

Sublingual immunotherapy, meta-analysis, and knowledge in the age of information

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"All men by nature desire knowledge," wrote Aristotle (384-322 BC).¹ All human beings wish to understand the world around them, and to that end, some construct theories of various kinds to help make sense of it. Plato (428-348 BC), Aristotle's mentor in the grand pursuit of humanist inquiry, provided a figurative account of prisoners chained deep inside a cave.² Their vision blocked, they see only the wall of the cave and some shadows of objects outside. One prisoner breaks free and escapes from the cave. In the light of the sun, he sees the real world for the first time. He returns with a message for his fellow prisoners: they had been seeing nothing but shadows; the real world lies beyond the cave. Plato distinguished between 2 levels of awareness: opinion and knowledge. Observation of the visible world represents opinion only. For Plato, knowledge stands for something certain and infallible, greatly exceeding mere sensory experience.

In current phrasing the product of observation might be described as "data" or "information," terms that are similar but not interchangeable. Data are unrelated facts. When a significant relation exists among data points, then data become information.³ Information is always about something, such as the size of a measurement, the occurrence of an event, or a blueprint. Any pattern that has an effect on the arrangement or transformation of other patterns is information. It does not need to be true or accurate. A signal that creates misunderstanding is still information. As a rule, as the amount of information increases, the message becomes more accurate.

There is no single widely accepted definition of knowledge, and there are many competing propositions. Philosophical debates generally start with Plato's formulation of knowledge as "justified true belief."⁴ Knowledge arises from information. "Transformation" is essential to that process.⁵ In the context of health care, transformation allows primary research or observation data to become usable for clinical decision making. Sources of knowledge include research findings and also experience, authority, trial and error, and theoretical principles. Professional culture in the field of medicine identifies knowledge with particular persons,

and the authority of individual physicians derives in large part from the general agreement that we have privileged access to medical knowledge.⁶

Broader access to scientific research evidence will likely reduce the influence of individual authority.⁶ The most dependable and stable knowledge is gained through systematic processes that control bias. Science is organized knowledge. Using controlled methods, scientists collect observable evidence of natural phenomena, record measurable data, and analyze the information to construct explanations of how things work. The objectivity of science is intimately related to verification and reproducibility. It rests on measurements made independently by any interested researcher. An objective investigation does not draw on prejudices or values. Challenges to earlier investigations are encouraged. It is important to note that objectivity is not the same as scientific consensus. Groups of researchers might share "subjective views" that could come to dominate both conceptual systems and the tools used for measurement.⁷

We live in the age of information.⁸ Technologic developments have expanded access to research evidence. High-performance computers have become so big and so fast (gigahertz speed) and data sets so large (measured in terabytes) that we have no choice but to develop new data paradigms for research and new ways of assimilating knowledge. We will have to turn to mathematical theories of probability and information to make knowledge a concrete concept and to evaluate the logical consistency and validity of information.

The appeal of meta-analysis is inherent in its ability to combine all research on one topic into one large study with many participants. It gathers knowledge in a systematic, organized, structured way to evaluate a problem of interest.⁹ "It is nothing more than the attitude of data analysis applied to quantitative summaries of individual experiments. By recording the properties of studies and their findings in quantitative terms, the meta-analysis of research ... integrates numerous and diverse findings and applies the full power of statistical methods to the task."⁹ Meta-analysis does not remove the need for large, randomized, double-blind clinical trials or traditional narrative reviews of the literature. It is a complementary statistical approach that provides a quantitative summary of pooled results. It generates larger numbers and more stable rates and proportions for statistical analysis and significance testing than any single study. It can be used to analyze a series of randomized controlled trials (or even nonrandomized studies), none of which on its own might have sufficient statistical power. An advantage lies in its apparent objectivity, but as in any research, some qualitative assessment of the pooled data is necessary.⁹

There are some essential prerequisites for the meta-analytic approach to work. Exclusion of patients from published analyses of trials is a widespread practice known to introduce bias.¹⁰ For this reason, reviews should obtain information on excluded

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individuals to carry out an appropriate intent-to-treat analysis of all randomized subjects. Furthermore, all studies included in a meta-analysis must fulfill predetermined inclusion criteria. All should have used similar methods and procedures; the populations studied must be comparable. The data should be relatively complete and free of bias, such as that due to selection or exclusion criteria. All eligible studies available at the time of the meta-analysis must be included. A deliberate exclusion of some suggests that this might have been done to reach an intended result. One standard for selection is prior publication in a peer-reviewed journal, but there are sound reasons for including unpublished studies.

Elsewhere in this issue of the *Journal*, Nieto et al¹¹ report on their evaluation of 5 published meta-analyses of sublingual immunotherapy (SLIT).¹²⁻¹⁷ Nieto et al¹¹ found discrepancies in effect estimates and standardized mean differences. Furthermore, they noted that the funnel plots showed asymmetry suggestive of publication bias, a predicament that typically turns up because authors are more likely to submit and journals to accept positive results and dismiss others that are negative or inconclusive.¹⁸ Hypothesizing after the results are known,¹⁹ a related problem, occurs when several outcomes of a trial are reported selectively depending on the strength and direction of those results. The meta-analyses reviewed by Nieto et al¹¹ evaluated 15 main outcomes, of which 10 showed benefits that reached statistical significance. Correction for publication bias by Nieto et al¹¹ led to the loss of statistical significance in 4 outcomes considered significant beforehand.

Nieto et al¹¹ state that the meta-analyses "reach inconsistent and discrepant conclusions" and that they "do not provide robust enough evidence to support the use of SLIT in the practical routine treatment of allergy." This latter judgment is at odds with those of the authors of the meta-analyses, who held that "in children, sublingual delivery of allergen vaccination constitutes a safe and effective alternative ... to reduce allergy respiratory symptoms and drug intake,"¹² that "SLIT is beneficial for asthma treatment albeit the magnitude of the effect is not very large,"¹³ and that, "compared with placebo, SLIT with standardized extracts is effective in pediatric patients with allergic rhinitis."¹⁴ As for appeal to authority, the British Society for Allergy and Clinical Immunology states in its guidelines that "sublingual immunotherapy has been shown to be effective in both rhinitis and asthmatic patients and to have a good safety profile."²⁰ However, no specific protocols for the use of SLIT have been endorsed.

We agree with Nieto et al¹¹ that there are difficulties with meta-analysis, but it is essential to remember that it is not a technique but rather a perspective that uses many techniques of measurement and statistical analysis. The practitioner of meta-analysis, like any other scientist, must use correct methods and sound judgment, and the readers, reviewers, and editors of journals that publish the results must be aware of potential pitfalls. The

meta-analyses discussed by Nieto et al¹¹ evaluated trials published from 1995 to 2005. For a very novel therapy, such as SLIT, initial studies might provide inconsistent results because they are assessing many fundamental variables, such as dosing, preparations, study design, and best population/disease target. As knowledge of and technology for SLIT advance, it is conceivable that both trial results and meta-analyses will become more consistent and positive.

In searching for knowledge, be ready for the unexpected.

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