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Placebo effects in allergen immunotherapy – an EAACI Task Force Position Paper

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Abbreviations

AEC	allergen exposure chambers
AI	artificial intelligence
AIT	Allergen immunotherapy
AR	Allergic rhinitis
ARIA	allergic rhinitis and its impact on asthma
ARC	Allergic rhinoconjunctivitis
CHMP	Committee for Medicinal Products for Human Use
CONSORT	Consolidated Standards of Reporting Trials
CSMS	combined symptom medication score
DBPC	double-blind, placebo-controlled
FEV1	forced expiratory volume
EAACI	European Academy of Allergy and Clinical Immunology
EMA	European Medicines Agency
ICH	International Conference on Harmonization
IG	Immunoglobulin
mHealth	mobile health
MRI	magnetic resonance imaging
PISWS	“peak placebo score” week
PNIF	peak nasal inspiratory flow
PoCW	“peak pollen count” week

RCT	randomized clinical trial
RWD	real-world data
SPIREs	synthetic peptide immunoregulatory epitopes
TF	Task Force
VAS	visual analogue scale

Abstract

The placebo (Latin “I will please”) effect commonly occurs in clinical trials. The psychological and physiological factors associated with patients’ expectations about a treatment’s positive and negative effects have yet to be well characterized, although a functional prefrontal cortex and intense bidirectional communication between the central nervous system and the immune system appear to be prerequisites for a placebo effect.

The use of placebo raises certain ethical issues, especially if patients in a placebo group are denied an effective treatment for a long period of time. The placebo effect appears to be relatively large (up to 77%, relative to pre-treatment scores) in controlled clinical trials of allergen immunotherapy (AIT), such as the pivotal, double-blind, placebo-controlled (DBPC) randomized clinical trials currently required by regulatory authorities worldwide.

The European Academy of Allergy and Clinical Immunology (EAACI) therefore initiated a Task Force, in order to better understand the placebo effect in AIT and its specific role in comorbidities, blinding issues, adherence, measurement time points, variability, and the natural course of the disease. In this Position Paper, the EAACI Task Force highlights several important topics regarding the placebo effect in AIT such as i) regulatory aspects,

ii) neuroimmunological and psychological mechanisms, iii) placebo effect sizes in AIT trials, iv) methodological limitations in AIT trial design and v) potential solutions in future AIT trial design.

In conclusion, this Position Paper aims to examine the methodological problem of placebo in AIT from different aspects and also to highlight unmet needs and possible solutions for future trials.

Introduction

The placebo effect is a common phenomenon in medicine (1). It has been investigated and described in several fields, including pain management (2), psychiatric and neurological disorders (3-5), and cardiovascular, gastrointestinal and respiratory diseases (6). Moreover, a systematic review highlighted the high observed frequency of placebo effects in randomised, sham-controlled trials of surgical and other invasive procedures (7). The word “placebo” comes from the Latin verb *placere* and means “*I will please*”. The placebo effect encapsulates the psychological and physiological benefits of seeking advice and receiving treatment for a medical problem, independently of the prescribed treatment’s pharmacological effects *per se* (8, 9). As a pioneer in the field of placebo research, Beecher was confronted with the finding that soldiers wounded in World War II were relieved by treatment with saline solution as a sham analgesic; he thereby prepared the ground for subsequent investigations of this phenomenon (10). Various research groups have hypothesized that medical treatments have both specific effects (e.g. pharmacodynamic effects) and non-specific effects (e.g. those related to psychocognitive effects, including the Hawthorne effect, regression to the mean of psychometric evaluations, patients’ perceptions and expectations, and spontaneous fluctuations of the severity of symptoms) (Figure 1) (11). One must also consider the negative corollary of the placebo effect: the so-called nocebo (“I will harm”) effect, in which some placebo-treated patients will report subjective adverse events or symptoms because they expect an active (*verum*) medication (or what they think is an active medication) to have side effects or to worsen the symptoms of their disease (12, 13).

Insert Figure 1 about here

Patients with IgE-mediated allergic diseases (such as allergic rhinitis (AR)/rhinoconjunctivitis (ARC)) are highly susceptible to placebo effects (9, 14). Since allergen immunotherapy (AIT) is a disease-modifying treatment option for patients with respiratory allergic diseases (15-17), accurate measurement of the placebo effect is critical. This treatment modality was introduced more than 100 years ago by Noon and Freeman (18, 19). However, it took 40 years before Bruun (1949) (20) and Frankland & Augustin (1954) (21) performed and reported on the first DBPC randomized clinical trials

of AIT, following on from the scientific exploration of placebo effects in medical interventions by Beecher and others (10). Since then, a large body of evidence has documented the safety and efficacy of AIT (15, 22). At present, regulatory bodies (such as the European Medicines Agency, EMA) require the manufacturers of AIT products seeking market authorization to perform DBPC randomized clinical trials (RCTs) as proof of efficacy. Many of these trials have highlighted a clear effect in the placebo group, which in turn has a critical impact on the size of the treatment effect associated with AIT. Indeed, a number of clinical trials reported negative results, in as much as the treatment effect in the AIT group did not differ significantly from that in the placebo group. However, this observation may be related not only to the placebo effect itself but also to various other factors, e.g. poor study design or performance, or a lack of allergen exposure in the field (e.g. low pollen counts).

Although placebo effects in DBPC RCTs of AIT products have been explored (23), many open questions remain, and there is a clear unmet need for methodological solutions for AIT clinical trials. The EAACI has therefore initiated a Task Force (TF) with the following goals: (i) gaining a better understanding of the placebo effect in AIT in general, (ii) suggesting harmonized standards for future trials (i.e. to minimize the placebo effect's impact on the trial results), and (iii) providing the clinician with guidance on administering AIT so that the latter treatment achieves its full therapeutic capacity. The expert panel comprises clinicians and scientists working in the field of allergy, representatives of regulatory bodies, and psychologists. Sections A to F present the TF's opinions with regard to regulatory aspects of the placebo effect, the underlying neuroimmunological and psychological mechanisms, the placebo effects observed in recent AIT trials, methodological limitations, possible solutions, and unmet needs/perspectives for future research.

Methods

An initial workshop on '*Placebo Effects in AIT*' was held during the EAACI's 2017 annual congress in Helsinki (Finland), under the chairmanship of the late Professor Anthony Frew. The workshop's main objectives were to (i) form the TF group with a balanced

panel of stakeholders in the field, (ii) review the current clinical data on placebo effects in general and those in AIT trials in particular, and (iii) identify possible solutions regarding regulatory demands and trial methodologies. Five working groups were formed on the topics included in Sections A to E. Details of the groups' work were then circulated to all of the TF members for further discussion. Based on this effort, the TF's second meeting was held at the EAACI's 2018 annual congress in Munich (Germany). The objective was to thoroughly discuss all topics and to draft a preliminary version of the present Position Paper. Thereafter, the TF's working groups finalized each section and outlined the unmet needs for future research in placebo. The Position Paper was then finalized by the corresponding author and presented to the TF at the EAACI 2019 congress in Lisbon (Portugal) for final evaluation and approval.

A. Regulatory aspects

The ethics of clinical research is a central component of licensing decisions for new therapies. For new AIT products under development, the EMA's currently applicable principles on study design and efficacy claims are laid down in (i) the '*Guideline on the clinical development of products for specific immunotherapy for the treatment of allergic diseases*' (24) for an indication in ARC or insect venom allergy, and in the '*Guideline on the clinical investigation of medicinal products for the treatment of asthma*' (25) for an indication in allergic asthma. Both guidelines request a DBPC randomized design, raising the question of whether this fits with ethical considerations.

All medical research involving human subjects must adhere to the Declaration of Helsinki on ethical principles for medical research involving human subjects (26). One of the Declaration's core beliefs is that "*The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best proven intervention(s), except in the following circumstances:*

- *Where no proven intervention exists, the use of placebo, or no intervention, is acceptable; or*

- *Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention*
- *And the patients who receive any intervention less effective than the best proven one, placebo, or no intervention will not be subject to additional risks of serious or irreversible harm as a result of not receiving the best proven intervention.*
- *Extreme care must be taken to avoid abuse of this option.”*

Regarding the second requirement, the question arises as to what is a “*compelling and scientifically sound methodological reason*” for placebo use. Furthermore, it has been argued that any additional risks of using placebo must be justified by the additional social value gained over other trial designs. In turn, this raises the question of what constitutes “*social value*” but nevertheless leaves the door open to the performance of placebo-controlled trials. As various interpretations of “*serious harm*” and “*methodological reasons*” are possible, the Declaration of Helsinki does not solve the debate about active-controlled trials vs. placebo-controlled trials. Although placebo-controlled trials are used extensively in the development of new medications, they are sometimes challenged as being unethical in settings in which patients could be treated with an existing therapy. Hence, the issues of when placebo controls are ethically acceptable and when they are scientifically necessary are important and worthy of discussion.

The EMA has considered these issues in a position statement (27) and a reflection paper (28) and concluded that two main conditions govern and restrict the use of placebos: (i) the period during which placebo is administered must not entail any additional risk of irreversible harm to the patients; and (ii) the patient included in the trial or his/her legal representative must receive and understand appropriate information on the trial, and give his/her written, informed consent.

However, the above-cited documents also state that there are several scenarios in which the use of placebo is justified. Provided that the ethical nature of placebo-controlled trials is clearly understood and implemented, the EMA and its Committee for Medicinal Products for Human Use (CHMP) consider that the continued availability of placebo-controlled trials is currently necessary for satisfying public health needs. Trials that seek

to prove that a new agent and a comparator treatment have similar efficacy are inherently less reliable than trials that seek to prove the superiority of the new agent over the comparator, whether inactive or active. In trials where it can be agreed (in line with a relevant CHMP guidance document or with scientific advice) that an appropriate primary objective is to demonstrate non-inferiority or equivalence to verum, the trial's assay sensitivity and the evidence (possibly indirect) of superiority to placebo must be established. Otherwise, a superiority trial is the only means of obtaining convincing scientific evidence of the efficacy of a new medicinal product.

General regulatory guidance on the choice of control groups is provided by the International Conference on Harmonization (ICH)'s Topic E 10 "*Choice of Control Groups in Clinical Trials*" (29). According to this document, the major purpose of control groups in clinical trials is to allow discrimination between patient outcomes caused by the test treatment and patient outcomes caused by other factors, such as natural progression of the disease, the observer's or patient's expectations, or other treatments. Four types of control treatment are defined: (i) a placebo, (ii) no treatment, (iii) a different dose regimen of the study treatment, and (iv) a different verum. Placebo-controlled trials are almost always double-blinded; they are usually designed to show a difference in efficacy between verum and placebo but may also seek to show a lack of difference in safety. The use of a placebo group does not imply that the control group does not receive any kind of treatment. In many placebo-controlled trials (including AIT trials), the new treatment and placebo are respectively added to a common, standard therapy (i.e. in so-called "*add-on studies*"). This is also true for long-term DBPC RCTs of AIT trials in children, as requested by the EMA's Paediatric Committee (30). It is also noteworthy that not all placebos are completely inactive. In this context, the ICH E 10 guideline states that some vehicle controls of topical skin preparations may have beneficial activity. Another example relates to SCIT placebo preparations that contain aluminium hydroxide.

Even though most recent AIT studies have used placebo as a comparator, there are a few examples of active-controlled trials. A comparison between AIT and nasal corticosteroids was hampered by a short study duration (31). A systematic review identified a medium risk of bias in comparisons of sublingual (SLIT) and subcutaneous

(SCIT) forms of AIT because only one study was blinded (32). Another recent study focused on the health effects one year after the cessation of active SLIT and placebo treatment; a study arm with SCIT was included as a positive control but the study was not powered to compare SLIT with SCIT (33). An exploratory study compared the efficacy of two birch SLIT preparations by measuring the reduction in allergic symptoms during a nasal provocation test (34). However, none of the studies appeared to be a viable alternative to a DBPC RCT of AIT.

The regulatory authorities typically take a balanced position by allowing placebo controls in some circumstances (35). The methodological reasons put forward to justify the use of placebo in general are also applicable to AIT trials in particular: (i) the recommended primary endpoint in AIT (a combined symptom and medication score) is a self-rated, subjective endpoint, and thus the “assay sensitivity” cannot be defined; (ii) a variable and potentially large placebo effect is often observed in AIT trials; (iii) there may be several non-responders, and (iv) placebo groups can be smaller than active control groups.

In summary, placebo-controlled trials remain the most rigorous test of efficacy in AIT. However, several prerequisites have to be met. For example, before consenting to participate in a trial, patients must be fully informed about the available therapies and the consequences of delaying active, allergen-specific treatment.

B. Placebo effects: neuroimmunological and psychological mechanisms

One of the pitfalls encountered in studies of allergic diseases is that of the placebo effect. It has been cited as high as 20-40% in clinical trials of pharmacotherapeutic agents (1, 10, 36, 37) and even higher in AIT studies, even though a double-blind, randomized design was used (38, 39). Placebo and nocebo responses are part of any medical intervention or treatment. Typical examples include (i) the increased frequency of reporting of adverse drug reactions after negative reports in the media, (ii) the loss of efficacy after switching from a brand-name drug to a generic drug, and (iii) impressive

improvements after applying a drug but before the biochemical action can have taken place (e.g. a marked reduction in pain within one minute of swallowing a tablet formulation of a nonsteroidal anti-inflammatory drug). Placebo effects have mainly been investigated in analgesia but have also been documented in Parkinson's disease, depression, irritable bowel syndrome, fatigue in cancer patients, and many other conditions (40). Various biological systems (such as opioids, cholecystokinin, cannabinoids and dopamine pathways) (11) can be involved. The corresponding neural processes can be visualized using functional magnetic resonance imaging (MRI) techniques. In view of the broad incidence and relevance of placebo effects, deeper knowledge of the mechanisms that drive these processes would probably increase the benefit associated with medical interventions.

In a clinical trial, the placebo effect (i.e. a reduction in symptoms following the administration of a pharmacologically inert treatment) is influenced by several factors, such as the natural history of the disease, fluctuations in symptoms (i.e. in chronic-intermittent diseases), response biases, effects of co-interventions, or statistical phenomena such as regression to the mean (Figure 1).

These factors can be distinguished from the genuine placebo response, which is mainly mediated by psychological and biological factors associated with patients' expectations about a treatment's positive and negative effects. A patient's expectations are stimulated not only by the information provided by medical experts but also by information received from other individuals or the media, or by social observations (e.g. in the doctor's waiting room) (41). Therefore, the quality and quantity of doctor-patient communication and patient's previous experiences with certain treatments (i.e. associative learning) contribute significantly to the development of placebo and nocebo effects (i.e. positive and negative effects that cannot be attributed to the medical intervention *per se*). A patient who repeatedly experiences adverse events may learn to become a side-effect responder in the future - even when placebos or other substances are administered (42). Other variables mediating placebo responses include the subjective value of a treatment and the patient's active involvement in treatment decisions (shared decision making). Anxiety can contribute substantially to the development of nocebo effects (11).

With respect to physiologic factors, various studies have shown placebo-induced changes in heart rate, blood pressure, and brain activity or chemical release. Many investigators in the field of neurology have demonstrated the release of hormones and endogenous endorphins in brain tissue. Studies have also shown that dopamine receptors are preferentially upregulated in the anterior cingulate, prefrontal, and orbitofrontal areas of the brain, and in the amygdala (43-45). Furthermore, patients with Alzheimer's disease no longer demonstrate the ability to respond to placebo. This action appears to be due to loss of the area of the prefrontal cortex that controls the ability to have expectations (46).

Meta-analyses and reviews have demonstrated differences in susceptibility to “*inert*” treatments in various immune-related pathological conditions. Data from animal models suggest that peripheral immune functions are affected by associative learning or conditioning paradigms as well as by cognitive factors (41). A prerequisite for a placebo effect on immune function is intense bidirectional communication between the central nervous system and the immune system. These two systems constantly exchange information on efferent and afferent pathways, and thus act together as an integrated physiological system that monitors and reacts to environmental stimuli, infection and inflammation (summarized in (47, 48)).

The responsiveness of allergic reactions to placebo-influencing psychological factors is highlighted by the high placebo response rates observed in clinical studies of allergic patients (49, 50). Early observations of allergic symptoms in the absence of allergens supported the notion whereby both the patient's expectations and learning mechanisms contribute to the pathophysiology of asthma (51). This notion is further supported by the observation that high mucosal mast cell tryptase levels can be induced as a conditioned response in patients with AR (52). Similarly, allergic subjects re-exposed to an olfactory cue that had originally been paired with a grass allergen challenge released higher levels of histamine (53). Conversely, the antihistaminergic properties of the H₁-receptor antagonist desloratadine were found to be behaviourally conditioned in patients suffering from house-dust-mite (HDM-) induced AR; the learned placebo response significantly reduced subjective symptoms, the skin prick test response, and basophil activation (54).

These results were recently confirmed and extended by the demonstration of reproducible allergy-like placebo responses induced by both verbally induced expectation and learning (55).

A study in patients with asthma demonstrated that “placebo bronchodilator administration” significantly reduced bronchial hyperreactivity (relative to baseline), and thus indicated that an objective placebo effect exists in asthma (56). In another asthma study, salbutamol was associated with an increase in the forced expiratory volume (FEV₁) but neither of the two placebo interventions (placebo inhaler and sham acupuncture) had an effect. However, salbutamol provided no incremental benefit with respect to the self-reported subjective improvement (57).

A series of surprising studies by Kimata and others further confirmed that psychological and neuroimmunological mechanisms are involved in the modulation of allergic and asthmatic responses. Kimata first reported that kissing or listening to music could reduce wheal responses induced by allergens but not those induced by histamine (58, 59). Kimata later reported that viewing a comedy film reduced non-specific bronchial responsiveness in patients with HDM-induced allergic asthma but not in healthy individuals (60).

In summary, these data show that placebo responses in patients with immune-related diseases in general and allergic diseases in particular are mediated by both associative learning processes and patient expectations and modulated by context effects (61). Furthermore, the data might have implications for clinical trials of new products in allergic patients, where minimizing placebo responses, optimizing drug-placebo differences and improving “assay sensitivity” are scientific, ethical and regulatory requirements (40). Lastly, greater knowledge of the mechanisms that steer placebo responses might provide a basis for systematically combining placebo responses with medical interventions (e.g. pharmacological treatments) in clinical practice, with the goal of maximizing treatment outcomes and patient benefit (41).

C. The placebo effect in recently published AIT trials

Table 1 summarizes the size of placebo effects in published AIT trials, systematic reviews or press releases. Studies with synthetic peptide immunoregulatory epitopes (SPIREs) have demonstrated placebo effects of up to 60% (for cat allergen AIT) and up to 39% (for HDM AIT) (Table 1) (38, 39) for the primary endpoint (a combined symptom medication score [CSMS]).

Insert Table 1 about here

These effects prompted the manufacturer to stop all investigations and further development of its peptide-based allergy treatment portfolio. Although allergic diseases may be more prone to the placebo effect (14), such a strong response was unexpected. Detailed data have not yet been published but the available evidence indicates that the extremely high expectations in the treatment by participating cat owners prompted such large placebo effects that no further improvement by the verum could be demonstrated.

Narkus et al. (23) were the first to analyse the placebo effect in six AIT trials (5 trials of SCIT products, and one trial of a SLIT product; only 3 of these 6 studies have been published) (Table 1). All the trials featured a prospective baseline observation period, the same inclusion and exclusion criteria, and the same primary endpoint (a CSMS). The size of the placebo effect ranged from 1% to 52% (Table 1). However, these changes may also be due to further confounders such as pollen-exposure in the respective years. Interestingly, this metaanalysis also evaluated Immunoglobulin (Ig-)G 4 levels as measured with comparable methods and demonstrated that there was no change in the placebo treated patients during the two year course of AIT compared to baseline (23) .

Wedi et al. (62) analyzed the placebo effects in all 33 DBPC RCTs of birch, grass, and HDM AIT formulations evaluated to support the German S2k guideline on AIT in IgE-mediated allergic diseases (63); the size of the placebo effect ranged from 11% to 77% (Table 1). No conclusion could be drawn regarding a “pure” placebo effect because all the studies authorized the use of symptomatic rescue medications. When an adequate baseline period was included, it was used for patient recruitment or calculation of the study’s statistical power. Only one study described a change in CSMS vs. placebo, using an adequate baseline period. Although nearly all the studies compared the relative

reduction in the efficacy score for verum vs. placebo, few reported the effect of placebo vs. baseline/no treatment. The impact of factors well known to influence the placebo effect (such as age, sex, administration route, placebo composition, initial symptom severity, prior exposure to an effective treatment, personality traits, cultural differences, and the patient's expectation of verum/study medication) could not be estimated from the available data - particularly due to a lack of a baseline period (62).

As of September 2019, seven new studies (2 of SCIT products and 5 of SLIT products) have been added to the German S2k guideline's supporting tables (22); however, appraisal of the placebo effect is still not possible because no statements regarding the placebo effect were given in five of the studies (Table 2). In a Japanese study of 5- to 17-year-old children, placebo effects of up to 61% were reported (Table 2) (64) while "hardly any allergy pharmacotherapy was used" - indicating a significant placebo effect. However, it should be emphasised that the symptoms were scored by the parents or legal guardians, rather than the children themselves.

Insert Table 2 about here

Abramowicz et al. (65) systematically reviewed 20 AIT trials in adults published between 1996 and 2010. The researchers found an overall placebo effect of 39%, with a significantly greater effect in SLIT trials (68%) than in SCIT trials (29%) (65). This review differed radically from the one performed by Wedi et al. (62) because Abramowicz et al. included only 1 of the 33 studies of AIT products available in Germany (22) as of July 2016.

Most AIT trials using an allergen exposure chamber (AEC) include a baseline period during which symptoms are scored; this enables placebo effects to be assessed (Table 3). Even under these tightly controlled exposure conditions, placebo effects of up to 38% relative to baseline can occur (Table 3).

Insert Table 3 about here

The currently published data demonstrate a significant placebo effect in AIT trials, irrespective of the application route. However, the true placebo effect cannot be established for several reasons. Firstly, most results obtained with placebos are not

described in detail. Secondly, the placebo is not always strictly identical to the verum (without the allergen); for example, histamine is sometimes added (in SCIT studies) or adjuvants (e.g. monophosphoryl lipid A) are not included (62). Lastly, placebo effects calculated from objective measurements (e. g. bronchial provocation tests to determine the dose producing a 50% fall in forced expiratory volume (FEV1) are smaller than those calculated from subjective evaluations (visual analogue scales (VASs) of symptom intensity, improvement or satisfaction, and quality of life questionnaires) (62, 65). Given the published data, we cannot say whether all clinical trial participants or just a subset are susceptible to placebo effects or whether participants who do manifest a placebo response on one occasion will manifest a placebo response to one or more subsequent administrations of a similar placebo (i.e. whether placebo responses are predictable).

The concept of an open-label (non-blinded) placebo was first introduced in 2010 for studies of irritable bowel syndrome (66). Since then, it has been shown that open-label placebo treatments are significantly more effective than the absence of any intervention in irritable bowel syndrome, depression, attention deficit hyperactivity disorder, back pain and AR (67). In two randomized controlled trials, significant reductions in composite AR symptom scores were observed for patients treated with an open-label placebo (regardless of whether or not they had received an additional “placebo briefing” intended to create positive expectations), relative to control, non-treated patients (68, 69).

D. Methodological limitations in AIT trial design

There are two types of methodological limitation in RCTs of AIT trials: (i) those that are inherent to all RCTs, and (ii) those that are related to or more prominent in trials investigating “personalised” treatments such as AIT.

With regard to the first category, the main challenge is external validity: the extent to which the results can be generalised to a patient population that differs from the carefully selected trial population. For drugs, it is generally assumed that a response is normally distributed across the wider population. Although other study design options exist (i.e.

responder trial designs), these are rarely implemented in the pivotal Phase III trials required for registration. These considerations have been extensively reviewed elsewhere (70) . Several studies have tried to identify “placebo responders” but this approach remains challenging. It has been suggested that placebo and nocebo responses are conditioned by certain individual variables, including psychological characteristics (optimism, neuroticism, catastrophizing, etc.), genetic predispositions, and cognitive factors (e.g. cognitive schemas) (1, 2). However, to the best of our knowledge, subsequent exclusion criteria have never been incorporated in AIT trials.

The methodological limitations that particularly affect AIT trials can be classified as being related to the patient (comorbidities, blinding issues, and adherence issues), the intervention (outcome measures and time points), the environment (variability in allergen exposure), and the disease (natural history and severity).

Patient-related factors

Comorbidities: there is now no doubt that (i) allergic diseases are systemic diseases that manifest themselves to a variable extent in different organs, and (ii) the proportions of polysensitized and polyallergic patients are increasing (71). It would be very difficult to recruit solely monosensitized, monoallergic participants for AIT trials. Comorbidities and polyallergy may influence outcomes to an extent that cannot be completely corrected for by applying statistical adjustments. The only apparent solution is the development of more precise “indications” that better reflect the true nature of the disease, rather than the conventional “allergic rhinitis” and “allergic asthma” designations (72).

Blinding issues: in AIT trials, the administration of an allergen formulation (even at very low doses) frequently induces a local reaction. Thus, placebo vs. verum blinding is very difficult to achieve unless a non-specific, similarly irritating substance (such as histamine) is included in the placebo. In the context of SCIT trials, histamine-containing placebos have been used for over 45 years (73). Eight other trials that used histamine in the placebo arm have been identified and summarised by Wedi et al. (62). One trial used

histamine and caramelized glucose to disguise the colour of the allergen extract (74). Fewer attempts have been made to disguise the placebo treatment in SLIT studies. In three published studies, dyes, caramel or glycerol were used to make the sublingual product taste and/or look like the verum as closely as possible (75-77). In a recent study of intradermal AIT, histamine was used in the placebo arm, and the efficacy of blinding was formally assessed (78). However, most studies do not formally address this aspect.

Adherence issues: adherence is often a key issue in SLIT, where the time, place and frequency of administration are sometimes difficult to account for. Patient training and the use of validated immunological assays of allergen exposure may help to overcome this issue (79, 80).

Treatment-related factors

Outcome measures: the ideal outcome measures for AIT trials have been extensively discussed (81). The main challenges include the multitude of allergic manifestations (many of which cannot be objectively quantified), and the effect of rescue medications taken regularly or for symptom exacerbations. These challenges are more prominent for upper airway symptoms, although lower respiratory tract and ophthalmic symptoms are also concerned. It is conceivable that subjective patient-related outcomes (such as numerical symptom scores, VAS, quality of life questionnaires, overall assessments by the physician, and overall patient satisfaction) are more likely to be influenced by a placebo effect (81). The use of medication can be quantified, although the symptom intensity threshold that triggers rescue medication use may differ considerably from one patient to another. Objective outcomes (such as rhinometry, rhinomanometry, peak nasal inspiratory flow (PNIF) and FEV₁) may improve accuracy in some settings/designs but also vary over time. *In vivo* challenge tests (such as the conjunctival provocation tests (82) or the nasal provocation test (83)) can be helpful, although they do not necessarily reproduce the pathophysiology of natural exposure (Figure 2).

Insert Figure 2 about here

For allergic asthma, outcomes have been validated to a much larger extent; in recent years, asthma exacerbations (defined as the need for emergency medical intervention with a change in the background treatment) have become the outcome of choice in large trials of controller medications, including biologics. However, exacerbations are rare events that require very large trial populations and are most relevant in severe disease. Asthma symptoms, quality of life, and overall impact still suffer from challenges described above for AR. Lung function measurements are more stable than PNIF measurements but are not always abnormal or correlated with inflammation or symptoms (84).

Outcome time point: an outcome may vary according to the time point at which it is measured. As discussed below, outcomes in AIT trials are particularly affected by fluctuations in natural exposure (e.g. seasonality) and the natural history and severity of the disease. On one hand, trial sponsors have logistical and financial incentives for not prolonging a trial once a statistically significant verum vs. placebo difference in the primary outcome is observed. On the other hand, patient expectations may be amplified or otherwise distorted if the study period is prolonged.

Environment/disease-related factors

Variability in exposure. Allergic manifestations depend directly on exposure to the relevant allergen. This response is not linear but has dynamic “cut-offs” that change in response to continuous exposure (i.e. a priming effect) (85) and can be modulated by exposure to other allergens or irritants (e.g. infection or pollution) (86) (87). It is difficult to distinguish between or predict specific and non-specific reactions - especially under natural exposure conditions. Patients often move between sites (work and home, for example), and the level of allergen exposure varies from one site to another. In a given area, the level of exposure to allergen varies from one day to the next during the pollen season. Patients receiving AIT are scattered over a large area that may not be covered by accurate pollen count measurements.(88, 89). There may be many days with absent/very low pollen counts, resulting in very low mean symptom scores. In contrast, individual days with high scores may result in high scores and thus have major impact on

patient performance. Patients may tend to remember their “hell days” more than their “well days” – leading to recall bias in subjective symptom scores. It has been pointed out that symptom severity is not necessarily directly correlated with the pollen count (90, 91). Next-generation real-time pollen monitoring (92) cannot be used throughout Europe and still does not account for individual exposure. Personal exposure data are needed but individual pollen samplers cannot be used daily in large-scale trials, and these methods have not been validated.

The natural history of the disease: Independently of exposure, allergic manifestations vary considerably over time within an individual. Although this is most relevant in children and adolescents, adults are also affected (93, 94). The variable natural history of the disease influences patient preconceptions; when combined with the need for long-term treatment for greater efficacy, these variations can accentuate placebo/nocebo reactions (95).

The impact of the placebo effect is a serious issue and needs to be considered in all types of clinical research. Several factors must be evaluated at various stages of trial development and implementation:

- i. *During trial design.* As recommended by the EMA’s CHMP (96), information on the chemical and pharmaceutical qualities of placebo products in clinical trials should be included in all protocols. This information includes: (a) the complete qualitative and quantitative composition of the placebo, (b) pre-fabricated components (e.g. capsule shells), (c) excipient mixtures (e.g. film-coating mixtures), (d) a short statement or a tabulation of the dosage form and the function of each excipient, (e) masking of possible differences between the placebo preparation and the investigational medicinal product regarding taste, appearance and smell, where applicable and (f) description of manufacturing process, batch formula and process controls, process validation and/or evaluation and control of excipients. However, while this data is collected in all trials, the information is not usually published in the scientific and medical literature.
- ii. *During implementation of the clinical protocol.* It is possible that giving a trial participant too much information about possible adverse events expected with the

verum product (either verbally or in the study information sheet) prior to informed consent can influence the response of participants receiving the placebo drug. It is also likely that participants and members of the research team will share information about side effects that have been reported by other participants during the trial; this might also influence the placebo effect. Of course, it is important that potential subjects are aware of possible side effects but a balance needs to be found.

- iii. *When reporting, interpreting and presenting the results of RCTs.* The Consolidated Standards of Reporting Trials (CONSORT) statement (97, 98) recommends that the trial report should give specific details about the “concealment of randomisation” (whether the allocation of patients was clearly concealed from both patients and investigators) and “adequate blinding” of the study drug and placebo. This information is considered to be important for comprehensive, transparent reporting. The double-blinding method should be described in detail - especially with regard to masking of the placebo. Furthermore, the placebo should be as similar as possible to the verum with regard to composition, aspect, colour, and taste. For SLIT studies, it is accepted that (i) an inert placebo substance cannot adequately mimic the local adverse events induced by allergen in a substantial proportion of patients, and (ii) ethical considerations prevent the inclusion of histamine in an “active placebo” (99, 100).
- iv. *When selecting and evaluating data and bias in systematic reviews and meta-analyses.* In DBPC RCTs, there may be concern about whether the participants or even the people caring for the patients were truly blinded. One option at the end of the trial is to ask participants to guess which treatment they had been receiving (1). A proportion of correct guesses substantially greater than 50% may suggest that blinding was imperfect but might also simply reflect the patients’ experiences in the trial: a good outcome or a major adverse event will tend to be attributed to a verum, and a poor outcome will tend to be attributed to a placebo (101). We would expect to see some successful “guessing” when there is a verum vs. placebo difference in either efficacy or adverse effects but not when the treatments have very similar effects - even when the blinding has been preserved. Accordingly, authors of reviews should consider carefully whether to take such findings into

account. A possibility could be to ask this question at an earlier time point during the trial, before the outcomes have been assessed.

- v. Meta-regression analyses have shown that larger placebo effects are associated with physical placebo interventions (e.g. sham acupuncture), patient involvement (e.g. patient-reported outcomes and observer-reported outcomes involving patient cooperation), trials with small numbers of participants, and trials designed explicitly to study the placebo effect. Larger placebo effects were also found in trials that did not tell the participants about the possible administration of a placebo (1).
- vi. In the analysis of the verum vs. placebo data, it is mandatory for the researcher to consider the natural history of the disease with a reduction in symptoms, and the effect of any other concomitant rescue medications (e.g. antihistamines and corticosteroids). For this reason, there is merit in including an additional control group with no verum and no placebo (62), although this clearly adds to the costs of any study and (unless larger groups are recruited) may weaken its statistical power.

E. Possible solutions in AIT trial designs

As described in the previous sections, it is still possible to conduct a DBPC RCT but care is needed to achieve the highest possible degree of blinding to minimize placebo effects related to a variety of patient-, intervention-, environment- and disease-related factors (102-104). The nature of SCIT and SLIT products means that blinding is difficult, and reliance on subjective endpoints may contribute to the substantial placebo effects observed. Ideally, the AIT trial's design would minimize or at least isolate placebo effects. A number of possible (but often only partial) solutions are discussed below.

Reinforcement of existing DBPC RCT designs.

Almost 20 years ago, Frew & Smith emphasized the need for large DBPC RCTs with carefully balanced groups of patients with moderate-to-severe disease and well-defined sensitivity to the target allergen. In principle, this will reinforce blinding and enable the detection of treatment effects with greater accuracy (105). Frew & Smith also suggesting the implementation of prolonged run-in periods prior to treatment allocation, careful documentation of side-effects, and trial settings that are more typical of where the treatment will subsequently be used (105).

Modification of the nature of the placebo.

The administration of AIT products (whether sublingual or subcutaneous) typically induces local reactions (e.g. pruritus and erythema). One can argue that to maintain blinding in a DBPC RCT of an AIT product, the supposedly identical placebo must also induce local reactions. In the past, histamine has been used in SCIT placebos but this is now no longer favoured by regulators in SCIT placebos. For ethical reasons, the addition of histamine to SLIT placebos is also discouraged. Furthermore, histamine will almost always induce an adverse reaction in all patients, whereas verum will only do so sometimes in some patients – meaning that blinding is not necessarily any better. One possible way of overcoming the placebo effect in trials with polysensitized trial participants (e.g. those sensitized to both birch- and grass pollen) is the double-dummy design. This is possible (106-110) but is logistically complex and cannot be performed with monosensitized individuals.

Trials in allergen exposure chambers (AECs)

The use of an AEC can standardize exposure to aeroallergens and thus remove one of the variables involved in field exposure studies (111). Of course, the replacement of natural exposure by exposure in an AEC has advantages and disadvantages; at present, the EMA accepts AEC studies for Phase II trials but not for Phase III studies. For pollen AIT, AEC trials are performed outside the pollen season; however, this approach has been criticized as not taking ongoing inflammation and possible priming effects into account. In-season AEC evaluations may also be considered. It should be noted that strong placebo effects are also observed in AEC studies (112-115). In an attempt to overcome this, objective nasal flow (such as PNIF, acoustic rhinometry, rhinomanometry or lung function (such as eg FEV1)) can be measured during standardized allergen exposure, where - in contrast to subjective measures - little or no placebo effect is observed (33). It will be important to establish correlations between AEC measurements, objective target organ measurements and patient-reported outcomes in Phase III RCTs.

Removal of the placebo arm

If a placebo effect is large, one could remove the study's placebo control arm – although the study would no longer be acceptable for marketing applications. As mentioned above in section A, four types of control treatment are defined: (i) a placebo, (ii) no treatment, (iii) a different dose regimen of the study treatment, and (iv) a different verum. Of course, the study is then no longer blinded. The pros and cons of head-to-head therapeutic trials with active comparators have been reviewed elsewhere (116, 117).

Post-marketing field trials constitute another practical alternative but are more useful for detecting rarer side-effects or long-term consequences than for providing primary efficacy data. Large observational implementation studies using mobile health (mHealth) tools reflect real-world data (RWD, i.e. everyday use and practice) more closely than DBPC RCTs because the former assess a greater variety of medical interventions in more heterogeneous patient populations (118) (119). Hence, observational studies provide

clinically relevant information that usefully complements the findings of DBPC RCTs; trials without a placebo arm may provide some hints about the impact of these effects on trial results (120, 121). Real-world evidence (derived from observational studies) combines the results of DBPC RCTs and RWD; this provides clinically relevant information that usefully complements DBPC RCTs (120-122). The real-life approach can be extended to a variety of allergens and AIT methods. However, these real-world strategies are currently unlikely to replace the “gold standard” DBPC studies requested by the authorities (24).

The growth of mHealth, “big data” and artificial intelligence (AI) may offer ways of analyzing and/or controlling for inherent sources of patient-to-patient variability and potential overall differences between verum and placebo groups. Hence, the assessment of environmental exposure requires more than pollen counts; mHealth and “big data” might enable the effects of weather parameters and pollutant levels on allergen exposure and symptom severity to be taken into account (123).

Moreover, assessing daily CSMS in geolocated patients for whom the air quality index (pollen exposure and air pollution) is known will enable a comparison of AIT and placebo only in patients who are sufficiently exposed to a noxious environment. Thus, fewer days of exposure will be considered, and there will be a larger difference between placebo (low CSMS scores) and AIT (high CSMS scores). This approach can be used in RCTs, observational studies with RWD, AEC studies, and clinical practice - allowing the harmonization of assessments and better comparability of the various settings. In the clinic, this approach will enable the physician to rapidly stratify patients for AIT and to monitor the treatment, as proposed in the allergic rhinitis and its impact on asthma (ARIA) care pathways for AIT (124). However, this type of approach must comply with the European Union’s General Data Protection Regulation, geolocation privacy rules, and database security criteria.

Use of novel efficacy scales.

Frew et al. sought to assess whether the symptomatology in placebo-treated patients is a better measure of the local allergen burden at individual centres (125). The researchers compared the difference in CSMS between verum and placebo groups observed during the four “peak placebo score” weeks (PISWs) with that observed during the four “peak pollen count” weeks (PoCWs). The benefit of immunotherapy over placebo was greater in the PISW analysis (18.5%) than in the PoCW analysis (13.6%).

F. Unmet needs and perspectives for the future research

The regulatory authorities have made it clear that despite the greater importance given to real-world evidence and tools such as AECs, a pivotal DBPC RCT in the field will remain the primary criterion for licencing a new AIT product. Hence, placebo-controlled trials will continue to be performed, and the placebo effect will have to be accounted for when interpreting the results of these trials. It may therefore be the right moment to launch in-depth investigations into the placebo effect in medicine in general, in AIT in particular, and perhaps in SLIT most precisely.

A large body of clinical evidence suggests that the placebo effect has a firm physiological and cognitive basis, and affects both subjective measurements of disease symptoms and (albeit to a lesser extent) objective measurements of disease signs. Modern analytical methods (including genomics, proteomics, metabolomics, data mining, artificial intelligence, and mHealth) should now be brought forward to evaluate the neural, immunologic and cognitive components of the placebo effect. In fact, the main problem seems to be not so much the presence of a placebo effect but the latter’s unpredictability in a given individual, in a given trial setting and for a given type of AIT formulation. If we knew how to identify “placebo responders”, we could exclude them from pivotal clinical trials and thus minimize and then perhaps correct for the placebo effect.

It is also clear that patient expectations, healthcare provider-patient dialogue, and the level of information given to patients before and during a DBPC RCT will influence the

placebo effect. It may therefore be of value to try to standardize these aspects when designing and implementing a clinical trial protocol.

Lastly, further research on sociology and ethics might usefully shed light on a patient's reasons for participating in *pro bono* randomized medical research without guaranteed individual benefit. It is clear that patients with an often progressive underlying disease must be well informed about the potential risks and benefits of being allocated to placebo treatment for weeks, months or even years during an AIT trial. Then again, discussing placebos in too much detail with the patient may itself modify the magnitude of the effect. Improved understanding of the placebo effect may enable it to be used for the benefit of patients. Despite the problems that it poses, the placebo effect is a fascinating scientific subject and a worthy challenge for physicians seeking to provide the best possible care to their patients.

Conclusion

The European Academy of Allergy and Clinical Immunology's Task Force aims at better understanding the placebo effect in AIT and its specific role for comorbidities, blinding issues, adherence, measurement time points, variability, and the natural course of the disease. This Position Paper reports the scientific opinion of key-stakeholders and highlights several important topics related to the placebo effect in AIT from different perspectives (Table 4). As such, it reviews the current understanding of this methodological problem but also identifies unmet needs and possible solutions for future trials.

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Insert Table 4 about here.

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Figures and Tables

Figure 1

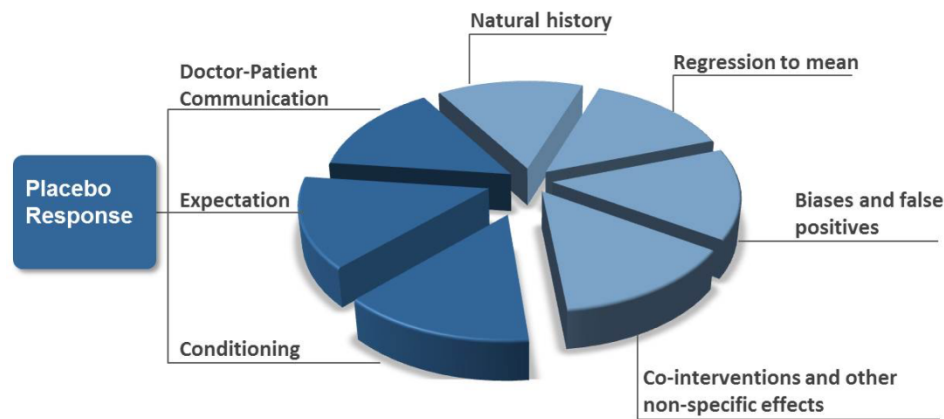


Figure 1. Unspecific or placebo effects from any medical treatment entail a number of subeffects (such as the natural history of disease and spontaneous symptom variations), statistical phenomena (such as regression to the mean, response biases and false positive responses), contextual factors, and the effects of co-interventions, in addition to the actual placebo response. The placebo response itself is mainly mediated by cognitive factors, such as a patient's expectation of treatment benefit; the latter is affected by the quality of physician-patient communication and the

patient's prior experience with a certain treatment (i.e. associative learning or conditioning processes). Adapted with permission from Schedlowski et al. (2015) (11).

Figure 2

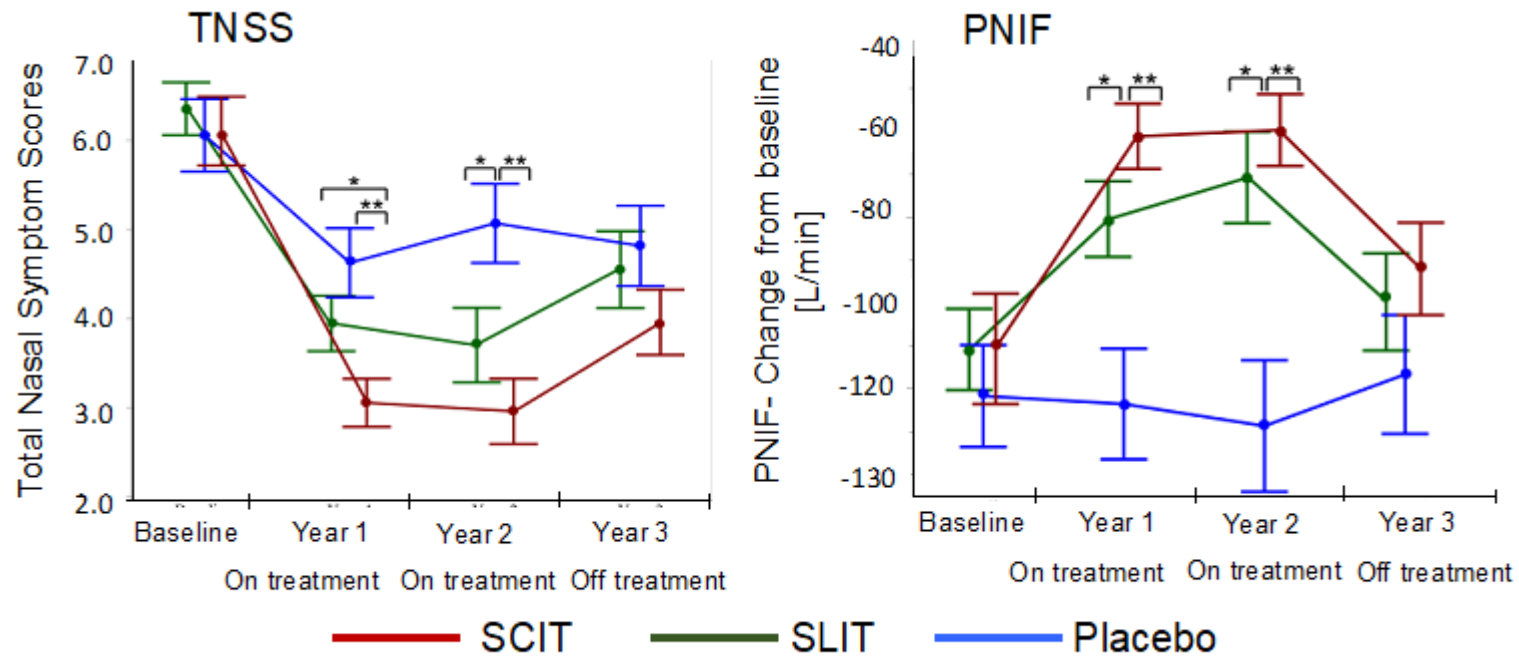


Figure 2. The time course of a total nasal symptom score (TNSS) and the change from baseline in peak nasal inspiratory flow (PNIF) in patients treated with grass pollen SCIT, grass pollen SLIT or placebo for two years, followed by a treatment-free year. Adapted with permission from Scadding et al. (2017) (33).

Tables

Table 1. Summary of the size of placebo effects in participants in AIT field trials, as described in systematic reviews or press releases.

Type of AIT	Average placebo effect	Smallest placebo effect	Largest placebo effect	Number of studies included	Ref, year
SCIT	<i>Not calculable</i>	6% (year 1) 18% (year 2)	52% (year 1) 41% (year 2)	5	Narkus et al. 2013 (23)
SLIT	<i>Not calculable</i>	1% (year 1) 1% (year 2)	1% (year 1) 1% (year 2)	1	
SCIT	<i>Not calculable</i>	11%	77%	19	Wedi, 2017 (62)
SLIT	<i>Not calculable</i>	55%	68%	14	
SCIT	29% (adults) 47% (children)	<i>Not available</i>	<i>Not available</i>	20*	Abramowicz et al. 2018 (65)
SLIT	68% (adults) 23% (children)				
IDIT (cat)	60% for the RTSS 59% for the CSMS	<i>Not available</i>	<i>Not available</i>	1	CIRCASSIA (press release and unpublished data) (38)

IDIT (HDM)	46% for the RTSS 39% for the CSMS			1	
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*21 studies are mentioned in the manuscript but the table indicates that studies #1 and #16 are the same.

SCIT, subcutaneous allergen immunotherapy; SLIT, sublingual allergen immunotherapy; RTSS, rhinoconjunctivitis total symptom score; CSMS: combined symptom medication score (combination of the RTSS with a rescue medication score), baseline versus after 50-52 weeks; IDIT, intradermal [peptide] allergen immunotherapy

Table 2. The placebo effect in seven studies added to the German S2k guideline tables between July 2016 and September 2019.

First author, type of AIT, and year of publication	Effect in the placebo group
Worm, Birch (allergoid) SCIT, 2019 (126)	No statement on the placebo effect. ^Δ The primary endpoint (symptom medication score) was not reached by verum vs. placebo. The placebo contained histamine.
Pfaar, Birch (liquid) SLIT, 2019 (127)	No statement on the placebo effect. The primary endpoint (combined symptom and medication score (EAACI CSMS)) was reached by verum vs. placebo.
Valovirta, Grass (tablet) SLIT, children, 2018 (128)	No statement on the placebo effect. The primary endpoint was not reached by verum vs. placebo.
Okubo,	No statement on the placebo effect.

HDM (tablet), SLIT, adolescents, 2017 (129)	The primary endpoint (TCRS) was reached by verum vs. placebo.
Masuyama, HDM (tablet), SLIT, children (5-17y) 2018 (64)	Global evaluation “much better or better”: By the physician: 56.7% By the participant: 61.3% JRQLQ general state* of 0 or 1: 45.6% AR symptom score: Baseline**: 8.5 → Week 4-6: 7.5 ($\cong -12\%$) → Week 44-52: 5.3 ($\cong -38\%$) AR-symptom severe days: Baseline**: 60 → Week 4-6: 42 ($\cong -30\%$) → Week 44-52: 21 ($\cong -35\%$) “A reduction over time in TCRSs in the placebo group was observed in this trial”. The primary endpoint (TCRS) was reached by verum vs. placebo.
Biedermann, Birch (tablet), SLIT 2019 (130)	No statement on the placebo effect. The primary endpoint (TCS) was reached by verum vs. placebo.
Frew, Grass (SCIT), 2018 (re-analysis)	Responders (“better or a lot better compared with previous years”): 55% <i>“The surprisingly high placebo responder rate was likely a result of the participant’s free and open access to usual antiallergic drugs”.</i>

(131)	Primary endpoint was reached by verum vs. placebo.
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CSMS, combined symptom medication score; TCRS, average total combined rhinitis score; TCS, average daily allergic rhinoconjunctivitis total combined score; JRQLQ: Japanese Rhinoconjunctivitis Quality of Life Questionnaire.

^Δ The researchers did not make any statements with regard to the placebo effect and did not present detailed results obtained with the placebo. If data regarding the placebo were presented, they are listed them. If a statement was given in the publication, it is given here within quotation marks.

* Rated from 0 (“fine”) to 4 (“crying”); **it is assumed that baseline score was obtained from the 2-week run-in period (*not described in detail in the manuscript*), values are extracted from Fig. 1 in the reference.

Table 3. Placebo effect in DBPC RCTs performed using AECs.

First author and year of publication	Allergen and administration route	placebo effect compared to screening challenge = baseline
Zieglmayer, 2016 (132)	HDM, SLIT (tablet)	TNSS: 7.13 at baseline, 7.88 at week 24: ($\cong +11\%$) → after 1 y: 6.44 ($\cong -10\%$) TOSS: baseline: 2.16 → week 24: 1.79 ($= -17\%$) → after 1 y: 1.76 ($\cong -18\%$) TASS: baseline: 1.87 → week 24: 1.61 ($= -14\%$) → after 1 y: not available (only cough was assessed) Cough score: baseline 0.53 → week 24: 0.57 ($\cong +6\%$) → after 1 y: 0.85 ($\cong +60\%$)
Roux, 2016 (133)	HDM, SLIT (tablet)	AUC_{RTSS} 0-4h*: baseline: 1753.2 → after 1 mo: minus 450.5 ($\cong -26\%$) → after 2 mo: minus 480.3 ($\cong -27\%$) → after 4 mo: minus 523.7 ($\cong -30\%$) → after 6 month: minus 639.4 ($\cong -37\%$) ARTSS 0-4h*: baseline: 6.81 → after 1 mo: minus 1.86 ($\cong -27\%$) → after 2 mo: minus 1.91 ($\cong -28\%$) → after 4 mo: minus 2.09 ($\cong -31\%$) → after 6 month: minus 2.59 ($\cong -38\%$)
Nolte, 2015 (134)	HDM, SLIT (tablet)	TNSS: baseline^{**}: 7.41 → week 8: 6.71 ($\cong -9.4\%$) → week 16: 6.9 ($\cong -7\%$) → week 24: 7.45 ($\cong +0.5\%$) TOSS: baseline^{**}: 1.94 → week 8: 1.79 ($\cong -8\%$) → week 16: 1.67 ($\cong -14\%$) → week 24: 1.87 ($\cong -4\%$)

		TNSS over 6 hours during chamber challenge session: similar at baseline. week 8. 16. and 24. Pre-challenge RQLQ: 2.26 → week 8: 2.24 ($\cong -1\%$) → week 16: 2.5 ($\cong +11\%$) → week 24: 2.46 ($\cong +9\%$) Pre-challenge VAS: 28.6 → week 8: 32.5 ($\cong +14\%$) → week 16: 34.7 ($\cong +21\%$) → week 24: 37.3 ($\cong +30\%$)
Couroux, 2015, (112), Patel, 2013 (135)	Cat, 4 intradermal administrations (SPIRE)	RTSS: baseline: 15.02 → week 18-22: 11.21 ($\cong -25\%$) → 1 yr: 12.03 ($\cong -20\%$) → 2 yrs: 13.0 ($\cong -13\%$) TNSS: baseline value not shown → week 18-22: minus 1.98 → 1 yr: minus 1.81 → 2 yrs: minus 0.85 TOSS: baseline value not shown → week 18-22: minus 1.83 → 1 yr: minus 1.17 → 2 yrs: minus 1.17
Meyer, 2013 (136)	rBet v 1-FV**, SCIT	TSS: baseline → week 10: minus 18.8% Placebo contained aluminium hydroxide.
Horak, 2009 (137)	Grass (tablet), SLIT	ARTSS: baseline → 4 mo: minus 18.5%**** “we observed a placebo effect over time...” No rescue medication was allowed.

TNSS, total nasal symptom score (4 symptoms); TOSS, total ocular symptom score; TASS, total asthma symptom score; RTSS, Rhinoconjunctivitis Total Symptom Score; *area under the curve of the average RTSS over the 4 hours of the challenge. **average score over the 4 hours immediately before the screening challenge; SPIRE, synthetic peptide immunoregulatory epitope; ***hypoallergenic folding variant of recombinant Bet v 1; mo, month(s); yr(s), year(s); ****the percentage of improvement at the end point (compared with baseline) could be calculated only for the first 2 hours of challenge.

Table 4. Key statements and unmet needs related to the placebo effect in AIT trials.

Chapter	Key statements	Unmet needs
Regulatory aspects	A DBPC randomized design is requested for pivotal Phase III trials of AIT products in an indication of AR or allergic asthma	There is a requirement for refinements of the DBPC RCT design that circumvent or minimize the placebo effect
	According to the Declaration of Helsinki, a placebo can be used to determine the efficacy or safety of an intervention when there are <i>“compelling and scientifically sound methodological reasons”</i>	Placebo controls are often ethically acceptable and scientifically necessary- a concept that requires reinforcement
	According to the EMA, placebo use is conditioned by (i) the duration of use and (ii) the full provision of information on placebo and other treatments	Determination of how placebo effects and “true” treatment effects vary over the course of a trial, and when these time durations pose ethical problems (notably in paediatric trials)

	Superiority trial designs are scientifically superior to non-inferiority or equivalence trial designs, and require fewer participants for adequate power to detect differences	Establish whether comparisons between active treatments can replace placebo in pivotal AIT trials - although a disadvantage is that without a true placebo, the true placebo effect cannot be estimated
Neuroimmune and psychological mechanisms	Various neural systems (prefrontal cortex, central nervous system < > peripheral nervous system interactions) and biological systems (such as opioids, cholecystokinin, cannabinoids and dopamine pathways) are involved in the placebo effect	Immunological and biological phenotypes (and the changes over time in these factors) when comparing “placebo responders” with “placebo non-responders” require exploration in placebo-controlled trials
	Objective placebo effects (respiratory parameters) have been documented in asthma treatment	The putative presence and magnitude of placebo effects for objective measurements in AR (AEC, provocation tests, etc.) requires further study (notably in comparison with subjective outcomes)
	Placebo responses in patients with allergic diseases are mediated by associative learning processes and patient expectations	When designing and implementing an AIT trial, it is not clear how the nature and frequency of healthcare provider-participant dialogue

		influence expectations of treatments and thus the placebo effect
The placebo effect in recently published AIT trials	Recent AIT studies have featured placebo effects of up to 60-70% (relative to baseline scores). The “average” value is around 30-40%.	It is not clear why the placebo effect in respiratory allergic diseases is large, relative to other diseases. Future studies should address broad clinical and psychosocial variables surrounding AIT vs. other long-term treatments
	A “pure” placebo effect is difficult to observe because AIT studies in respiratory allergic diseases authorize the concomitant use of symptomatic rescue medications	There is a need for innovative methods of distinguishing between the effects of AIT and the effects of symptomatic medications
	Some researchers have found a greater placebo effect in SLIT trials than in SCIT trials	It is necessary to determine whether daily or frequent self-administration (as for SLIT) influences the placebo effect more than infrequent administration by medical personnel (as for SCIT)
Methodological limitations in AIT trial design	Methodological limitations in AIT trials can be classified as patient-related factors, treatment-related factors, and environment/disease-	The relative magnitudes of patient-, treatment- and environment/disease-related factors remains to be explored

	related factors	
	The length of an AIT trial and the time point at which the primary efficacy endpoint is judged will influence the magnitude of the placebo effect	The optimal duration of an AIT trial (depending on the allergen, the formulation, the study population, logistic factors and ethical factors) must be determined
	Detailed information on placebo composition and preparation is often not published in the scientific and medical literature	There is a need for prospective studies of how a placebo's formulation and administration may influence the placebo effect
	In SLIT studies, an inert placebo cannot adequately mimic local (buccal) irritation, and (ii) ethical considerations prevent the inclusion of an irritant in a more "active" placebo	There is a need to development a "true" placebo (one which looks, tastes and feels like the verum but lacks pharmacologic action)
Possible solutions in AIT trial design	Strong placebo effects for subjective endpoints are also observed in AEC studies	Why the use of "hi-tech" objective AECs and provocation tests may also result in observable placebo effects in AIT trials requires further study

	An app-based VAS has been used to assess the impact of allergic diseases in daily life (real-world data)	Large-scale, geolocated, individual-patient data gathered through mHealth and analyzed with artificial intelligence will provide additional information on the nature of the placebo effect and how to more effectively quantify and possibly even minimise placebo effects