clinical practice guidelines when consensus is elusive. BMJ 2008 Jul 31;337:a744. https://doi.org/10.1136/bmj.a744. PMID: 18669566.

[5] Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol 2001 Nov;108(5 Suppl):S147−334. https://doi.org/10.1067/mai.2001.118891. PMID: 11707753.

[6] Rosner AL. Evidence-based medicine: revisiting the pyramid of priorities. J Bodyw Mov Ther 2012 Jan;16(1):42−9. https://doi.org/10.1016/j.jbmt.2011.05.003. Epub 2011 Jun 24. PMID: 22196426.

[7] Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ 2010 Mar 23;340:c869. https://doi.org/10.1136/bmj.c869. PMID: 20332511; PMCID: PMC2844943.

[8] Ioannidis JPA. Correction: Why Most Published Research Findings Are False. PLoS Med. 2022 Aug 25;19(8):e1004085. doi: 10.1371/journal.pmed.1004085. Erratum for: PLoS Med 2005 Aug;2(8):e124. PMID: 36007233; PMCID: PMC9410711.

[9] Fava GA. May antidepressant drugs worsen the conditions they are supposed to treat? The clinical foundations of the oppositional model of tolerance. Ther Adv Psychopharmacol. 2020 Nov 2;10:2045125320970325. https://doi.org/10.1177/2045125320970325. PMID: 33224471; PMCID: PMC7649913.

[10] Hill KP, Ross JS, Egilman DS, Krumholz HM. The ADVANTAGE seeding trial: a review of internal documents.

Ann Intern Med 2008 Aug 19;149(4):251—8. https://doi.org/10.7326/0003-4819-149-4-200808190-00006. PMID: 18711155.

[11] Moynihan R. Key opinion leaders: independent experts or drug representatives in disguise? BMJ 2008 Jun 21;336(7658): 1402—3. https://doi.org/10.1136/bmj.39575.675787.651. PMID: 18566074; PMCID: PMC2432185.

[12] Meltzer EO, Wallace D, Friedman HS, Navaratnam P, Scott EP, Nolte H. Meta-analyses of the efficacy of pharmacotherapies and sublingual allergy immunotherapy tablets for allergic rhinitis in adults and children. Rhinology 2021 Oct 1; 59(5):422—32. https://doi.org/10.4193/Rhin21.054. PMID: 34463311.

[13] Drug Development & Delivery. MARKET BRIEF — Allergic Rhinitis Immunotherapy: Opportunity Analysis & Forecasts to 2028. https://drug-dev.com/market-brief-allergic-rhinitis-immunotherapy-opportunity-analysis-forecasts-to-2028/. [Accessed 19 November 2023].

[14] Vinkers CH, Tijdink JK, Otte WM. Use of positive and negative words in scientific PubMed abstracts between 1974 and 2014: retrospective analysis. BMJ 2015 Dec 14;351:h6467. https://doi.org/10.1136/bmj.h6467. PMID: 26668206; PMCID: PMC4677695.

[15] Bailey Bill, Let's Abolish Pre-Publication Peer Review and Print Journals (October 23, 2018). Available at SSRN: https://ssrn.com/abstract=3170307 or https://dx.doi.org/10.2139/ssrn.3170307.

[16] Matsui A, Chen E, Wang Y, Ferrara E. The impact of peer review on the contribution potential of scientific papers. PeerJ 2021 Sep 15;9:e11999. https://doi.org/10.7717/peerj.11999. PMID: 34616596; PMCID: PMC8459734.

[17] Holt Jr LE. A non allergist looks at allergy. N Engl J Med 1967 Jun 29; 276(26):1449—54. https://doi.org/10.1056/NEJM196706292762601. PMID: 6027659.

[18] Lowell FG, Franklin W. Correspondence: injection therapy. J Allergy 1968 Mar;41(3):174—5. https://doi.org/10.1016/0021-8707(68)90057-9. PMID: 5238594.

[19] Ansotegui IJ, Melioli G, Canonica GW, Caraballo L, Villa E, Ebisawa M, Passalacqua G, Savi E, Ebo D, Gómez RM, Luengo Sánchez O, Oppenheimer JJ, Jensen-Jarolim E, Fischer DA, Haahtela T, Antila M, Bousquet JJ, Cardona V, Chiang WC, Demoly PM, DuBuske LM, Ferrer Puga M, Gerth van Wijk R, González Díaz SN, Gonzalez-Estrada A, Jares E, Kalpaklıoğlu AF, Kase Tanno L, Kowalski ML, Ledford DK, Monge Ortega OP, Morais-Almeida M, Pfaar O, Poulsen LK, Pawankar R, Renz HE, Romano AG, Rosário Filho NA, Rosenwasser L, Sánchez Borges MA, Scala E, Senna GE, Sisul JC, Tang MLK, Yu-Hor Thong B, Valenta R, Wood RA, Zuberbier T. Erratum to "IgE allergy diagnostics and other relevant tests in allergy, a World Allergy Organization position paper" World Allergy Organ J 13/2 (2020) 100080. World Allergy Organ J. 2021 Jun 17;14(7):100557. doi: 10.1016/j.waojou.2021.100557. Erratum for: World Allergy Organ J 2020 Feb 25;13(2):100080. PMID: 34221218; PMCID: PMC8225965.

[20] Passalacqua G, Bagnasco D, Canonica GW. 30 years of sublingual immunotherapy. Allergy 2020 May;75(5):1107—20. https://doi.org/10.1111/all.14113. Epub 2019 Dec 20. PMID: 31715001.

[21] Hansel FK. Sublingual testing and therapy. A comparison with injectable methods. Trans Am Soc Ophthalmol Otolaryngol Allergy; 1972. p. 93—103.

[22] Dickey LW. In: Dickey L, editor. Sublingual antigen testing and therapy for inhalants, foods and petrochemicals. Clinical ecology. Springfield (IL): Charles C. Thomas; 1976. p. 544—53.

[23] Pfeiffer GO. Sublingual procedures. Trans Am Soc Ophthalmol Otolaryngol Allergy; 1970. p. 104.

[24] Ruddy LW. Why sublingual therapy in otolaryngologic allergy. Trans Am Soc Ophthalmol Otolaryngol Allergy; 1976. p. 93—102.

[25] Waickman FJ. Pediatric allergy. Trans Am Soc Ophthalmol Otolaryngol Allergy; 1965. p. 39.

[26] Hansel FK. Allergy of the nose and paranasal sinuses. St Louis (MO: CV Mosby Co; 1936. p. 755.

[27] Kleine-Tebbe J, Ribel M, Herold DA. Safety of a SQ-standardised grass allergen tablet for sublingual immunotherapy: a randomized, placebo-controlled trial. Allergy 2006 Feb; 61(2):181—4. https://doi.org/10.1111/j.1398-9995.2006.00959.x. PMID: 16409193.

[28] Samter M. Questions and answers: Sublingual desensitization for allergy not recommended. JAMA. 1971;215(13): 2119—20. https://doi.org/10.1001/jama.1971.03180260061038.

[29] Morris DL. Treatment of respiratory disease with ultra-small doses of antigens. Ann Allergy 1970 Oct;28(10):494—500. PMID: 5521180.

[30] Nelson HS, Oppenheimer J, Vatsia GA, Buchmeier A. A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract. J Allergy Clin Immunol 1993 Aug;92(2):229—36. https://doi.org/10.1016/0091-6749(93)90166-d. PMID: 8349933.

[31] Domdey A, Njue A, Nuabor W, Lyall M, Heyes A, Elliott L. Allergy immunotherapies for allergic rhinitis: systematic review and assessment of evolving quality. Eur Ann Allergy Clin Immunol 2019 Jul;51(4):147—58. https://doi.org/10.23822/EurAnnACI.1764-1489.100. Epub 2019 Jun 12. PMID: 31187972.

[32] Scala G, Peroni D, Traina G, et al. Immunoterapia Specifica. Oltre i prodotti registrati. Focus sugli NPP. Rivista di Immunologia e Allergologia Pediatrica 2018;1:2—6.

[33] Paoletti G, Di Bona D, Chu DK, et al. Allergen immunotherapy: The growing role of observational and randomized trial "Real-World Evidence". Allergy 2021;76(9):2663—72.

[34] Healy D. Did regulators fail over selective serotonin reuptake inhibitors? BMJ 2006 Jul 8;333(7558):92—5. https://doi.org/10.1136/bmj.333.7558.92. PMID: 16825234; PMCID: PMC1489234.

[35] Cox LS, Casale TB, Nayak AS, Bernstein DI, Creticos PS, Ambroisine L, Melac M, Zeldin RK. Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: the importance of allergen-specific serum IgE. J Allergy Clin Immunol 2012 Dec;130(6):1327—13234.e1. https://doi.org/10.1016/j.jaci.2012.08.032. Epub 2012 Oct 31. PMID: 23122534.

[36] Blanco C, Bazire R, Argiz L, Hernández-Peña J. Sublingual allergen immunotherapy for respiratory allergy: a systematic review. Drugs Context 2018 Nov 5;7:212552. https://doi.org/10.7573/dic.212552. PMID: 30416528; PMCID: PMC6220898.

[37] Canonica GW, Cox L, Pawankar R, Baena-Cagnani CE, Blaiss M, Bonini S, Bousquet J, Calderón M, Compalati E, Durham SR, van Wijk RG, Larenas-Linnemann D, Nelson H, Passalacqua G, Pfaar O, Rosário N, Ryan D, Rosenwasser L, Schmid-Grendelmeier P, Senna G, Valovirta E, Van Bever H, Vichyanond P, Wahn U, Yusuf O. Sublingual immunotherapy: World Allergy Organization position paper 2013 update. World Allergy Organ J 2014 Mar 28;7(1):6. https://doi.org/10.1186/1939-4551-7-6. PMID: 24679069; PMCID: PMC3983904.

[38] Bachert C, Larché M, Bonini S, Canonica GW, Kündig T, Larenas-Linnemann D, Ledford D, Neffen H, Pawankar R, Passalacqua G. Allergen immunotherapy on the way to product-based evaluation-a WAO statement. World Allergy Organ J. 2015 Sep 16;8(1):29. https://doi.org/10.1186/s40413-015-0078-8. PMID: 26417398; PMCID: PMC4571059.

[39] Di Bona D, Plaia A, Leto-Barone MS, La Piana S, Di Lorenzo G. Efficacy of Grass Pollen Allergen Sublingual Immunotherapy Tablets for Seasonal Allergic Rhinoconjunctivitis: A Systematic Review and Meta-analysis. JAMA Intern Med 2015 Aug;175(8):1301—9. https://doi.org/10.1001/jamainternmed.2015.2840. PMID: 26120825.

[40] Devillier P, Chassany O, Vicaut E, de Beaumont O, Robin B, Dreyfus JF, Bousquet PJ. The minimally important difference in the Rhinoconjunctivitis Total Symptom Score in grass-pollen-induced allergic rhinoconjunctivitis. Allergy 2014 Dec;69(12):1689—95. https://doi.org/10.1111/all.12518. Epub 2014 Oct 6. PMID: 25155425.

[41] Di Lorenzo G, Mansueto P, Pacor ML, Rizzo M, Castello F, Martinelli N, Ditta V, Lo Bianco C, Leto-Barone MS, D'Alcamo A, Di Fede G, Rini GB, Ditto AM. Evaluation of serum s-IgE/total IgE ratio in predicting clinical response to

allergen-specific immunotherapy. 1110.e1-4 J Allergy Clin Immunol 2009 May;123(5):1103—10. https://doi.org/10.1016/j.jaci.2009.02.012. Epub 2009 Apr 7. PMID: 19356792.

[42] Devillier P. Allergic rhinitis treatment with sublingual immunotherapy. J Pediatr 2015 Nov;167(5):1169—70. https://doi.org/10.1016/j.jpeds.2015.08.056. PMID: 26603712.

[43] Cox LS, Didier A, Demoly P, Wahn U, Pradalier A, Frew AJ, Devillier P. Methodological aspects of a meta-analysis of grass pollen allergen sublingual immunotherapy tablets. J Allergy Clin Immunol 2016 Jul;138(1):314—315.e4. https://doi.org/10.1016/j.jaci.2016.01.039. Epub 2016 Apr 12. PMID: 27084407.

[44] Ridolo E, Incorvaia C, Gritti BL, Passalacqua G. The current overuse and misuse of meta-analyses on sublingual immunotherapy: the case of grass pollen allergy. Curr Opin Allergy Clin Immunol 2017 Feb;17(1):12—6. https://doi.org/10.1097/ACI.0000000000000330. PMID: 27922912.

[45] Anonymous. Timothy pollen oral lyophilisate (standardised allergenic extract): new drug. Hay fever: 4 months' treatment for 4 days' relief? Prescrire Int 2008;17(97):196.